Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis (TARGET Trial): Does Ticagrelor Improve Graft Patency after Coronary Bypass?

Study Number – Brilinta ISSBRIL0220

Version 4 – October 17, 2013

Principal Investigator: Alexander Kulik, MD MPH
Lynn Heart and Vascular Institute
Boca Raton Regional Hospital
800 Meadows Road
Boca Raton, Florida, 33486

Drug Manufacturer: AstraZeneca LP
1800 Concord Pike
Wilmington, Delaware, 19850

Introduction

Background

Coronary artery bypass graft surgery (CABG) is the definitive surgical approach for the treatment of ischemic heart disease, with >400,000 procedures performed annually in the United States alone [1]. Despite the increasing use of arterial grafts during CABG, the saphenous vein remains an important conduit that is still used for more than 70% of grafts, due to its ease of use and ready availability [2]. While convenient as a conduit however, the saphenous vein is severely limited by the progressive development of saphenous vein graft disease. With important clinical sequalae, saphenous vein graft disease remains an unresolved medical problem, as up to 20% of venous grafts occlude in the first year after bypass surgery [3]. Between 1 and 6 years, the graft attrition rate is 1% to 2% per year, and between 6 and 10 years it rises to 4% per year. By 10 years after surgery, only 60% of grafts are patent and only 50% of patent vein grafts are free of significant stenosis. In addition, native coronary artery disease (CAD) progresses in 5% of patients annually [4-7]. As a result of graft and native vessel attrition, this population is at high risk for subsequent ischemic events, including myocardial infarction (MI) and death [6]. Further revascularization, either reoperation or percutaneous coronary intervention (PCI), is required in 4% of patients by 5 years, 19% of patients by 10 years, and 31% of patients by 12 years after the initial bypass surgery [2, 8].

Saphenous vein graft disease is composed of three discrete stages: thrombosis, intimal hyperplasia, and atherosclerosis. These processes are interlinked pathologically in the evolution of vein graft disease [5-6, 8-10]. Early thrombosis is a major cause of vein graft attrition during the first month after CABG. Even when preformed under optimal conditions, the harvesting of venous conduits is associated with focal endothelial disruption that results in the accumulation of fibrin on the luminal surface, the adherence and aggregation of platelets, and the activation of the extrinsic coagulation cascade by subendothelium tissue factor [11-12]. Grafts that survive this early period develop a progressive thickening of the media with neointimal formation that begins within days of implantation. This continues over the subsequent months, and forms a template for the development of superimposed atherosclerotic changes [9-10].

Aspirin is recommended for secondary prevention after CABG because of its effects on early patency and reduction in cardiac events [13-16]. By decreasing thromboxane-A2 production, aspirin prevents platelet aggregation [14]. When administered within 48 hours following cardiac surgery, aspirin is associated with a lower risk of death and ischemic complications of the heart, brain, kidneys, and gastrointestinal tract [17]. Several randomized controlled trials have demonstrated that aspirin significantly improves graft patency after CABG [18-21]. In the largest trial on the subject, the Veterans Administration Cooperative Study enrolled 772 CABG patients, noting that, compared to placebo, aspirin at a dose of 325 mg/day or higher increased vein graft patency both at 60 days [22]

and 1 year after surgery [23]. Despite its established benefit in patients with CAD, aspirin therapy does have limitations. It is a relatively weak antiplatelet agent and does not inhibit platelet aggregation by thromboxane A2-independent pathways (e.g. ADP or collagen stimulation). Even with aspirin therapy for secondary prevention, a large number of recurrent events occur [24]. Moreover, a significant proportion of patients undergoing CABG may be aspirin resistant, as defined as undetectable platelet inhibition after 1 week of therapy [25-26]. Depending on the population studied and the specific definition of aspirin resistance, anywhere from 10-40% of patients have an inadequate antiplatelet response to aspirin [25, 27]. Such patients appear to be at increased risk for the development of vascular events. In theory, these aspirin-resistant patients may derive particular benefit from alternative antiplatelet therapy (such as ticagrelor) instead of aspirin [28].

Because of the concerns regarding aspirin resistance [25, 27], and the high vein graft occlusion rate noted in recent trials [3], several investigators have sought to evaluate the role of clopidogrel after CABG. A thienopyridine that irreversibly inhibits the platelet $P2Y_{12}$ adenosine diphosphate receptor, clopidogrel has been shown to have important antithrombotic effects [29] and clinical benefits in several CAD trials [30-31]. Following CABG surgery however, observational and clinical trials have failed to convincingly demonstrate that its use improves clinical outcomes [32-35] or postoperative graft patency [36-39] compared to aspirin therapy. To date, 4 clinical trials involving 659 patients have evaluated the impact of clopidogrel on the process of vein graft disease after CABG (with cardiopulmonary bypass) [36-39]. Only one of these trials found a benefit in terms of vein graft patency with clopidogrel treatment. Nevertheless, this study was limited by the lack of blinding and placebo-control, and the control arm received a fairly low dose of aspirin (100 mg) [38]. Using a higher dose of aspirin, Kulik et al. performed a randomized double-blind placebo-controlled trial comparing 162 mg aspirin daily to aspirin 162 mg plus clopidogrel 75 mg daily, and no difference in vein graft patency was noted [39].

Overall, the experience with clopidogrel after CABG has been unimpressive in terms of improving graft patency or clinical outcomes. In keeping with the American Heart Association guidelines [40-41], the current standard of care for postoperative antiplatelet therapy is isolated aspirin therapy, in doses of 100-325 mg daily. Interestingly, a favorable experience with ticagrelor was recently noted after CABG. Like clopidogrel, ticagrelor inhibits the platelet $P2Y_{12}$ adenosine diphosphate receptor, but has a more rapid onset of action and more consistent and pronounced platelet inhibition than clopidogrel [42-43]. In the PLATO study, 18,624 patients with acute coronary syndrome were randomized for 1-year treatment with aspirin plus ticagrelor 90 mg twice daily or aspirin plus clopidogrel 75 mg daily. The primary end point of the study (cardiovascular death, MI, or stroke) was significantly reduced by ticagrelor compared to clopidogrel (9.8% versus 11.7%, ticagrelor versus clopidogrel, $P<0.001$) [42]. In a subsequent sub-group analysis of the 1,261 PLATO patients who underwent CABG, ticagrelor

treatment led to a non-significant reduction in the primary end-point at 1 year (10.6% versus 13.1%, ticagrelor versus clopidogrel, P=0.29), and a significant reduction in cardiovascular mortality (4.1% versus 7.9%, ticagrelor versus clopidogrel, P<0.01) [43].

To date, no data is available regarding the impact of ticagrelor on saphenous vein graft patency following CABG. 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. In contrast to clopidogrel, ticagrelor treatment leads to a more pronounced platelet inhibition, and may substantially improve graft patency following CABG compared to aspirin therapy. We therefore propose a randomized controlled trial to compare postoperative graft patency between patients treated after CABG with aspirin therapy, the current standard of care, to those treated with ticagrelor starting in the early postoperative period.

Research Hypothesis

The hypothesis of this clinical trial is that ticagrelor treatment will improve postoperative saphenous vein graft patency 1 and 2 years after CABG surgery, as compared to standard aspirin therapy.

Study Rationale

Saphenous vein graft disease remains an unresolved medical problem. Many vein grafts occlude in the first year after bypass surgery, leading to adverse cardiovascular outcomes, including recurrent angina, myocardial infarction, and the need for repeat coronary intervention. While aspirin is the standard antiplatelet treatment after CABG surgery, 10-20% of vein grafts continue to occlude despite contemporary secondary preventative therapy. Compared to aspirin and other antiplatelet therapies like clopidogrel, ticagrelor treatment leads to a more pronounced platelet inhibition, and may substantially improve graft patency following CABG compared to aspirin. No data has yet to be collected regarding the impact of ticagrelor on saphenous vein graft patency following CABG. In this context, we seek to compare vein graft patency between patients randomized to receive aspirin therapy, the current standard of care, or ticagrelor treatment, starting in the early postoperative period, and continuing for 2 years after CABG.

Benefits, Risks and Ethical Assessment

It is anticipated that ticagrelor will improve vein graft patency in this clinical trial. To maximize the benefits and minimize the risks associated with ticagrelor, concomitant aspirin treatment will not be administered to patients randomized to receive ticagrelor in order to prevent bleeding complications associated with dual antiplatelet therapy. Patients who are randomized to aspirin treatment will receive 162 mg daily in keeping with current clinical guidelines, since a lower daily dose of 81 mg daily may be under-treatment and insufficient for antiplatelet therapy after CABG. In addition to graft patency at 1 and 2 years after surgery,

major adverse cardiovascular events and adverse bleeding events will be recorded in the 2-year interval after surgery. The study will be conducted with the highest ethical standards, in accordance with the applicable United States Food and Drug Administration (FDA) regulations and institutional review board requirements. This trial will be submitted to the FDA for review. Moreover, research ethics approval will be sought from the Western Institutional Review Board (WIRB).

Study Objectives

Primary Objective

The primary objective of this clinical trial will be to evaluate whether, as compared to usual aspirin treatment, ticagrelor early after CABG prevents saphenous vein graft *occlusion* 1 year after surgery, as assessed by computed tomography (CT) coronary angiography, as well as 2 years after surgery via study extension.

Secondary Objective

The secondary objective of this clinical trial will be to evaluate whether, as compared to usual aspirin treatment, ticagrelor early after CABG prevents saphenous vein graft *stenosis,* defined as >50% narrowing of the graft, 1 year after surgery, as assessed by computed tomography (CT) coronary angiography, as well as 2 years after surgery via study extension.

Exploratory Objectives

Additional exploratory objectives of this clinical trial will include the impact of ticagrelor treatment, as compare to aspirin, on the incidence of major adverse cardiovascular events (mortality, myocardial infarction, cerebrovascular accident, hospitalization for coronary ischemia, and need for coronary intervention) and bleeding events in the first year and second year study after CABG (Appendix B). It is recognized that the study will be under-powered in the evaluation of these outcomes, which will be defined using the previously published definitions from the CURE and CASCADE trials [30, 39, 44]. Specifically, major bleeding episodes will be defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood. Major bleeding is classified as life-threatening if the bleeding episode is fatal, leads to a reduction in the hemoglobin level of at least 5 grams per deciliter or to substantial hypotension requiring the use of intravenous inotropic agents, if it necessitates a surgical intervention, if it is a symptomatic intracranial hemorrhage, or if it necessitates the transfusion of four or more units of blood. Minor bleeding episodes will include other hemorrhages (i.e. nose bleeds) that lead to the interruption of the study medication.

Study Plan and Procedures

Overall Study Design

This clinical trial will be a randomized double-blind study comparing two postoperative antiplatelet regimens after CABG. The trial will be conducted over a 4 year period in order to achieve the study objectives. Patients will be recruited during the first and second years of the study. Graft evaluation will be performed during the second, third and fourth years of the study. Each patient will participate in the trial for 1 year following surgery, at which point a CT coronary angiogram will assess graft patency. Patients will then be invited to continue participating in the study for a second year (study extension). A CT coronary angiogram will subsequently asses 2-year graft patency.

AstraZeneca LP (Wilmington, Delaware) will provide the ticagrelor tablets for the study (Appendix C). The ticagrelor tablets will be submitted by AstraZeneca to Compounding Docs Pharmacy (Boca Raton, Florida), a pharmaceutical custom compounding company. The aspirin drug for the study will be provided by Compounding Docs. The ticagrelor and aspirin study drug will be crushed and compounded into capsules for the trial. The compounding process does not affect the bioavailability of ticagrelor or aspirin, and the bioavailability of the capsules will be confirmed through independent biochemical analysis. A bullet pulverizer will be used to crush a pool of 300 tablets at a time (aspirin or ticagrelor). A ProFiller 3600 capsule filling system will then prepare 300 capsules containing the active powder (aspirin or ticagrelor), with inert microcrystalline cellulose used to fill the remaining capsule space. The crushed tablets will not be used beyond the expiration of the original product.

Compounding Docs will prepare identical capsules containing either 81 mg of aspirin or 90 mg of ticagrelor. These prepared capsules will appear identical for the purpose of blinding in this study. Patients in the trial will be assigned to receive either one aspirin 81 mg capsule 2 times per day (Arm A – aspirin) or one ticagrelor 90 mg capsule 2 times per day (Arm B – ticagrelor). Compounding Docs will prepare pill bottles containing 180 capsules to cover for a 3-month supply. The blinded capsules will be stored at room temperature (25°C), as indicated on the bottle container label. These pill bottles will then be submitted to the Boca Raton Regional Hospital (BRRH) pharmacy. Ordering and dispensing of the blinded study medication will be coordinated by the BRRH pharmacy. Shipment of study medication to the second recruitment site at the University of Ottawa Heart Institute (Ottawa, Ontario, Canada) will also be coordinated by the BRRH pharmacy. After surgery, each trial participant will be provided with a 3-month supply of study medication, and a new pill bottle will be provided to each patient every 3 months over the course of the 1- or 2-year trial enrollment.

The study population will include all patients undergoing CABG over the study period at the Lynn Heart and Vascular Institute of the Boca Raton Regional

Hospital in Boca Raton, Florida, and the University of Ottawa Heart Institute in Ottawa, Ontario, Canada. Patients undergoing on-pump or off-pump CABG will be eligible for this study, as long as at least one saphenous vein graft is used. Patients undergoing concurrent valve repair or replacement surgery will also be eligible, unless postoperative warfarin anticoagulation is anticipated (i.e. mechanical prosthetic valve). CABG patients will be pre-screened and evaluated for study eligibility in the perioperative period (Appendix A). Study eligible patients will be selected and approached by the study coordinator to explain the trial. Consent and randomization will occur within 5 days after surgery. Randomization will be stratified based on the surgical site, the presence of diabetes mellitus, and the use of cardiopulmonary bypass (on-pump or off-pump).

Prior to trial enrollment, in the early postoperative period, patients will be treated with usual aspirin antiplatelet therapy (typically 325 mg daily) starting within 24 hours after surgery, in keeping with current clinical guidelines [41]. At the time of randomization following surgery, this standard aspirin treatment will be discontinued. Patients will be randomized into an aspirin group (Arm A - aspirin 81 mg bid) or a ticagrelor group (Arm B - ticagrelor 90 mg bid). The study capsules will be identical to ensure blinding. Medication administration and data collection will be performed in a double-blind manner, such that neither the patient nor the healthcare personnel will be aware of the medication assignment.

Recruitment and written consent will be performed either prior to surgery or within 5 days after surgery. This interval of time after surgery will enable subjects to recover from anesthesia and the occasional confusion associated with postoperative narcotic use, in order to provide informed consent. Randomization will occur following surgery. Patients who are requiring high levels of hemodynamic support (more than 2 inotropes) within 48 hours after surgery will not be randomized into the study. Patients requiring postoperative anticoagulation with warfarin will also not be recruited. Following surgery, the study medication will be administered daily via nasogastric tube (if patient is intubated) or orally, starting on postoperative days 1-5, for the duration of 1-2 years.

Treatment will continue for 1 year, at which time patients will undergo a CT coronary angiogram to assess graft patency. Patients will then be invited to continue participating in the trial for 1 more year with the same study treatment. A repeat CT coronary angiogram will subsequently be performed for another graft evaluation at the 2-year time point after surgery. Because cholesterol levels can impact postoperative graft patency, current clinical guidelines recommend lipid-lowering therapy after CABG to achieve low-density lipoprotein (LDL) levels <100 mg/dL [41]. As such, patients in this trial will undergo lipid level evaluation at baseline before surgery and every 3 months during study enrollment. This information will be made available to clinicians involved in the care of study subjects to facilitate modification of lipid-lowering therapy, as needed, in keeping

with guideline recommendations. A creatinine level will be obtained before the 1-year and 2-year CT coronary angiogram, given the potential renal toxic effects associated with intravenous contrast.

Trial Timeline

CABG Patient Consented Pre-op or Within 5 Days after Surgery

⇓

Double-Blind Randomization based on Stratification factors

⇓

Initiate Aspirin 81 mg bid or Ticagrelor 90 mg bid
Within 5 days post-CABG

⇓

Discharge from hospital
With supply of meds for 3 months

⇓

Physician follow-up
Within 1 month

⇓

Research Coordinator follow-up
Lipid profile
Assessment of major adverse cardiovascular and safety events
Resupply study medication
At 3, 6, 9 and 12 months

⇓

CT coronary angiogram, Creatinine level
Consent for study extension (year 2)
At 12 months

⇓

Research Coordinator follow-up
Lipid profile
Assessment of major adverse cardiovascular and safety events
Resupply study medication
At 15, 18, and 21 months

⇓

Lipid profile
Assessment of major adverse cardiovascular and safety events
CT coronary angiogram, Creatinine level
At 24 months

Rationale for Study Design and Doses

The TARGET study will be a randomized double-blind controlled trial, which will generate the highest quality data regarding the potential patency benefits associated with ticagrelor after CABG. The study design will ensure that ticagrelor patients do not receive aspirin, to prevent bleeding complications associated with dual antiplatelet therapy. For the control patients who receive aspirin, 81 mg bid (162 mg daily) will be used. This relates to the fact that post-CABG patients have relative aspirin resistance postoperatively, and 81 mg of aspirin daily may be insufficient as the sole antiplatelet therapy. This relative aspirin resistance of post-CABG patients constitutes yet another biologic basis for investigating of the use of ticagrelor after bypass surgery. A higher dose of aspirin (162 mg daily) will ensure that aspirin patients receive adequate antiplatelet treatment after CABG, in keeping with current clinical guidelines [41]. At 1- and 2-years after surgery, graft patency will be evaluated by CT coronary angiography. Compared to conventional coronary angiography, CT angiography is a non-invasive diagnostic test that does not require an arterial puncture or catheter manipulation within the aorta, native coronary arteries, or bypass grafts. In a meta-analysis of 14 studies, CT coronary angiography was shown to have a sensitivity of 97.6% and a specificity of 98.5% for the assessment of graft occlusion, as compared to conventional coronary angiography [45].

Subject Selection Criteria

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. Female and/or male patients aged 18-90 years
3. Patients undergoing first-time CABG with at least 1 saphenous vein graft, irrespective of concurrent valve surgery

Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:
1. Inability to provide informed consent
2. Pregnancy or seeking pregnancy
3. Patients undergoing redo-CABG
4. Serum creatinine >1.8 mg/dL (need for contrast with CT coronary angiogram)
5. Hypersensitivity or allergy to aspirin or ticagrelor
6. Anticipated need for postoperative anticoagulation with coumadin, dabigatran or rivaroxaban (mechanical valve, chronic atrial fibrillation, DVT/PE)
7. History of gastrointestinal hemorrhage
8. Active pathological bleeding
9. History of intracranial hemorrhage

10. Severe hepatic impairment
11. Current or anticipated use of strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir)

Study Conduct

Restrictions during the Study

Patients who require long-term anticoagulation (chronic atrial fibrillation, mechanical valve) will not be recruited into the TARGET trial, due to the higher risk of bleeding complications associated with the combination of both ticagrelor and coumadin. Despite this exclusion, subjects who are recruited into the trial may subsequently develop an indication for anticoagulation after study enrollment. As an example, anticoagulation may be necessary starting 10 days after surgery for a TARGET participant who has developed new-onset postoperative atrial fibrillation or deep vein thrombosis. In this scenario, the trial subject will discontinue the blinded study medication (aspirin or ticagrelor) and receive open label treatment as indicated by the clinicians involved in the patient's care (i.e. open label 81 mg aspirin daily plus coumadin). When anticoagulation is no longer needed (resolved atrial fibrillation), or the course of coumadin has been completed, open label treatment will cease, and the trial subject will resume the blinded study medication. The subject will continue to followed as part of the trial and undergo CT graft evaluation irrespective of study medication interruptions.

In the case of a serious bleeding event (i.e. gastrointestinal bleeding requiring hospitalization) while enrolled in TARGET, a study subject will permanently discontinue the study medication. The patient will continue to be followed for the duration of trial enrollment, but the subject will receive open label treatment as indicated by the clinicians involved in the patient's care (i.e. open label 81 mg aspirin daily).

Subject Enrollment and Randomization

CABG patients will be evaluated by the study coordinator for pre-screening and trial eligibility in the perioperative period. Consent and randomization will occur within 5 days after surgery. Randomization will be stratified based on the surgical site, the presence of diabetes mellitus, and the use of cardiopulmonary bypass (on-pump or off-pump). A block randomization technique will ensure an equal distribution of diabetic patients in both arms of the trial, in addition to an equal distribution of on-pump and off-pump CABG patients. The randomization schedule will be generated using SAS 9.1 software (SAS, Cary, NC). All patients and study personnel will be blinded to the treatment assignment which will be performed by hospital pharmacies at the Boca Raton Regional Hospital or

University of Ottawa Heart Institute. While consent may be performed before surgery, randomization will not be performed until after surgery when clinical stability has been ensured (patients who are requiring high levels of hemodynamic support and are at high risk of perioperative death will not be randomized into the study). At the time of randomization following surgery, standard aspirin treatment will be discontinued. Patients will be randomized into an aspirin group (Arm A - aspirin 81 mg bid) or a ticagrelor group (Arm B - ticagrelor 90 mg bid).

Procedures for Randomization

Once a patient has been identified and consented, the pharmacy will be notified that the patient needs to be randomized. A Randomization Form will be completed and faxed to the pharmacy. In addition, protocol orders will be entered into the patient's medical record. The hospital pharmacist will refer to the randomization schedule and assign the patient to the appropriate group. In addition, a second pharmacist will be required to sign off on the Randomization Form to confirm that the patient was assigned to the appropriate group.

Procedures for Handling Subjects Incorrectly Randomized

The Randomization Form will be designed in a manner that the subgroups will be clearly identified. In addition, the process of utilizing a second pharmacist during the randomization phase will avoid incorrect assignments. If a subject has been incorrectly enrolled, the unblinded pharmacist will be notified and the randomization number will be corrected. The patient will remain on the same blinded study medication.

Blinding and Procedures for Unblinding the Study

The study personnel will be blinded, with the exception of the pharmacy staff involved in randomizing the trial subjects. Only unblinded pharmacy personnel will have access to any unblinded patient logs. Unblinded pharmacy personnel will be notified by the Principal Investigator or his designee that a patient requires unblinding. A patient should not be unblinded without the authorization of the Principal Investigator. Any requests for unblinding should be directed to the Principal Investigator and/or the research coordinator. Upon approval of the Principal Investigator, a patient may be unblinded if this information is essential in determining the continued care of the patient.

Methods for Ensuring Blinding

The study personnel will not have access to any of the unblinded patient logs. This includes patient assignment logs and/or drug accountability logs. These logs will be maintained in the pharmacy.

Treatments

Investigational product	Dosage form and strength	Provider
Aspirin	81 mg PO bid	Compounding Docs
Ticagrelor (Brilinta)	90 mg PO bid	AstraZeneca

Doses and Treatment Regimens

Patients randomized into Arm A will be treated twice daily with blinded aspirin capsules containing aspirin 81 mg. Patients randomized into Arm B will be treated twice daily with blinded ticagrelor capsules containing ticagrelor 90 mg.

Labeling

The label will include the following information: Facility Name, Patient Name, Dose (1 capsule bid), Prescription Number, and Dispensing Date. In addition, the drug name will be included as "Investigational Drug: Ticagrelor 90 mg versus Aspirin 81 mg". The bottle container label will also note that the capsules need to be stored at room temperature (25°C).

Storage

The investigational drug will be stored in the hospital pharmacy. This area has limited and restricted access.

Concomitant and Post-Study Treatments

Patients will receive concomitant therapies in both 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 [41, 46-47]. Target LDL values (less than 100 mg/dL) will be those recommended as per current guidelines. In the absence of specific contraindications, all patients will be on postoperative lipid lowering therapy, and lipid profiles will be assessed every 3 months following surgery. Diabetic patients will have aggressive perioperative glycemic control, including an intravenous insulin infusion both in the operating room and in the intensive care unit, and a subcutaneous insulin sliding scale while recovering on the surgical ward. Once drinking well, diabetic patients will be restarted on their original preoperative diabetic regimens (oral agents and/or insulin therapy). The treatment of diabetes during this study will be closely monitored in collaboration with endocrinologists.

Treatment Compliance

The research coordinators involved in the trial and the Principal Investigator will answer questions, assess patient compliance with the trial protocol, and evaluate

safety issues throughout trial enrollment. Telephone calls by the research coordinator will be performed every 3 months after surgery. Additionally, trial participants will meet with a research coordinator every 3 months to receive a new 3-month supply of the study medication. These visits and telephone calls will help in the retention of study subjects. Patient compliance will be evaluated through personal interviews and the counting of remaining pills at 3-month intervals (at the time that new study medication is provided to patients).

Accountability

The research coordinator will count remaining investigational drug at the time of study drug return. This information will be maintained in the study patient's chart. In addition, patient assignment logs and drug accountability logs will be maintained in the hospital pharmacy. These logs will be maintained by unblinded pharmacy personnel.

Discontinuation of Investigational Drug

A recruited subject who subsequently develops an indication for anticoagulation (i.e. new-onset postoperative atrial fibrillation or deep vein thrombosis) will be asked to discontinue the TARGET blinded study medication. The participant will then receive open label treatment as indicated by the clinicians involved in the patient's care (i.e. open label 81 mg aspirin daily plus coumadin). When anticoagulation is no longer needed (resolved atrial fibrillation), or the course of coumadin has been completed, open label treatment will cease, and the trial subject will be asked to resume the blinded study medication.

In the case of a serious bleeding event (i.e. gastrointestinal bleeding requiring hospitalization) while enrolled in TARGET, a study subject will permanently discontinue the study medication.

Procedures for Discontinuation of a Subject from Investigational Drug

If it is determined that a patient will be discontinued from the investigational drug, then alternate medication will be prescribed, if applicable, by the Principal Investigator or the patient's health care provider. Attempts will be made to obtain any remaining investigational drug in the patient's possession.

Withdrawal from Study

A patient may be withdrawn from study medication at any time by the study doctor or the sponsor without the patient's consent. For example: if it is in the patient's best interest, if the patient has problems complying with study procedures, if the patient becomes pregnant, if the patient does not consent to continue in the study after being told of changes in the research, if the patient makes a request, if the patient has a serious adverse event (GI bleed), or for any other reason.

Collection of Study Variables

Recording of Data

Case report forms will be designed and utilized to collect all pertinent data.

Data Collection at Enrollment and Follow-up

Saphenous vein graft patency and stenosis will be assessed by CT coronary angiography at 1 year and 2 years after CABG. The incidence of major adverse coronary events and safety outcomes will be documented during postoperative visit at 1 month after surgery and every 3 months thereafter. A research coordinator will phone each patient every 3 months to document any other events and ensure study drug compliance. This data will be recorded on the case report forms.

Enrollment Procedures

Patients undergoing CABG procedures will be pre-screened for eligibility in the study. Inclusion and exclusion criteria will be reviewed. The research coordinator will consult with the Principal Investigator or sub-investigator(s) regarding patient's eligibility prior to enrollment. Once a patient is deemed eligible for the study, the patient will be invited to participate.

Follow-up Procedures

Patients will be contacted by the research coordinator for all follow-up visits. Appointments will be scheduled and laboratory tests and/or CT scan will be completed. Patients will receive a resupply of study drug at these appointments, if applicable. The Principal Investigator and/or sub-investigator(s) will be informed of the patient's status.

Safety

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 (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, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

Definitions of Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e. 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
- Results in 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 serious adverse events (SAEs) and their relationship to the study treatment will be assessed by the investigators and communicated to AstraZeneca.

Causality Assessment of Adverse Event to Treatment

The investigator will assess the relationship of any AE to the use of the study drug, based on available information, using the following guidelines:

Unlikely related – no temporal association, or the cause of the event has been identified, or the drug, biological or device cannot be implicated

Possibly related – temporal association, but other etiologies are likely to be the cause; however involvement of the drug, biological, or device cannot be excluded

Probably related – temporal association and other etiologies are possible but unlikely

Recording of Adverse Events

Adverse events will be recorded for study subjects while they are enrolled in the trial (maximum 2 year enrollment). Serious adverse events that occur at any time after the inclusion of the subject in the study (defined as the time when the subject is randomized) up to 30 days after the subject completed or discontinued the study medication must be reported. The subject is considered to have completed the study either after the completion of the last visit or contact (e.g. phone contact with the investigator or designee), or 30 days after the last dose of the study medication, whichever is later.

As noted above, the incidence of major adverse cardiovascular events (mortality, myocardial infarction, cerebrovascular accident, hospitalization for coronary ischemia, and need for coronary intervention) and bleeding events will be recorded (and noted as adverse events) for trial subjects in the 2 year period after CABG. If, during trial enrollment, a participant develops a major adverse cardiovascular event or major bleeding event, the TARGET blinded study

medication will be discontinued. The participant will then receive open label treatment as indicated by the clinicians involved in the patient's care.

The following variables will be collected for each AE:
- Adverse event description
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the study medication
- Action taken with regard to study medication
- Whether AE caused subject's withdrawal from study
- Patient 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
- Reason AE is serious (i.e. hospitalization, probable cause of death)
- Dates of hospitalization, discharge, and/or death
- Whether autopsy performed
- Investigator causality rating against the study medication or other medications

Reporting of Serious Adverse Events

Investigators and other site personnel will inform the FDA, via a MedWatch form, of any serious, *unexpected*, possibly related adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch report will 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 will accompany the MedWatch form indicating the following:
- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial title and AstraZeneca ISS reference number

The investigative site will also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications as determined by the principal investigator.

The SAE report and accompanying cover page will be sent 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 will be reported to AstraZeneca using the MedDRA coding language for serious adverse events.

All SAEs will be reported to AstraZeneca, whether or not considered causally related to the study drug. All SAEs will be documented.

The investigator will be responsible for informing the institutional review board (IRB) as soon as possible, in accordance with local laws and regulations. All SAEs will be reported to the Western Institutional Review Board (WIRB). The development of serious adverse events that might be attributable to the study medication will lead to the termination of the study drug.

Ethical and Regulatory Requirements

Ethical Conduct of the Study

The TARGET trial will adhere to the highest research ethics standards, in accordance with the applicable FDA regulations and IRB requirements. The study protocol will be reviewed by the Research Committee of the Boca Raton Regional Hospital. Thereafter, the protocol, the Informed Consent Form (ICF), and relevant supporting information will be submitted to the Western Institutional Review Board (WIRB) for human research ethics approval. The trial protocol will also be submitted to the United States Food and Drug Administration (FDA) to obtain exemption status from Investigational New Drug Application (IND) regulations.

Patients will be approached before or after CABG surgery for enrollment in the trial. As part of the consent process, patients will be explained the rationale of the trial and the potential adverse side effects associated with enrollment. Patients will be reminded that they are free to choose to either participate or not participate in the study.

Ethics and Regulatory Review

The TARGET trial will not begin subject recruitment until approval has been granted by WIRB and the FDA. The investigator will be responsible for reporting to WIRB of the progress of the study at least once per year or as required. In addition, the Investigator will be responsible for obtaining WIRB approval for any changes made to the protocol or Informed Consent prior to implementation, except where study subject safety is affected.

The Investigator will promptly notify WIRB, AstraZeneca, and the FDA of all serious, *unexpected*, possibly related adverse events.

Informed Consent

The Informed Consent will be approved by WIRB prior to subject enrollment. Patients will be consented in accordance with Good Clinical Practice guidelines, prior to enrollment in the trial.

Changes to the Protocol and Informed Consent Form

The Investigator will be responsible for obtaining WIRB approval for any changes made to the protocol or Informed Consent prior to implementation, except where the study subject safety is affected. AstraZeneca will be notified of any changes to the Protocol and/or Informed Consent.

Audits and Inspections

AstraZeneca will be notified of any audits or inspections conducted at the study locations. The Principal Investigator and study staff will make themselves available, in accordance with federal guidelines.

Study Management

Training of Study Site Personnel

All personnel will be properly trained in the protocol and procedures expected of them. In addition, refresher training may be conducted, as needed. Training logs will be kept in the study regulatory binders.

Monitoring of the Study

The sites will perform self monitoring of this study.

Source Data

All source documents will be maintained in the research chart for each subject. In addition, electronic medical records (EMR) may also be utilized by the study facility. It is the practice of the research facility to allow EMR access to monitors or auditors, if requested.

Study Timetable and End of Study

Patient recruitment is expected to be completed within 2 years of initiating the study. Once the final patient has been recruited, follow-up will last for 2 additional years. The study duration is estimated at 4 years.

During the time of enrollment, patients will be seen every three months. This includes the 3 month visit, 6 month visit, 9 month visit, and 12 month visit. At the 12 month visit, patients will be given the opportunity to continue in the study for an additional 12 months. This would include the 15 month visit, 18 month visit, 21 month visit, and 24 month visit.

Data Management

All data will be recorded on preprinted case report forms (CRF) suitable for electronic data capture. The case report forms will be kept in the patient's research chart. The research charts will be stored in a locked, secure location. Data will be entered by qualified personnel at the conclusion of study.

Statistical Methods

Sample Size

This trial will be a pilot study. Outcome estimates will form the basis for assessing the feasibility of designing a future large and definitive trial. One hundred fifty patients in each study arm will be enrolled (300 total patients). Since each patient will receive 2 vein grafts, on average, there will be approximately 300 vein grafts in each group (600 vein grafts total). This sample size will be large enough to detect whether a clinically important difference exists in terms of vein graft patency between the groups, but small enough that subject recruitment can be performed in an expedient manner, likely within the first 24 months of the study.

This trial will not be designed or powered as a definitive clinical trial. Based on several previously published clinical trials, it is anticipated that 10-20% of vein grafts will be documented as occluded at the 1-year time point after CABG. Should ticagrelor improve graft patency and reduce vein occlusion from 20% to 10%, power calculations suggest that this pilot trial will have 96% power to detect a significant difference ($P<0.05$) between the groups. Alternatively, if ticagrelor were to decrease the occlusion rate from 15% to 10%, the power will be approximately 58%.

Statistical Analysis

All study data will be collected in a blinded fashion during the course of the trial. At 1- and 2-years after surgery, the CT coronary angiograms will be read and interpreted by board-certified radiologists with expertise in cardiac CT imaging. The radiologists will be blinded to study treatment assignment. The data analysis will also be performed in a blinded fashion, with un-blinding at the conclusion of the analysis. Study outcomes will be compared on an intention-to-treat basis according to the randomization study-group assignment. Vein graft occlusion, the primary outcome of the study, will be compared between the two randomization groups using a Fisher's exact test. To account for within-patient correlation and the possibility of multi-graft occlusion within individual patients, vein graft data will also be analyzed using logistic regression fit with generalized estimating equations methods. For secondary outcomes, continuous data will be compared between the two groups using two-sided Student's t tests, two-sample Wilcoxon rank-sum tests, or ANOVA, and a Fisher's exact test will be used for categorical data. Time to major adverse cardiovascular event will be determined for the study groups using the Kaplan-Meier method, and groups will be compared with a log-rank test. In accordance with intention-to-treat analysis, clinical and safety data will be analyzed for all randomized patients in the study. This will include data collected

from subjects who have dropped out of the trial or who refuse postoperative CT coronary angiography (5% expected refusal).

Study analysis will be performed at the 1-year and 2-year time-points. The first analysis will be conducted when the last recruited patient has passed the 1-year time interval after surgery and has undergone CT angiography. The second analysis will be performed when all recruited patients have crossed the 2-year time-point after surgery.

Important Medical Procedures to be followed by the Investigator

Overdose

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

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

Pregnancy

Patients who are pregnant or seeking to become pregnant will be excluded from trial recruitment. All outcomes of pregnancy, should they occur, will be reported to AstraZeneca.

References

1. American Heart Association: Heart Disease and Stroke Statistics - 2011 Update. Circulation. 2011;123:e1-e192.
2. Weintraub WS, Jones EL, Craver JM, Guyton RA. Frequency of repeat coronary bypass or coronary angioplasty after coronary artery bypass surgery using saphenous venous grafts. Am J Cardiol. 1994;73:103-12.
3. Alexander JH, Hafley G, Harrington RA, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. JAMA. 2005;294:2446-54.
4. Campeau L, Enjalbert M, Lesperance J, et al. The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. A study 10 years after aortocoronary bypass surgery. N Engl J Med. 1984;311:1329-32.
5. Bourassa MG. Fate of venous grafts: the past, the present and the future. J Am Coll Cardiol. 1991;17:1081-3.
6. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts

related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol. 1996;28:616-26.
7. Alderman EL, Corley SD, Fisher LD, et al. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. J Am Coll Cardiol. 1993;22:1141-54.
8. van Brussel BL, Ernst JM, Ernst NM, et al. Clinical outcome in venous coronary artery bypass grafting: a 15-year follow-up study. Int J Cardiol. 1997;58:119-26.
9. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation. 1998;97:916-31.
10. Bryan AJ, Angelini GD. The biology of saphenous vein graft occlusion: etiology and strategies for prevention. Curr Opin Cardiol. 1994;9:641-9.
11. Roubos N, Rosenfeldt FL, Richards SM, Conyers RA, Davis BB. Improved preservation of saphenous vein grafts by the use of glyceryl trinitrate-verapamil solution during harvesting. Circulation. 1995;92:II31-6.
12. Verrier ED, Boyle EM, Jr. Endothelial cell injury in cardiovascular surgery. Ann Thorac Surg. 1996;62:915-22.
13. Fuster V, Dyken ML, Vokonas PS, Hennekens C. Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group. Circulation. 1993;87:659-75.
14. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Bmj. 2002;324:71-86.
15. Johnson WD, Kayser KL, Hartz AJ, Saedi SF. Aspirin use and survival after coronary bypass surgery. Am Heart J. 1992;123:603-8.
16. Farooq V, Serruys PW, Bourantas C, et al. Incidence and multivariable correlates of long-term mortality in patients treated with surgical or percutaneous revascularization in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial. Eur Heart J. 2012;33:3105-13.
17. Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med. 2002;347:1309-17.
18. Chesebro JH, Clements IP, Fuster V, et al. A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med. 1982;307:73-8.
19. Chesebro JH, Fuster V, Elveback LR, et al. Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations. N Engl J Med. 1984;310:209-14.
20. Fremes SE, Levinton C, Naylor CD, Chen E, Christakis GT, Goldman BS. Optimal antithrombotic therapy following aortocoronary bypass: a meta-analysis. Eur J Cardiothorac Surg. 1993;7:169-80.
21. Lim E, Ali Z, Ali A, et al. Indirect comparison meta-analysis of aspirin therapy after coronary surgery. Bmj. 2003;327:1309.
22. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation. 1988;77:1324-32.
23. Goldman S, Copeland J, Moritz T, et al. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy. Results of a Veterans Administration Cooperative Study. Circulation. 1989;80:1190-7.
24. Bhatt DL, Topol EJ. Antiplatelet and anticoagulant therapy in the secondary prevention of ischemic heart disease. Med Clin North Am. 2000;84:163-79, ix.

25. Helgason CM, Bolin KM, Hoff JA, et al. Development of aspirin resistance in persons with previous ischemic stroke. Stroke. 1994;25:2331-6.
26. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol. 2003;41:961-5.
27. Buchanan MR, Brister SJ. Individual variation in the effects of ASA on platelet function: implications for the use of ASA clinically. Can J Cardiol. 1995;11:221-7.
28. Chopra V, Marmur JD, Cavusoglu E. The role of clopidogrel in the management of patients with ischemic heart disease. Cardiovasc Drugs Ther. 2003;17:467-77.
29. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. Circulation. 2000;101:2823-8.
30. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494-502.
31. Steinhubl SR, Berger PB, Mann JT, 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. Jama. 2002;288:2411-20.
32. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004;110:1202-8.
33. Saw J, Topol EJ, Steinhubl SR, Brennan D, Berger PB, Moliterno DJ. Comparison of long-term usefulness of clopidogrel therapy after the first percutaneous coronary intervention or coronary artery bypass grafting versus that after the second or repeat intervention. Am J Cardiol. 2004;94:623-5.
34. Kim DH, Daskalakis C, Silvestry SC, et al. Aspirin and clopidogrel use in the early postoperative period following on-pump and off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2009;138:1377-84.
35. Sorensen R, Abildstrom SZ, Hansen PR, et al. Efficacy of post-operative clopidogrel treatment in patients revascularized with coronary artery bypass grafting after myocardial infarction. J Am Coll Cardiol. 2011;57:1202-9.
36. David JL, Limet R. Antiplatelet activity of clopidogrel in coronary artery bypass graft surgery patients. Thromb Haemost. 1999;82:1417-21.
37. Sun JC, Teoh KH, Lamy A, et al. Randomized trial of aspirin and clopidogrel versus aspirin alone for the prevention of coronary artery bypass graft occlusion: the Preoperative Aspirin and Postoperative Antiplatelets in Coronary Artery Bypass Grafting study. Am Heart J. 2010;160:1178-84.
38. Gao G, Zheng Z, Pi Y, Lu B, Lu J, Hu S. Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery a single-center, randomized, controlled trial. J Am Coll Cardiol. 2010;56:1639-43.
39. Kulik A, Le May MR, Voisine P, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) Trial. Circulation. 2010;122:2680-7.
40. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-73.
41. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology

Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e652-735.
42. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-57.
43. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011;57:672-84.
44. Kulik A, Le May M, Wells GA, Mesana TG, Ruel M. The clopidogrel after surgery for coronary artery disease (CASCADE) randomized controlled trial: clopidogrel and aspirin versus aspirin alone after coronary bypass surgery [NCT00228423]. Curr Control Trials Cardiovasc Med. 2005;6:15.
45. Jones CM, Athanasiou T, Dunne N, et al. Multi-detector computed tomography in coronary artery bypass graft assessment: a meta-analysis. Ann Thorac Surg. 2007;83:341-8.
46. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation. 2004;110:e340-437.
47. Smith SC, Jr., Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006;113:2363-72.

Appendix A - Study Inclusion and Exclusion Criteria

Inclusion Criteria:	***Reason:***
- Patients undergoing first-time CABG with at least one saphenous vein graft	- The population of clinical interest
- Female or male patients aged 18-90 years	
- On-pump or off-pump CABG	
- Concurrent valve repair or replacement	
Exclusion Criteria:	***Reason:***
- Redo CABG	- Higher risk of graft occlusion and poor long-term outcome
- Serum creatinine >1.8 mg/dL	- Contraindication to use of postoperative CT coronary angiography
- Hypersensitivity or allergy to aspirin or ticagrelor	- Contraindication to use of aspirin or ticagrelor
- Anticipated need for postoperative anticoagulation with coumadin, dabigatran or rivaroxaban (mechanical valve, chronic atrial fibrillation, DVT/PE)	- Contraindication to use of ticagrelor
- History of gastrointestinal hemorrhage	- Contraindication to use of ticagrelor
- Active pathological bleeding	- Contraindication to use of ticagrelor
- History of intracranial hemorrhage	- Contraindication to use of ticagrelor
- Severe hepatic impairment	- Contraindication to use of ticagrelor
- Pregnancy or seeking pregnancy	- Contraindication to use of ticagrelor
- Current or anticipated use of strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir)	- Contraindication to use of ticagrelor
- Inability to provide informed consent	- Ineligible for research study enrollment
- Postoperative low cardiac output syndrome requiring more than 2 inotropes 48 hours after surgery	- Unstable patient unlikely to benefit from treatment

Appendix B – Definitions of Outcomes

As per the and CASCADE and CURE Trials [30, 39, 44]

Death from Cardiovascular Cause
Death from cardiovascular cause is defined as any death for which there is no clearly documented nonvascular cause.

Myocardial Infarction
Myocardial infarction is defined by the presence of at least two of the following: ischemic chest pain, the elevation of the serum levels of cardiac markers or enzymes (troponin, creatinine kinase, creatinine kinase MB isoenzyme, or other cardiac enzymes) to at least twice the upper limit of the normal reference range or three times the upper limit of normal within 48 hours after percutaneous coronary intervention or CABG (or to a level 20% higher than the previous value if the level has already been elevated because of an earlier myocardial infarction), and electrocardiographic changes compatible with infarction.

Cerebrovascular Accident
Stroke is defined as a new focal neurologic deficit of vascular origin lasting more than 24 hours. Stroke is further classified as the result of intracranial hemorrhage, ischemia (if a computed tomographic or magnetic resonance imaging scan is available), or uncertain cause.

Angina
Recurrent angina after surgery is defined by the Canadian Cardiovascular Society (CCS) classification and the need for anti-angina agents (i.e. nitrates). Refractory ischemia after surgery is defined by re-hospitalization lasting at least 24 hours for unstable angina, with ischemic electrocardiographic changes.

Bleeding
Major bleeding episodes are defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood. Major bleeding is classified as life-threatening if the bleeding episode is fatal, leads to a reduction in the hemoglobin level of at least 5 grams per deciliter or to substantial hypotension requiring the use of intravenous inotropic agents, if it necessitates a surgical intervention, if it is a symptomatic intracranial hemorrhage, or if it necessitates the transfusion of four or more units of blood. Minor bleeding episodes included other hemorrhages that lead to the interruption of the study medication.

Appendix C – Ticagrelor Drug Information

2569300

BRILINTA®
(ticagrelor)
Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA® (ticagrelor) tablets, for oral use

Initial U.S. Approval: 2011

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

---------- RECENT MAJOR CHANGES ----------

Contraindications, Hypersensitivity (4.4)	01/2013
Warnings and Precautions, Dyspnea (5.4)	03/2013

----------INDICATIONS AND USAGE ----------

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1)

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily. (1, 5.2, 14)

---------- DOSAGE AND ADMINISTRATION ----------

- Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. (2)
- Continue treatment with 90 mg twice daily. (2)
- After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- 90 mg tablets (3)

---------- CONTRAINDICATIONS ----------

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Severe hepatic impairment (4.3)
- Hypersensitivity to ticagrelor or any component of the product (4.4)

---------- WARNINGS AND PRECAUTIONS ----------

- Like other antiplatelet agents, BRILINTA increases the risk of bleeding. (5.1)
- In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. (5.2, 14)
- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. (5.3)
- Dyspnea: Dyspnea was reported more frequently with BRILINTA than with clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes. (5.4)
- Discontinuation of BRILINTA: Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.4, 6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------

- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.3)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)

See 17 For PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndromes

BRILINTA is a $P2Y_{12}$ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [see *Clinical Studies* (14)].

BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14)].

2 DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily.

After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA.

BRILINTA can be administered with or without food.

A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

3 DOSAGE FORMS AND STRENGTHS

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

4 CONTRAINDICATIONS

4.1 History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see *Clinical Studies* (14)].

4.2 Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.1)].

4.3 Severe Hepatic Impairment

BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [see *Clinical Pharmacology* (12.3)].

4.4 Hypersensitivity

BRILINTA is contraindicated in patients with hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product [see *Adverse Reactions* (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [see *Adverse Reactions* (6.1)].

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDS]).

When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see *Warnings and Precautions* (5.5) and *Adverse Reactions* (6.1)].

5.2 Concomitant Aspirin Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [see *Dosage and Administration* (2) and *Clinical Studies* (14)].

5.3 Moderate Hepatic Impairment

BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

5.4 Dyspnea

In PLATO, dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but occasionally required discontinuation (0.9% of patients taking BRILINTA versus 0.1% of patients taking clopidogrel). If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In the case of intolerable dyspnea requiring discontinuation of BRILINTA, consider prescribing another antiplatelet agent.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV_1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

5.5 Discontinuation of BRILINTA

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

5.6 Strong Inhibitors of Cytochrome CYP3A

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [see *Drug Interactions* (7.1) and *Clinical Pharmacology* (12.3)].

5.7 Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [see *Warnings and Precautions* (5.4)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

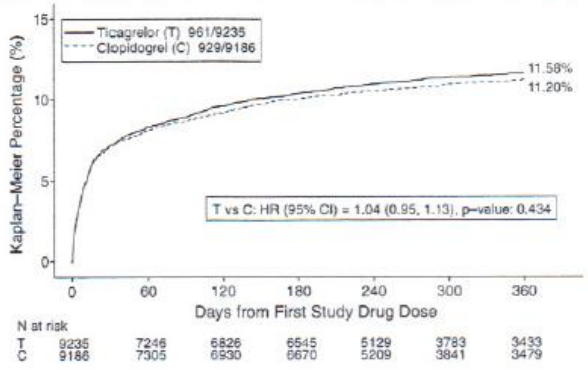
Bleeding

PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL, transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding P2Y12 inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

Common Adverse Events

A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

Table 3 Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

	BRILINTA N=9235	Clopidogrel N=9186
Dyspnea[1]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[1] Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders – Hypersensitivity reactions including angioedema [see *Contraindications* (4.4)].

7 DRUG INTERACTIONS

Effects of other drugs

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

7.1 CYP3A inhibitors

Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) [see *Warnings and Precautions* (5.6) and *Clinical Pharmacology* (12.3)].

7.2 CYP3A inducers

Avoid use with potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) [see *Warnings and Precautions* (5.7) and *Clinical Pharmacology* (12.3)].

7.3 Aspirin

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [see *Warnings and Precautions* (5.2) and *Clinical Studies* (14)].

Effect of BRILINTA on other drugs

Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

7.4 Simvastatin, lovastatin

BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [see *Clinical Pharmacology* (12.3)].

7.5 Digoxin

Digoxin: Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [see *Clinical Pharmacology* (12.3)].

7.6 Other Concomitant Therapy

BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m^2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m^2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m^2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m^2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m^2 basis).

8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

8.5 Geriatric Use

In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups.

No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [see *Contraindications* (4), *Warnings and Precautions* (5.3) and *Clinical Pharmacology* (12.3)].

8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [see *Clinical Pharmacology* (12.3)].

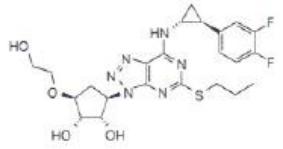
10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µM ADP.

As shown in Figure 3, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 3 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect [see *Dosage and Administration* (2)].

12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.

Figure 2 Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor, or 600 mg clopidogrel

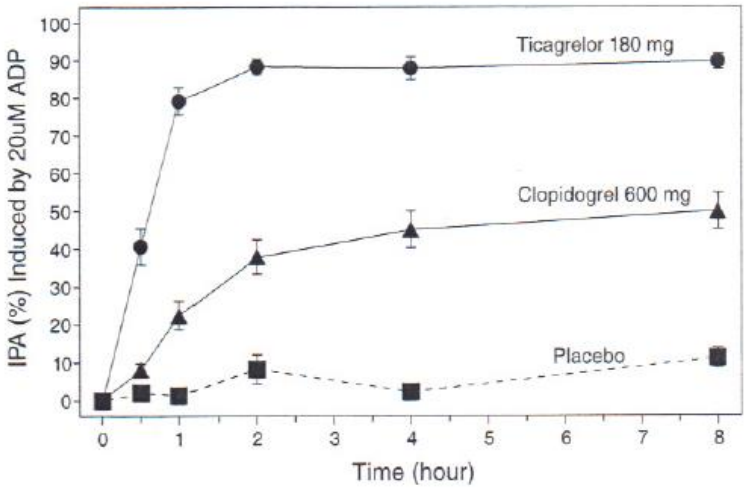
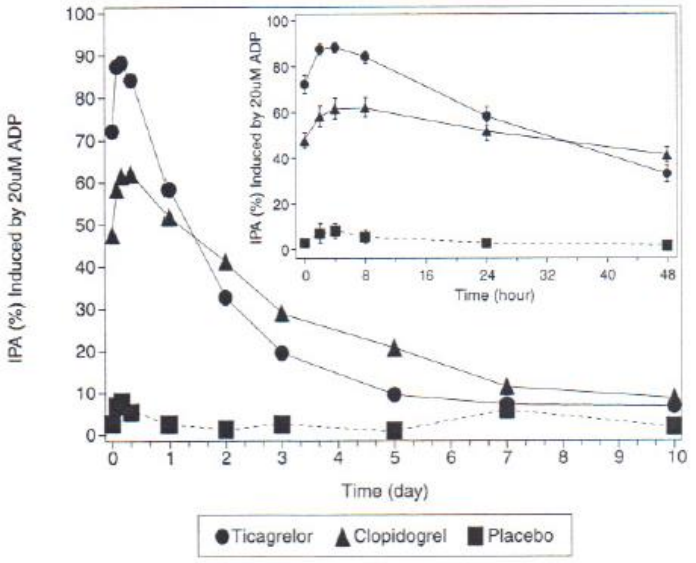


Figure 3 Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

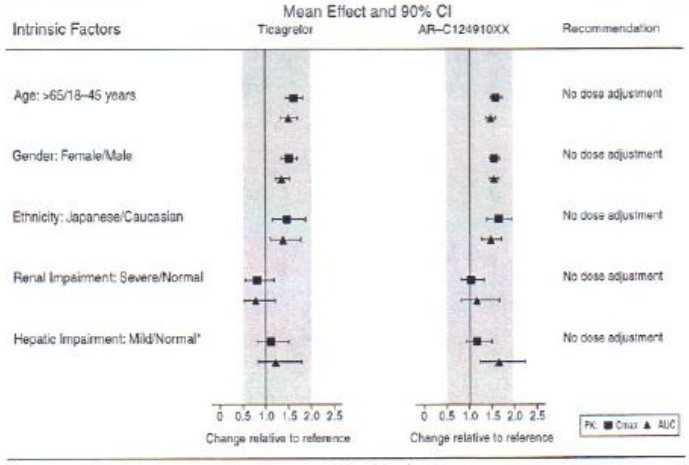
Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations

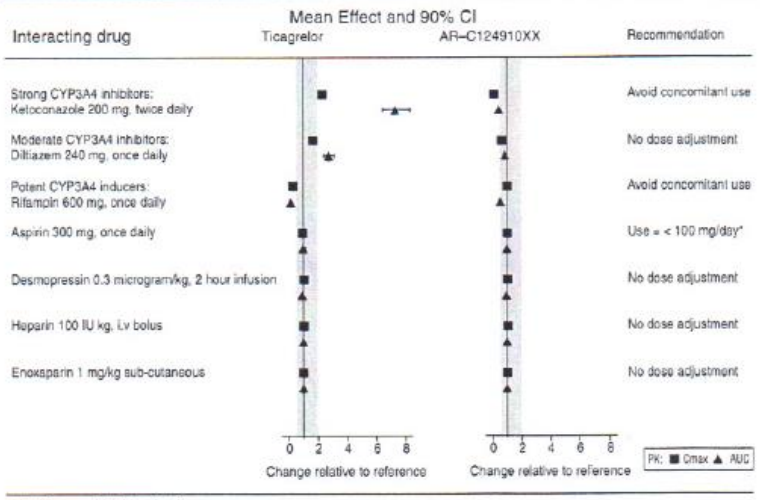
The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 4. Effects are modest and do not require dose adjustment.

Figure 4 Impact of intrinsic factors on the pharmacokinetics of ticagrelor



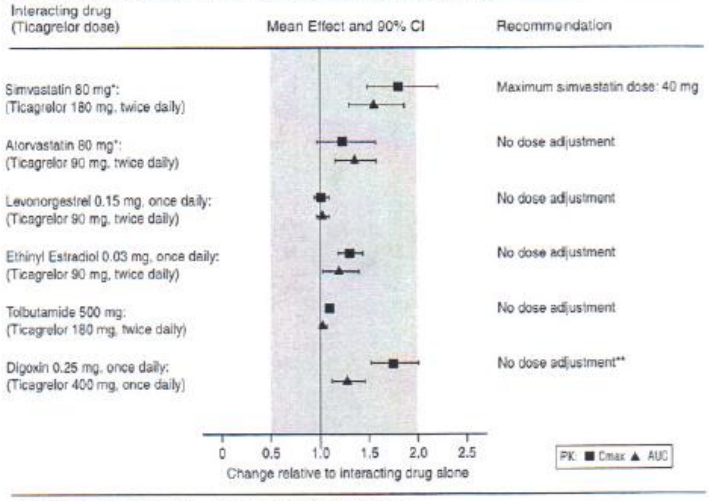
*BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

Figure 5 Effect of co-administered drugs on the pharmacokinetics of ticagrelor



*See *Dosage and Administration (2)*.

Figure 6 Impact of BRILINTA on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

Pediatric

Ticagrelor has not been evaluated in a pediatric population [see *Use in Specific Populations* (8.4)].

Body Weight

No dose adjustment is necessary for ticagrelor based on weight.

Smoking

Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status.

Effects of Other Drugs on BRILINTA

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 5 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels.

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, and digoxin, see Figure 6.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BRILINTA is derived from PLATO, a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. Study endpoints were obtained until the study was complete, even if drug was discontinued.

Patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms were randomized to receive BRILINTA or clopidogrel. Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent. Subjects in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if previous clopidogrel therapy had not been given prior to

randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. All subjects randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at a loading dose of 160-500 mg. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment.

Because of ticagrelor's metabolism by CYP3A enzymes, the protocol recommended limiting the maximum dosage of simvastatin and lovastatin to 40 mg in both study arms. Because of an increased bleeding risk, the study excluded patients with previous intracranial hemorrhage, a gastrointestinal bleed within the past 6 months, or other factors that predispose to bleeding.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years.

The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints.

Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 4 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78.

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.0091). The results were similar for drug-eluting and bare metal stents.

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study.

The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTEMI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance

Table 4 Patients with Outcome Events, in PLATO (KM%)

	BRILINTA N=9333	Clopidogrel N=9291	Hazard Ratio (95% CI)	p-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints[1]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[2]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[2]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

1 First occurrence of specified event at any time 2 Including patients who could have had other non-fatal events or died

Figure 7 Time to First Occurrence of CV Death, MI, or Stroke in PLATO

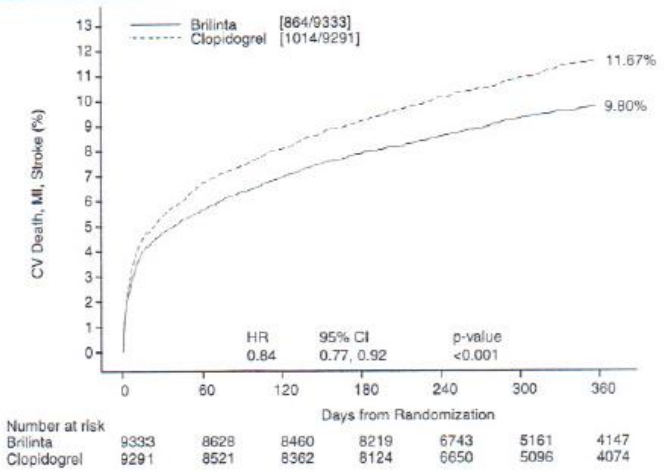


Figure 8 Subgroup analyses of PLATO

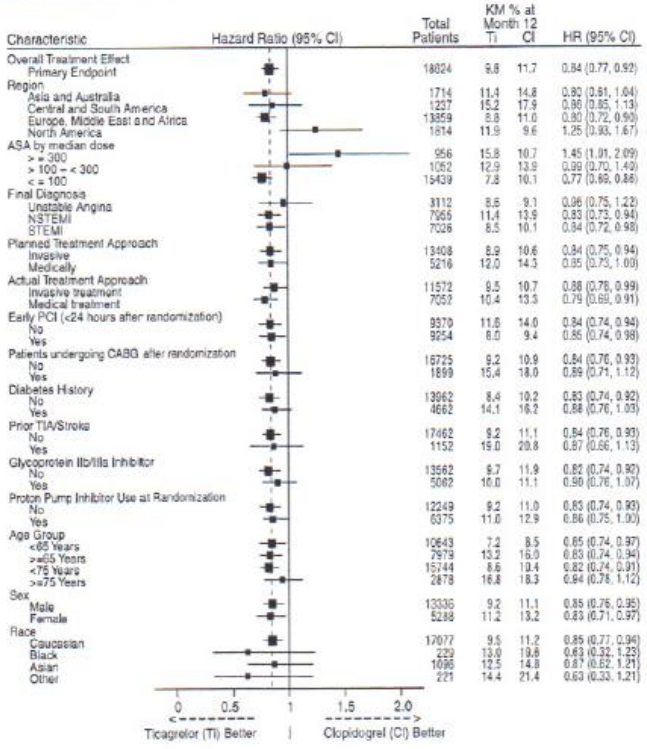
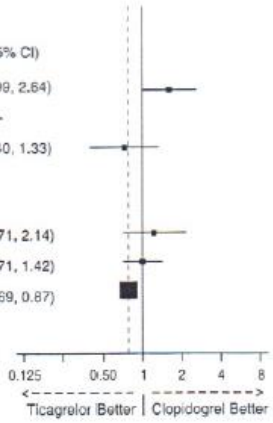


Table 5 PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor Events	Clopidogrel N	Clopidogrel Events	HR (95% CI)
US	>=300	324	40	352	27	1.62 (0.99, 2.64)
	>100 -<300	22	2	16	2	-
	<=100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	>=300	140	28	140	23	1.23 (0.71, 2.14)
	>100 -<300	503	62	511	63	1.00 (0.71, 1.42)
	<=100	7449	546	7443	699	0.78 (0.69, 0.87)



findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were very different in the US and elsewhere, with about 8% of non-US investigators using aspirin doses above 100 mg, and about 2% using doses above 300 mg, in contrast with US practice, where 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 8 shows overall results by median aspirin dose. Table 5 shows results by region and dose.

Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

Pharmacogenetics

In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

Bottles of 60 – NDC 0186-0777-60
Bottles of 180 – NDC 0186-0777-18
100 count Hospital Unit Dose – NDC 0186-0777-39

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Benefits and Risks

- Tell patients to take BRILINTA exactly as prescribed.
- Inform patients not to discontinue BRILINTA without discussing it with the prescribing physician.
- Tell patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
- Tell patients to read the Medication Guide.

17.2 Bleeding

Inform patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding
- Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that BRILINTA can cause shortness of breath. Tell them to contact their doctor if they experience unexpected shortness of breath, especially if severe.

17.4 Invasive Procedures

Instruct patients to:

- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure.
- Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

17.5 Concomitant Medications

Tell patients to list all prescription medications, over-the-counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g. warfarin, heparin).

Issued: March 29, 2013

Distributed by: AstraZeneca LP, Wilmington, DE 19850

3/13 2569300 4/13

AstraZeneca