

# Impact of ticagrelor versus aspirin on graft patency after CABG: Rationale and design of the TARGET (ticagrelor antiplatelet therapy to reduce graft events and thrombosis) randomized controlled trial (NCT02053909)

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## ABSTRACT

**Rationale:** Saphenous vein graft disease remains a major limitation of coronary artery bypass graft surgery (CABG). Up to 20% of vein grafts will occlude within the first year after CABG despite standard aspirin antiplatelet therapy. However, more potent postoperative platelet inhibition with ticagrelor may improve graft patency. The goal of this study will be to evaluate the efficacy of ticagrelor, as compared to aspirin, for the prevention of saphenous vein graft occlusion following CABG.

**Study design:** The Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis (TARGET) study is a multi-center double-blind randomized controlled trial enrolling patients who have undergone multi-vessel CABG with at least one saphenous vein graft. Patients are being randomized to receive either aspirin 81 mg twice per day or ticagrelor 90 mg twice per day for 2 years starting within 7 days after surgery. The projected enrollment is 150 patients in each arm (300 total patients). Patients will undergo computed tomography (CT) coronary angiography at 1 and 2 years after surgery to assess the incidence of vein graft occlusion and stenosis.

**Conclusion:** To our knowledge, this trial is the first prospective study to evaluate the impact of early postoperative ticagrelor on 1- and 2-year graft patency after CABG. Furthermore, it is also the first trial to use a novel antiplatelet agent as a standalone, without aspirin, after CABG. Should ticagrelor reduce the incidence of postoperative graft occlusion, the results of this study will redefine modern antiplatelet management following coronary bypass surgery ([ClinicalTrials.gov](http://ClinicalTrials.gov) NCT02053909).

## 1. Introduction

Coronary artery bypass graft surgery (CABG) is an effective treatment for patients with ischemic heart disease. During surgery, the saphenous vein is the most commonly used conduit, primarily due to its ease of use and ready availability [1]. However, limitations associated with use of saphenous vein grafts become apparent in the years that follow CABG. Termed “saphenous vein graft disease”, vein grafts develop intimal hyperplasia and smooth muscle cell proliferation after surgery, ultimately leading to atherosclerosis and graft occlusion [2–6]. Up to 20% of vein grafts will occlude in the first year after bypass surgery, primarily due to focal endothelial disruption, technical factors, or primary graft thrombosis [2,7–9]. By 10 years after surgery, the majority of vein grafts have either occluded or developed a heavy

burden of atherosclerosis [2,4]. Due to graft and native vessel attrition, patients who have undergone CABG are at risk for subsequent ischemic events, including myocardial infarction (MI) and death [2,4].

Aspirin is the mainstay for secondary prevention after CABG because it improves early graft patency and reduces cardiac events [10–13]. Several placebo-controlled trials in the 1980's demonstrated that aspirin significantly improves graft patency following bypass surgery [14–17]. Notwithstanding its established benefits, significant limitations remain with aspirin therapy. Aspirin is a relatively weak antiplatelet agent, and a large number of cardiovascular events continue to occur despite its administration for secondary prevention [18]. Importantly, many CABG patients are “aspirin resistant” after surgery, with undetectable platelet inhibition noted following 1 week of therapy [19,20].

**Abbreviations:** CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CASCADE, Clopidogrel after Surgery for Coronary Artery Disease Trial; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial; CT, computed tomography; FDA, Food and Drug Administration; MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes; SVG, saphenous vein graft; TARGET, Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis Trial; WIRB, Western Institutional Review Board

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Due to growing concerns regarding aspirin resistance [19,21] and less than optimal patency rates in contemporary trials [9], several investigators have evaluated alternative antiplatelet therapies for patients recovering from CABG. Clopidogrel is a thienopyridine that irreversibly inhibits the platelet P2Y12 receptor, and has been shown to be beneficial in several CAD clinical trials [22,23]. Following CABG surgery however, observational and clinical trials have failed to convincingly demonstrate an improvement in clinical outcomes [24–27] or postoperative graft patency [7,28–31] with clopidogrel, as compared to usual aspirin therapy.

More recently, favorable data has accumulated regarding the use of ticagrelor in patients with ischemic heart disease [32–34]. Like clopidogrel, ticagrelor inhibits the platelet P2Y12 receptor, but it has a more rapid onset of action, and more consistent and potent platelet inhibition than clopidogrel [32,33]. In a post hoc analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial that enrolled acute coronary syndrome patients, among those who subsequently underwent CABG, ticagrelor treatment led to a significant reduction in cardiovascular mortality, compared to those who received clopidogrel [33].

With growing interest regarding the use of ticagrelor after bypass surgery [35–37], it remains unclear whether more potent platelet inhibition with ticagrelor can improve post-CABG vein graft patency. We therefore designed the Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis (TARGET) randomized controlled trial to compare graft patency between patients treated with aspirin therapy, the current standard of care, to those treated with ticagrelor, starting in the early postoperative period. The primary aim of TARGET will be to evaluate the efficacy of ticagrelor for the prevention of saphenous vein graft occlusion following CABG, compared to aspirin, by using computed tomography (CT) coronary angiography at 1 and 2 years after surgery.

## 2. Methods

### 2.1. Study population and recruitment procedure

The study population will include all patients undergoing elective or urgent CABG over the study period at the Lynn Heart and Vascular Institute of Boca Raton Regional Hospital (Boca Raton, Florida), the University of Ottawa Heart Institute (Ottawa, Ontario, Canada), and Missouri Baptist Medical Center (St. Louis, Missouri). CABG patients at the three institutions will be evaluated for study eligibility in the perioperative period, and study eligible subjects will be selected and approached by a study coordinator to explain the trial and obtain consent. Patients undergoing on-pump or off-pump CABG will be eligible for this study, if at least one saphenous vein graft was used. Patients requiring concurrent valve repair or replacement will also be included in the study, unless a mechanical prosthetic valve is implanted (mandating warfarin treatment). Patients with aspirin or ticagrelor allergies will be excluded from the trial, as will patients who require postoperative anticoagulation (atrial fibrillation, chronic deep vein thrombosis). Patients with severe renal insufficiency (preoperative creatinine > 1.8 mg/dL), contraindicating postoperative CT coronary angiography, will also be excluded (see Appendix A for inclusion and exclusion criteria). Women who are pregnant or seeking to become pregnant will be excluded from the study because of the potential pregnancy risks associated with ticagrelor.

### 2.2. Description of intervention and control

Initiated in November 2014, TARGET is a prospective multicenter randomized double-blinded clinical trial that will compare two

postoperative antiplatelet regimens on graft patency 1- and 2-years after CABG. Patients will receive aspirin 81 mg twice per day (Arm A – aspirin) or ticagrelor 90 mg twice per day (Arm B – ticagrelor). The antiplatelet medications will appear identical to ensure blinding in this study. Medication administration and data collection will be performed in double-blind fashion, such that neither the patient nor the healthcare personnel will be aware of the medication assignment. Recruitment and written consent can be performed prior to surgery, or within 7 days after surgery for subjects who have adequately recovered from the operation and are able to provide postoperative informed consent. Patients who require high levels of hemodynamic support after surgery (> 2 inotropes within 48 h) will not be randomized into the study. Following surgery, the study medication will be administered daily via nasogastric tube (intubated patient) or orally, starting within 7 postoperative days, for the duration of one year.

Each patient will undergo a CT coronary angiogram at the 1-year time-point after surgery, to assess the impact of ticagrelor on 1-year (early) graft patency. Patients will then be invited to participate in the study for a second year, continuing the same study medication. A CT coronary angiogram will subsequently be performed, to assess the impact of ticagrelor on 2-year (mid-term) graft patency.

When ticagrelor is administered in combination with aspirin, patients are at greater risk for bleeding complications [32,33]. As such, TARGET was designed as a comparative trial of single antiplatelet regimens. Ticagrelor patients will not receive aspirin, in order to prevent adverse bleeding events with dual antiplatelet therapy. For the patients randomized to receive aspirin, 81 mg twice a day (162 mg total per day) will be used, since the administration of only 81 mg daily would be insufficient, given the concerns regarding aspirin resistance after CABG [19–21,35,38]. This relative aspirin resistance of post-CABG patients constitutes yet another biologic basis for investigating the use of ticagrelor after bypass surgery.

Patients who require long-term anticoagulation will not be recruited into this study due to the higher risk of bleeding complications associated with the combination of ticagrelor and warfarin. Despite this exclusion, subjects who are recruited into the trial may subsequently develop an indication for anticoagulation after study enrollment (new-onset atrial fibrillation or deep vein thrombosis). In this scenario, a 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 warfarin). When anticoagulation is no longer needed or the course of warfarin has been completed, open label treatment will cease, and the patient will resume the blinded study medication. The subject will continue to be followed as part of the trial and undergo CT graft evaluation regardless of study medication interruptions.

### 2.3. Allocation procedure

The allocation procedure will be performed by using a stratified random design, accounting for the presence or absence of diabetes, as well as the use or nonuse of cardiopulmonary bypass (standard CABG versus off-pump CABG). A block randomization scheme will ensure equal distribution of diabetic patients in both arms of the trial, and equal distribution of on- and off-pump patients. Separate randomization schedules will be generated for the three recruiting institutions using SAS 9.1 software (SAS, Cary, NC). Each hospital pharmacy will coordinate treatment assignment. All other study personnel and all patients will be blinded to the treatment assignment.

#### 2.4. Study medication preparation and dispensing

AstraZeneca LP (Wilmington, Delaware) will provide the ticagrelor tablets for the study. The ticagrelor tablets will be submitted by AstraZeneca to a pharmaceutical compounding company (Commcare Pharmacy Inc., Fort Lauderdale, Florida) where they will be crushed and compounded into 90 mg ticagrelor capsules. Identical capsules will similarly be prepared contained 81 mg of aspirin. The compounding process is known to not affect the bioavailability of ticagrelor or aspirin, and will be confirmed with frequent bioavailability testing. Patients in the trial will be assigned to receive either aspirin 81 mg twice per day (Arm A – aspirin) or ticagrelor 90 mg twice per day (Arm B – ticagrelor). Bottles will be prepared containing 180 capsules to cover for a 3-month supply. These bottles will be submitted to each hospital pharmacy. Ordering and dispensing of the blinded study medication will be coordinated by each institution's hospital pharmacy. After surgery, each trial participant will be provided with a 3-month supply of study medication. A new bottle will then be provided to each patient every 3 months over the course of the 1- or 2-year trial enrollment.

#### 2.5. Concomitant medication and treatments

Patients will receive concomitant therapies in both groups as recommended by contemporary American College of Cardiology/American Heart Association guidelines during the time period of the trial [39,40]. Prior to trial enrollment, in the early postoperative period, patients will be treated with usual aspirin antiplatelet therapy (81–325 mg daily) starting within 24 h after surgery, until the time of randomization. After surgery, patients will receive smoking cessation counseling, if needed, as well as statins, beta blockers, and angiotensin converting enzyme inhibitors, as indicated [39,40].

Diabetic patients will be eligible for enrollment in this study, regardless of their preoperative need for insulin therapy. Diabetic patients will receive 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 specializing in the management of diabetes.

#### 2.6. Laboratory tests

Routine baseline blood work will be obtained prior to surgery and during the immediate postoperative period. Because cholesterol levels can impact postoperative graft patency [39,40], all patients in this trial will undergo lipid level evaluation at baseline before trial enrollment, 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 if necessary, and the administration of high-intensity statin therapy if tolerated, in keeping with guideline recommendations [39,40]. 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.

#### 2.7. Primary outcomes

The primary endpoint of this study will be vein graft occlusion 1-year and 2-years after surgery. To assess the efficacy of ticagrelor in reducing vein graft occlusion, as compared to usual aspirin therapy, graft patency will be evaluated with high resolution 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 [41].

#### 2.8. Secondary outcomes

In addition to vein graft occlusion, vein graft stenosis (> 50% narrowing) will be documented as a secondary outcome at the time of the 1- and 2-year CT coronary angiography. Major adverse cardiovascular events during the time period of the study will also be recorded, including cardiovascular mortality, MI, cerebrovascular accident, hospitalization for coronary ischemia, and need for coronary intervention.

#### 2.9. Safety outcomes and adverse events

Adverse events will be recorded at each study visit throughout the study, with a specific focus on bleeding complications, applying definitions from the previously published Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel after Surgery for Coronary Artery Disease Trial (CASCADE) trials [7,22,42]. 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 g/dl 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. In the case of a serious bleeding event while enrolled in the trial (i.e. gastrointestinal bleeding requiring hospitalization), 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).

#### 2.10. Data collection and safety monitoring

Saphenous vein graft patency and stenosis is being assessed by CT coronary angiography 1 year after CABG. Physician follow-up and research coordinator contact will occur at the 1-month time point. Patients will then follow-up with a research coordinator at 3, 6, 9, and 12 months to document any adverse events and ensure study drug compliance (Appendix B). Patients will then be invited to participate in the study for a second year, continuing on the same study medication. Follow-up will then occur with a research coordinator at 15, 18, 21, and 24 months, and a CT coronary angiogram will subsequently assess 2-year graft patency. Patients will be contacted by a research coordinator 30 days after the end of study visits (or the discontinuation of the investigational drug) to assess major adverse cardiovascular and safety events. All serious adverse events will be reported to local ethics committees. The development of a serious adverse event that could be attributable to the study medication will lead to the immediate discontinuation of the study drug.

### 2.11. Ethics

This trial is being conducted under a United States Investigational New Drug Application and will adhere to the highest research ethics standards in accordance with applicable Food and Drug Administration (FDA) regulations and institutional review board requirements. The protocol, informed consent form, and relevant supporting information were submitted and approved by each center's human research ethics board, as well as the Western Institutional Review Board (WIRB), and the study was approved by both the FDA and Health Canada.

### 2.12. Sample size

This trial will be a pilot study. Outcome estimates will form the basis for assessing the feasibility of designing a future large definitive trial. One hundred fifty patients in each study arm will be enrolled (300 total patients). Since each patient will receive approximately 2 vein grafts (on average), there will be roughly 300 vein grafts in each group (600 vein grafts total). This sample size should 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 expedited manner.

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%.

### 2.13. 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 medication assignment. 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.

## 3. Discussion

More than 400,000 Americans undergo CABG each year [43]. While effective as a treatment for CAD, saphenous vein graft disease continues to be one of the main limitations associated with bypass surgery. Aspirin is the standard antiplatelet therapy after CABG based on numerous trials and observational studies [39,40,44], and yet graft occlusion and clinical events continue to occur despite its administration [9,18]. Given the phenomenon of “aspirin resistance” and resultant insufficient postoperative platelet inhibition [19–21], there remains a need for a more potent and reliable antiplatelet regimen following CABG.

The TARGET study is a novel multi-center randomized double-blind trial that will help evaluate the optimal antiplatelet regimen following CABG surgery. Specifically, it will answer the questions of whether ticagrelor is safe for administration after CABG and whether it improves saphenous vein graft patency. Although subgroup analysis of the PLATO trial suggested a benefit associated with ticagrelor in cardiac surgery patients [32,33], no trial to date has specifically focused on 1-year clinical or angiographic outcomes of patients treated with ticagrelor immediately after surgical revascularization. Should ticagrelor reduce vein graft occlusion, the TARGET trial has the potential to re-define the modern antiplatelet management for CABG patients, ushering in a new standard of care [35].

To our knowledge, TARGET is the only trial evaluating the impact of early postoperative ticagrelor on 1- and 2-year graft patency after CABG. We believe the strengths of this study are its novel focus and randomized-blinded design. The results of this trial will likely be generalizable to all patients undergoing CABG with saphenous vein. The 300 patient sample size was chosen for TARGET since it will yield approximately 600 total vein grafts. As such, it is anticipated that the trial will be large enough to detect whether a difference exists in terms of vein graft patency between the groups, but small enough that recruitment can be performed in a reasonable timeframe. To date, only one trial has been published on the subject, featuring 3-month graft patency data from 56 patients [37]. Unfortunately, this study had insufficient power to detect a significant difference between the graft occlusion rate of patients who received the combination of ticagrelor and aspirin, compared to those who received aspirin alone (graft occlusion: 10.3% versus 18.3%, ticagrelor plus aspirin versus aspirin alone,  $P = 0.11$ ). Moreover, a significantly higher risk of bleeding was seen in the dual antiplatelet arm of this study (minor bleeding requiring medical intervention: 31.4% versus 2.9%, ticagrelor plus aspirin versus aspirin alone,  $P = 0.003$ ) [37]. Given the greater risks of bleeding associated with dual antiplatelet therapy [22,34], we and others [36] believe that ticagrelor monotherapy offers the best balance of safety and benefit, with a lower bleeding complication rate compared to dual antiplatelet therapy, and an anticipated improved efficacy over aspirin alone.

## 4. Conclusion

Saphenous vein graft disease continues to be a major limitation of surgical coronary revascularization. The process of saphenous vein graft disease starts early after surgery, setting the stage for graft atherosclerotic disease and its sequelae. Important clinical benefits have been noted with ticagrelor in several CAD trials. However, no prospective study to date has evaluated the use of early ticagrelor therapy for the prevention vein graft disease 1 and 2 years after CABG. The TARGET study is a randomized double-blind trial comparing ticagrelor to standard aspirin therapy for the prevention of vein graft occlusion following CABG using CT coronary angiography 1- and 2-years after surgery.

**Competing interests**

Dr. Kulik received research support from the Investigator-Sponsored Study Program of AstraZeneca for the conduct of this trial.

**Authors' contributions**

All authors read and approved the final manuscript. Specifically, AK is the principal investigator who conceived of the study, designed the protocol design, obtained trial funding, and drafted the manuscript. AMA participated in the protocol design, helped draft the manuscript, and was the primary study coordinator for the trial. VB helped draft the manuscript and helped coordinate the trial. NTK and MR are secondary investigators who helped with trial design and coordination, subject recruitment, and drafting of the manuscript.

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**Appendix A. Study inclusion and exclusion criteria**

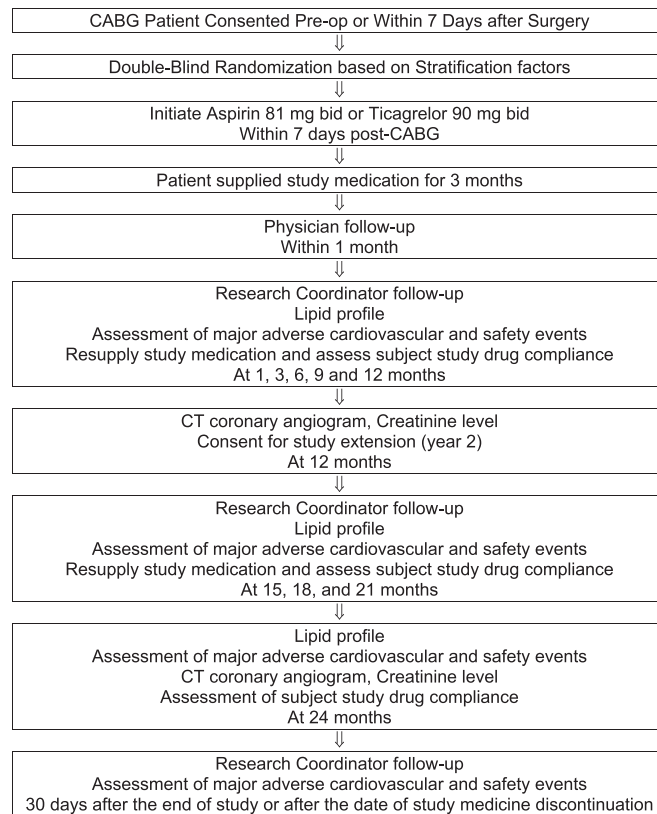
<i>Inclusion Criteria</i>	<i>Reason</i>
<ul style="list-style-type: none"> <li>- Patients undergoing first-time CABG with at least one saphenous vein graft</li> <li>- Female or male patients aged 18–90 years</li> <li>- On-pump or off-pump CABG</li> </ul>	<ul style="list-style-type: none"> <li>- The population of clinical interest</li> </ul>
<p><i>Exclusion Criteria</i></p> <ul style="list-style-type: none"> <li>- Redo CABG</li> <li>- Preoperative serum creatinine &gt; 1.8 mg/dL</li> <li>- Hypersensitivity or allergy to aspirin or ticagrelor</li> <li>- Anticipated need for postoperative anticoagulation with warfarin, dabigatran or rivaroxaban (mechanical valve, chronic atrial fibrillation, deep vein thrombosis)</li> <li>- History of gastrointestinal hemorrhage</li> <li>- Active pathological bleeding</li> <li>- History of intracranial hemorrhage</li> <li>- History of underlying bleeding disorder</li> <li>- Severe hepatic impairment</li> <li>- Current or anticipated use of strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir)</li> <li>- Current or anticipated use of strong CYP3A4 inducers (e.g. phenytoin, phenobarbital, carbamazepine, oxcarbazepine, rifampin, modafinil, dexamethasone)</li> <li>- Current use of lovastatin 80 mg daily or simvastatin 80 mg daily</li> <li>- Pregnancy or seeking pregnancy</li> <li>- Inability to provide informed consent</li> <li>- Postoperative low cardiac output syndrome requiring &gt; 2 inotropes 48 h after surgery</li> </ul>	<p><i>Reason</i></p> <ul style="list-style-type: none"> <li>- Higher risk of graft occlusion and poor long-term outcome</li> <li>- Contraindication to use of postoperative CT coronary angiography</li> <li>- Contraindication to use of aspirin or ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Contraindication to use of ticagrelor</li> <li>- Ineligible for research study enrollment</li> <li>- Unstable patient unlikely to benefit from treatment</li> </ul>

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## Appendix B. Trial timeline



## References

- [1] W.S. Weintraub, E.L. Jones, J.M. Craver, R.A. Guyton, Frequency of repeat coronary bypass or coronary angioplasty after coronary artery bypass surgery using saphenous venous grafts, *Am. J. Cardiol.* 73 (2) (1994) 103–112.
- [2] J.G. Motwani, E.J. Topol, Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention, *Circulation* 97 (9) (1998) 916–931.
- [3] M.G. Bourassa, Fate of venous grafts: the past, the present and the future, *J. Am. Coll. Cardiol.* 17 (5) (1991) 1081–1083.
- [4] G.M. Fitzgibbon, H.P. Kafka, A.J. Leach, W.J. Keon, G.D. Hooper, J.R. Burton, 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.* 28 (3) (1996) 616–626.
- [5] A.J. Bryan, G.D. Angelini, The biology of saphenous vein graft occlusion: etiology and strategies for prevention, *Curr. Opin. Cardiol.* 9 (6) (1994) 641–649.
- [6] B.L. van Brussel, J.M. Ernst, N.M. Ernst, et al., Clinical outcome in venous coronary artery bypass grafting: a 15-year follow-up study, *Int. J. Cardiol.* 58 (2) (1997) 119–126.
- [7] A. Kulik, M.R. Le May, P. Voisine, et al., Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (cascade) trial, *Circulation* 122 (25) (2010) 2680–2687.
- [8] N.D. Desai, E.A. Cohen, C.D. Naylor, S.E. Frelles, A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts, *N. Engl. J. Med.* 351 (22) (2004) 2302–2309.
- [9] J.H. Alexander, G. Hafley, R.A. Harrington, 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* 294 (19) (2005) 2446–2454.
- [10] V. Fuster, M.L. Dyken, P.S. Vokonas, C. Hennekens, Aspirin as a therapeutic agent in cardiovascular disease. Special writing group, *Circulation* 87 (2) (1993) 659–675.
- [11] Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients, *BMJ* 324 (7329) (2002) 71–86.
- [12] W.D. Johnson, K.L. Kayser, A.J. Hartz, S.F. Saedi, Aspirin use and survival after coronary bypass surgery, *Am. Heart J.* 123 (3) (1992) 603–608.
- [13] V. Farooq, P.W. Serruys, C. Bourantas, 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.* 33 (24) (2012) 3105–3113.
- [14] J.H. Chesebro, I.P. Clements, V. Fuster, 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.* 307 (2) (1982) 73–78.
- [15] J.H. Chesebro, V. Fuster, L.R. Elveback, et al., Effect of dipyridamole and aspirin on late vein-graft patency after coronary bypass operations, *N. Engl. J. Med.* 310 (4) (1984) 209–214.
- [16] S.E. Frelles, C. Levinton, C.D. Naylor, E. Chen, G.T. Christakis, B.S. Goldman, Optimal antithrombotic therapy following aortocoronary bypass: a meta-analysis, *Eur. J. Cardiothorac. Surg.* 7 (4) (1993) 169–180.
- [17] E. Lim, Z. Ali, A. Ali, et al., Indirect comparison meta-analysis of aspirin therapy after coronary surgery, *BMJ* 327 (7427) (2003) 1309.
- [18] D.L. Bhatt, E.J. Topol, Antiplatelet and anticoagulant therapy in the secondary prevention of ischemic heart disease, *Med. Clin. North Am.* 84 (1) (2000) 163–179 (ix).
- [19] C.M. Helgason, K.M. Bolin, J.A. Hoff, et al., Development of aspirin resistance in persons with previous ischemic stroke, *Stroke* 25 (12) (1994) 2331–2336.
- [20] P.A. Gum, K. Kottke-Marchant, P.A. Welsh, J. White, E.J. Topol, A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease, *J. Am. Coll. Cardiol.* 41 (6) (2003) 961–965.
- [21] M.R. Buchanan, S.J. Brister, Individual variation in the effects of asa on platelet function: implications for the use of asa clinically, *Can. J. Cardiol.* 11 (3) (1995) 221–227.
- [22] S. Yusuf, F. Zhao, S.R. Mehta, S. Chrolavicius, G. Tognoni, K.K. Fox, Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without st-segment elevation, *N. Engl. J. Med.* 345 (7) (2001) 494–502.
- [23] S.R. Steinhubl, P.B. Berger, J.T. Mann III et al., Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial, *JAMA* 288 (19) (2002) 2411–2420.
- [24] K.A. Fox, S.R. Mehta, R. Peters, 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* 110 (10) (2004) 1202–1208.
- [25] J. Saw, E.J. Topol, S.R. Steinhubl, D. Brennan, P.B. Berger, D.J. Moliterno, 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.* 94 (5) (2004) 623–625.
- [26] D.H. Kim, C. Daskalakis, S.C. Silvestry, 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.* 138 (6) (2009) 1377–1384.

- [27] R. Sorensen, S.Z. Abildstrom, P.R. Hansen, et al., Efficacy of post-operative clopidogrel treatment in patients revascularized with coronary artery bypass grafting after myocardial infarction, *J. Am. Coll. Cardiol.* 57 (10) (2011) 1202–1209.
- [28] J.L. David, R. Limet, Antiplatelet activity of clopidogrel in coronary artery bypass graft surgery patients, *Thromb. Haemost.* 82 (5) (1999) 1417–1421.
- [29] J.C. Sun, K.H. Teoh, A. Lamy, 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.* 160 (6) (2010) 1178–1184.
- [30] G. Gao, Z. Zheng, Y. Pi, B. Lu, J. Lu, S. Hu, Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery a single-center, randomized, controlled trial, *J. Am. Coll. Cardiol.* 56 (20) (2010) 1639–1643.
- [31] R. Ebrahimi, F.G. Bakaeen, A. Uberoi, et al., Effect of clopidogrel use post coronary artery bypass surgery on graft patency, *Ann. Thorac. Surg.* 97 (1) (2014) 15–21.
- [32] L. Wallentin, R.C. Becker, A. Budaj, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, *N. Engl. J. Med.* 361 (11) (2009) 1045–1057.
- [33] C. Held, N. Asenblad, J.P. Bassand, 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.* 57 (6) (2011) 672–684.
- [34] M.P. Bonaca, D.L. Bhatt, M. Cohen, et al., Long-term use of ticagrelor in patients with prior myocardial infarction, *N. Engl. J. Med.* 372 (19) (2015) 1791–1800.
- [35] A. Kulik, Secondary prevention after coronary artery bypass graft surgery: a primer, *Curr. Opin. Cardiol.* 31 (6) (2016) 635–643.
- [36] A. de Waha, S. Sandner, M. von Scheidt, et al., A randomized, parallel group, double-blind study of ticagrelor compared with aspirin for prevention of vascular events in patients undergoing coronary artery bypass graft operation: rationale and design of the ticagrelor in cabg (ticab) trial. An investigator-initiated trial, *Am. Heart J.* 179 (2016) 69–76.
- [37] J. Saw, G.C. Wong, J. Mayo, et al., Ticagrelor and aspirin for the prevention of cardiovascular events after coronary artery bypass graft surgery, *Heart* 102 (10) (2016) 763–769.
- [38] A. Kulik, V. Chan, M. Ruel, Antiplatelet therapy and coronary artery bypass graft surgery: perioperative safety and efficacy, *Expert Opin. Drug Saf.* 8 (2) (2009) 169–182.
- [39] A. Kulik, M. Ruel, H. Jneid, et al., Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association, *Circulation* 131 (10) (2015) 927–964.
- [40] L.D. Hillis, P.K. Smith, J.L. Anderson, et al., 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* 124 (23) (2011) e652–735.
- [41] C.M. Jones, T. Athanasiou, N. Dunne, et al., Multi-detector computed tomography in coronary artery bypass graft assessment: a meta-analysis, *Ann. Thorac. Surg.* 83 (1) (2007) 341–348.
- [42] A. Kulik, M. Le May, G.A. Wells, T.G. Mesana, M. Ruel, 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.* 6 (2005) 15.
- [43] A.S. Go, D. Mozaffarian, V.L. Roger, et al., Heart disease and stroke statistics—2014 update: a report from the American Heart Association, *Circulation* 129 (3) (2014) e28–e292.
- [44] S.C. Smith Jr., E.J. Benjamin, R.O. Bonow, et al., AHA/ACC 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* 124 (22) (2011) 2458–2473.