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Intensive versus moderate atorvastatin therapy and one-year graft patency after CABG: Rationale and design of the ACTIVE (Aggressive Cholesterol Therapy to Inhibit Vein Graft Events) randomized controlled trial (NCT01528709)

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ABSTRACT

Rationale: Saphenous vein graft disease remains a major limitation of coronary artery bypass graft surgery (CABG). Statin therapy inhibits the development of vein graft disease and improves outcomes after CABG. However, it is unclear whether treatment with high-dose statins will further slow the process of vein graft disease and improve graft patency, as compared to conventional moderate doses. Therefore, the goal of this study will be to evaluate the efficacy of high-dose statin therapy versus moderate-dose statin therapy for the prevention of saphenous vein graft occlusion following CABG.

Study design: The Aggressive Cholesterol Therapy to Inhibit Vein Graft Events (ACTIVE) trial 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 will be randomized to receive either atorvastatin 80 mg daily or atorvastatin 10 mg daily for one year starting within 5 days after surgery. The target enrollment is 100 patients in each arm (200 patients total). Lipid levels will be assessed every 3 months. After one year, patients will undergo computed tomography (CT) coronary angiography to assess the incidence of vein graft occlusion and stenosis.

Conclusion: This trial is the first prospective study to evaluate the impact of early postoperative high-dose statin therapy on graft patency after CABG. Should high-dose statin therapy reduce the incidence of postoperative graft occlusion, the results will add to the growing evidence supporting the role of high-intensity statins for modern lipid management after coronary surgical revascularization (ClinicalTrials.gov NCT01528709).

1. Introduction

The saphenous vein is the most commonly utilized conduit during coronary artery bypass graft surgery (CABG) because of its ease of use and ready availability. While convenient for use at the time of surgery, limitations associated with the saphenous vein become apparent in the years that follow. Termed “saphenous vein graft disease”, vein grafts develop intimal hyperplasia and smooth muscle cell proliferation after surgery, ultimately leading to atherosclerosis and graft occlusion [1–5]. Influenced by hyperlipidemia [6–7], up to 20% of saphenous vein grafts (SVG) occlude within the first year [8–9]. By 10 years after surgery, only 60% of SVG are patent, and half of those that are patent have marked atherosclerosis [1,3].

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 [1,3]. Secondary preventive therapies, including statins, are therefore an essential component to the management of patients recovering from CABG [10–11]. By reducing low-density lipoprotein (LDL) levels, statins have been shown to reduce the progression of atherosclerosis, improve survival, and reduce the risks of MI, stroke and the need for coronary revascularization in patients with coronary artery disease (CAD) [12–13].

The importance of statins after coronary surgery was confirmed in the post-CABG Trial, a landmark study that compared aggressive cholesterol reduction (to achieve LDL levels < 100 mg/dL) to moderate cholesterol reduction among 1351 patients who had undergone CABG years earlier. In this trial, aggressive statin therapy led to a lower rate of vein graft occlusion on follow-up imaging [14], and a significant reduction in subsequent clinical events [15]. Based on this study and others [14–20], clinical guidelines for many years recommended statins

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Nomenclature

ACTIVE - Aggressive Cholesterol Therapy to Inhibit Vein Graft Events Trial
ALT - alanine aminotransferase
AST - aspartate aminotransferase
CABG - coronary artery bypass graft surgery
CASCADE - Clopidogrel after Surgery for Coronary Artery Disease Trial
CCS - Canadian Cardiovascular Society
CK - creatine kinase
CT - computed tomography
FDA - Food and Drug Administration
IMPROVE-IT - Improved Reduction of Outcomes: Vytorin Efficacy International Trial
LDL - low-density lipoprotein
MI - myocardial infarction
NYHA - New York Heart Association
PCI - percutaneous coronary intervention
SVG - saphenous vein graft
TNT - Treating to New Targets Trial
ULN - upper limit of normal
WIRB - Western Institutional Review Board

to achieve an LDL treatment goal of < 100 mg/dL after CABG [21–24]. More recently however, several cardiology trials have demonstrated that even more intensive lipid reduction with high-dose statin therapy can further improve cardiovascular outcomes [25–29]. Post-hoc analyses from these trials suggested that patients with a remote history of CABG may also benefit from high-dose statin therapy [25,30].

However, little data exists regarding the use of high intensity statins immediately following CABG [31–33]. Further, it remains unclear whether LDL levels approaching 70 mg/dL can improve postoperative graft patency [34–35]. Given the promising results from the TNT (Treating to New Targets) Trial and others [25–30], we theorized that high-dose statin therapy after CABG would slow the process of saphenous vein graft disease and lead to improved graft patency, as compared to usual moderate-dose statin therapy. We therefore launched the Aggressive Cholesterol Therapy to Inhibit Vein Graft Events (ACTIVE) trial as the first randomized double-blinded clinical study to explore the impact of early high-intensity statin therapy on vein graft patency after CABG. The primary aim of ACTIVE was to evaluate the efficacy of early high-dose statin therapy for the prevention of saphenous vein graft occlusion following CABG, compared to standard moderate-dose statin therapy, using computed tomography (CT) coronary angiography 1 year after surgery.

2. Methods

2.1. Study population and recruitment procedure

The study population included 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) and the University of Ottawa Heart Institute (Ottawa, Ontario, Canada). CABG patients at the two institutions were evaluated for study eligibility in the perioperative period, and study eligible subjects were selected and approached by a study coordinator to explain the trial and obtain consent. Patients undergoing on-pump or off-pump CABG were eligible for this study, as long as at least one saphenous vein graft was used. Patients requiring concurrent valve repair or replacement were also included in the study. Patients with statin allergies were excluded from the trial. Patients with severe renal insufficiency (preoperative creatinine > 1.8 mg/dL), contraindicating postoperative CT coronary angiography, were also excluded (see Appendix A for inclusion and exclusion criteria). Because statins are potential teratogens, women who were pregnant or seeking to become pregnant were excluded from the study.

2.2. Description of intervention and control

This prospective randomized double-blinded controlled trial was initiated in March 2012. Patients were recruited over the first 4 years of the study, and graft evaluation is being performed 1 year after surgery for each patient. Graft assessment is scheduled to be complete in 2017. Patients were randomized into a moderate-dose statin group (receiving atorvastatin 10 mg daily – Arm A) or a high-dose statin group (receiving atorvastatin 80 mg daily – Arm B). The atorvastatin medications appeared identical for the purpose of blinding in this study. Medication administration and data collection were performed in a double-blind manner, such that neither the patient nor the healthcare personnel would be aware of the medication assignment. Recruitment and written consent could be performed prior to surgery, or within 5 days after surgery for subjects who had adequately recovered from surgery to be able to provide postoperative informed consent. Patients who required high levels of hemodynamic support (> 2 inotropes) within 48 h after surgery were not randomized into the study. Following surgery, the study medication could be administered daily via nasogastric tube (intubated patient) or orally, starting within 5 postoperative days, for the duration of one year.

Patients who previously received lipid-lowering therapy prior to CABG were eligible to enroll in the study. However, preoperative cholesterol medications (including statins, niacin, fibrate, or ezetimibe) were all discontinued after surgery to ensure a standardized lipid-lowering regimen during the 1 year period following CABG. Atorvastatin 10 mg daily was chosen for the moderate-dose statin group because it was anticipated that this would yield LDL levels approximating 100 mg/dL over the time period of the study. Atorvastatin 80 mg daily was chosen for the high-dose statin group because it was anticipated that this would yield LDL levels approximating 70 mg/dL, as demonstrated in previous clinical trials [25–27].

Clinical guidelines during the time period of the trial recommended statin treatment to achieve LDL levels of 100 mg/dL or less after CABG [21–24]. However, it remained possible that a few patients randomized to atorvastatin 10 mg daily would not achieve this postoperative target LDL level of 100 mg/dL. As such, in order to ensure that all study subjects received the standard of care (based on the guidelines at that time), an escape criterion was incorporated into the trial. Lipid levels were monitored every 3 months during the study (see below). Patient un-blinding would occur for patients who had LDL levels > 115 mg/dL at the 3 or 6 month time point after surgery. Such patients would then have their atorvastatin dose increased from 10 mg to 20 mg (or higher) in an open label fashion for the remainder of their enrolment in the trial. Outcome assessment at one year would then continue for these patients as per study protocol, despite un-blinding.

2.3. Allocation procedure

The allocation procedure was performed 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 technique ensured an equal distribution of diabetic patients in both arms of the trial and an equal distribution of on- and off-pump patients. Separate randomization schedules were generated for the two recruiting institutions using SAS 9.1 software (SAS, Cary, NC). All patients and study personnel were

blinded to the treatment assignment, which was performed by each hospital pharmacy.

2.4. Study medication preparation and dispensing

Pfizer Inc. (New York, New York) provided 10 mg and 40 mg atorvastatin tablets for this trial. The atorvastatin tablets were submitted by Pfizer to Commcare Pharmacy Inc. (Fort Lauderdale, Florida), a pharmaceutical compounding company, where the tablets were crushed and compounded into capsules. This compounding process did not affect the bioavailability of atorvastatin, as confirmed with frequent bioavailability testing. Commcare then prepared 5 mg and 40 mg capsules using the crushed atorvastatin tablets. These capsules appeared identical for the purpose of blinding in this study. Patients in the trial were assigned to receive either two 5 mg capsules per day (Arm A - 10 mg) or two 40 mg capsules per day (Arm B - 80 mg). Commcare prepared pill bottles containing 180 capsules to cover for a 3-month supply. These pill bottles were then submitted to each hospital pharmacy. Ordering and dispensing of the blinded study medication was then coordinated by each institution's hospital pharmacy. After surgery, each trial participant was provided with a 3-month supply of study medication. A new pill bottle was then provided to each patient every 3 months over the course of the 1-year trial enrollment.

2.5. Concomitant medication and treatments

Patients received concomitant therapies in both groups as recommended by contemporary American College of Cardiology/American Heart Association guidelines during the time period of the trial. This included smoking cessation counseling and the administration of antiplatelet agents, beta blockers, and angiotensin converting enzyme inhibitors, as indicated [21–22]. Lipid medications prescribed prior to surgery were discontinued after CABG to ensure a standardized postoperative regimen. In keeping with usual practice, aspirin alone was administered after on-pump CABG, whereas both aspirin and clopidogrel were prescribed following off-pump CABG [10,36].

Diabetic patients were eligible for enrollment in this study, regardless of their preoperative need for insulin therapy, and were allocated equally into both groups through stratified randomization. Diabetic patients received 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 were restarted on their original preoperative diabetic regimens (oral agents and/or insulin therapy). The treatment of diabetes during this study was closely monitored in collaboration with endocrinologists specializing in the management of diabetes.

2.6. Laboratory tests

Routine baseline blood work was obtained prior to surgery and during the immediate postoperative period. Laboratory assessments specific to the trial [including a fasting lipid profile, liver function tests, and a creatine kinase (CK) level] were performed prior to study drug initiation and at months 3, 6, 9 and 12 (Appendix B). A creatinine level was also assessed prior to the 1-year CT coronary angiogram.

2.7. Primary outcomes

The primary endpoint of this study is vein graft occlusion 1 year after surgery, in keeping with other cardiac surgery patency trials [9,37]. To assess the efficacy of high-dose statin therapy in reducing vein graft occlusion, graft patency is being 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. CT coronary angiography was employed in this trial, rather than conventional coronary angiography, to limit the number of patients who would drop-out and refuse invasive testing one year after surgery. 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 [38].

2.8. Secondary outcomes

In addition to vein graft occlusion, vein graft stenosis is being documented at the time of the 1-year CT coronary angiography. Major adverse cardiovascular events during the time period of the study are also being recorded, including mortality, MI, cerebrovascular accident, hospitalization for coronary ischemia, and need for coronary intervention.

2.9. Safety outcomes and adverse events

Adverse events are being recorded at each study visit during the 1-year time period of the study. Similar to previous high-dose statin trials [25–28], the safety outcomes have included: 1) elevations in levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) higher than 3 times the upper limit of normal (ULN); 2) myopathy, defined as a CK level > 10 times the ULN associated with muscle symptoms; and 3) rhabdomyolysis, defined as a CK level higher than 10,000 units/L, with or without muscle symptoms [39–40]. In a systematic review of controlled trials and cohort studies involving nearly 3 million patients, the estimated rates for myopathy and rhabdomyolysis were 11 and 3.4, respectively, during 100,000 patient-years of follow-up [40].

For patients with ALT or AST levels higher than 3 times the ULN, a repeat measurement would be obtained within 3 days. Withdrawal from the study was mandated for patients with consecutive elevations in ALT or AST higher than 3 times the ULN. For patients with CK levels higher than 5 times the ULN, a repeat measurement would be obtained within 3 days. Withdrawal from the study was mandated for patients with a single measurement of CK higher than 10 times the ULN with muscle symptoms, or consecutive measurements of CK levels higher than 10 times the ULN without symptoms.

2.10. Data collection and safety monitoring

Saphenous vein graft patency and stenosis is being assessed by CT coronary angiography 1 year after CABG. After physician follow-up at the 1-month time point, patients continue to follow-up with research coordinators thereafter at 3, 6, 9, and 12 months to document any major adverse coronary events and ensure study drug compliance. Safety outcomes are being noted during laboratory testing at 3, 6, 9 and 12 months following CABG (Appendix B). All serious adverse events are being reported to local ethics committees. The development of a serious adverse event that could be attributable to the study medication would lead to the immediate discontinuation of the study drug.

2.11. Ethics

This protocol, the informed consent form, and relevant supporting information was submitted and approved by each the center's human research ethics board, including the Western Institutional Review Board (WIRB). The study was reviewed and approved by the Food and Drug Administration (FDA) and Health Canada, and was conducted in accordance with their applicable regulations.

2.12. Sample size

This trial was designed as a pilot study. Outcome estimates from this

study could then guide the design of a larger definitive trial, should interest and support for such an initiative remain thereafter. One hundred patients in each study arm were to be enrolled, with a planned total of 200 patients. Since each patient would receive 2 vein grafts on average, there would be approximately 200 vein grafts in each group (400 vein grafts total). This sample size would 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 could be performed in an expedited manner.

This study was not designed or powered as a definitive clinical trial. Based on several previously published clinical trials, it was anticipated that 10–20% of vein grafts would be occluded at the 1-year time point after CABG. Should high-dose statin therapy improve graft patency and reduce vein occlusion from 20% to 10% in this study, power calculations suggest that we would have 88% power to detect a significant difference ($P < 0.05$) between the groups. Alternatively, if high-dose statin therapy were to decrease the occlusion rate from 15% to 10%, the power would be approximately 45%.

2.13. Statistical 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. Graft patency will be compared between groups according each patient's initial randomized study group, even if unblinding occurs during the trial (intention-to-treat analysis). Additional analysis will then be performed with the exclusion of patients who did not complete the one year trial protocol (on-protocol analysis). 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 (GEE) methods. Any potential confounding variables that differ between the two groups despite randomization will be incorporated into the GEE analysis for risk adjustment. 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 by using the Kaplan-Meier method, and groups will be compared with a log-rank test. In the investigators' experience, up to 20% of patients refuse conventional angiography 1 year after CABG in research studies [41]. However, a far lower drop-out rate is anticipated in the current trial with the use of postoperative CT coronary angiography.

3. Discussion

More than 400,000 Americans undergo CABG each year [42]. While effective as a treatment for CAD, saphenous vein graft disease continues to be one of the main limitations of CABG. Elevated cholesterol levels are associated with faster progression of saphenous vein graft disease after CABG [6–7], but statin treatment can slows this process by inhibiting neointimal formation and smooth muscle proliferation [14,34,43–45]. Indeed, lipid-lowering therapies reduce the risk of myocardial events and graft occlusions after CABG [14–16,30,46–49]. In the past, low to moderate doses of statins were recommended postoperatively to achieve LDL levels of 100 mg/dL for prevention of vein graft occlusion [21–24]. Over time, as favorable experience accumulated with high intensity statins [25–30], we speculated that targeting LDL levels to 70 mg/dL after CABG with high-dose statin therapy could further slow the process of vein graft disease and perhaps lead to improved graft patency, as compared to moderate doses. Little is known regarding the role of high-intensity statin therapy following CABG, and no trial has yet to evaluate their impact on graft function when initiated in the early postoperative period.

The ACTIVE study is a novel randomized double-blind controlled trial that will help determine whether high-dose statin therapy reduces graft occlusion after CABG. Previous post hoc subgroup data from the TNT Trial suggested that patients with a history of remote CABG had improved outcomes when treated with atorvastatin 80 mg daily, as compared with atorvastatin 10 mg daily [25,30]. Aggressive LDL reduction also appeared to benefit patients with a history of CABG in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study that focused on combination therapy with simvastatin and ezetemibe [50]. However, no graft patency data was collected in TNT or IMPROVE-IT. Furthermore, patients in these subgroup analyses had undergone CABG many years earlier and likely had evidence of vein graft disease at the time of enrollment [25,30,50]. In contrast to these studies, high-dose statin therapy is being administered immediately after CABG in the ACTIVE trial.

Very few studies to date have evaluated the impact of high-dose statins early following surgical coronary revascularization. One small observational study of surgical patients reported an association between preoperative high-dose statin therapy and a lower incidence of postoperative adverse events, as compared to conventional lower doses of statins [51]. Recently, two randomized controlled trials evaluated the potential benefits of perioperative high-dose statin therapy, yielding negative results. High-dose statins did not lead to any clinical gains in terms of reducing the risk of perioperative atrial fibrillation, myocardial damage, or kidney injury early after CABG [32–33]. Regarding graft function, Hata et al. noted yellow plaque and thrombus using intracoronary angioscopy in the vein grafts of patients with high LDL levels (> 100 mg/dL) one year after surgery. However, plaque and thrombus were absent for those patients with low LDL levels (< 80 mg/dL), suggesting that aggressive lipid-lowering therapy after CABG may prevent the development of saphenous vein graft disease [35]. In a *post-hoc* analysis of the CASCADE (Clopidogrel after Surgery for Coronary Artery Disease) Trial, 1-year graft patency was significantly better for patients with LDL levels < 100 mg/dL compared to those with LDL levels > 100 mg/dL ($P = 0.03$), but there was no further improvement in graft patency when LDL levels were reduced to < 70 mg/dL [34].

It remains unclear whether high-dose statin therapy and LDL levels approaching 70 mg/dL will improve postoperative graft patency. We hope that ACTIVE will definitively address this issue with the collection of high quality prospective trial data. Nevertheless, the results from ACTIVE may not ultimately alter modern-day practice, since the clinical guidelines changed during the conduct of the trial. Prior to initiating ACTIVE, earlier guidelines had recommended statins to achieve an LDL treatment goal of < 100 mg/dL after CABG [21–24]. However, as we attempted to complete ACTIVE enrollment, new American Heart Association documents were published in 2014 and 2015, citing several primary and secondary prevention studies that had reported benefits with high-dose statins [10,25,30,52]. At that time, clinical trial data specific to the CABG population and the early postoperative period had yet to be presented. Regardless, the guideline committees chose to recommended high-intensity statin therapy for all patients with clinical atherosclerotic disease, including nearly all patients who had previously undergone CABG [10,52]. Interestingly, the cardiovascular community has been hesitant to adopt these guidelines since their publication [53]. In any event, we sought to be compliant with the new recommendations [10,52], and we were faced with slow study enrollment. As such, we elected to close our trial early, after having recruited 173 subjects (see Table 1), instead of 200 as originally planned. Ultimately, should ACTIVE demonstrate that high-dose statin therapy prevents graft occlusion, we believe the results will strengthen the new guidelines [10,52], help promote the implementation of their recommendations [53], and reinforce the role of high-intensity statins for all patients after coronary surgical revascularization.

To our knowledge, ACTIVE is the only trial evaluating the impact of early postoperative high-intensity statins on graft patency after CABG.

Table 1
Patient characteristics.

Characteristic	Patients (N = 173)
Preoperative characteristics	
Age, years	68.9 ± 10.5
Male gender, %	141 (81.5%)
Body-mass index, kg/m^2	29.7 ± 5.0
Diabetes mellitus, %	74 (42.8%)
Current smoker, %	25 (14.4%)
Hypertension, %	144 (83.7%)
Hyperlipidemia, %	153 (89.0%)
Acute coronary syndrome[a], %	75 (43.6%)
Previous myocardial infarction, %	39 (22.5%)
Previous PCI, %	43 (24.9%)
CCS class 3–4, %	114 (67.1%)
Heart failure NYHA class 3–4, %	69 (41.1%)
Preoperative atrial fibrillation, %	18 (10.4%)
Chronic obstructive pulmonary disease, %	12 (6.9%)
Cerebrovascular disease, %	17 (9.8%)
Peripheral vascular disease, %	11 (6.4%)
Preoperative creatinine, mg/dL	1.08 ± 0.23
Preoperative LDL, mg/dL	81.7 ± 32.4
Preoperative medication use	
Aspirin, %	150 (87.2%)
Clopidogrel, %	33 (19.1%)
Statin, %	145 (83.8%)
Beta-blocker, %	135 (78.0%)
Angiotensin converting enzyme inhibitor, %	101 (58.7%)
Operative details	
Number of distal anastomoses, n	2.8 ± 0.7
Left internal thoracic graft, %	157 (91.3%)
Second arterial conduit, %	24 (14.0%)
Cross-clamp time, min	90.5 ± 40.0
Cardiopulmonary bypass time, min	123.0 ± 46.3
Concurrent valve surgery, %	21 (12.2%)
Off-pump surgery, %	10 (5.8%)

CCS, Canadian Cardiovascular Society; LDL, low-density lipoprotein; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
[a] Recent acute coronary syndrome within 1 month.

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. We anticipate the 1-year graft patency data will be available for presentation in 2017. After participating in ACTIVE for one year, patients are thereafter being treated with open label (usually high dose) statin therapy. Nevertheless, we plan to continue following ACTIVE participants with additional CT coronary angiography at the 2-year and 3-year time points to assess the mid- to long-term effects of initiating early intensive statin therapy after CABG.

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 sequalae. High-dose statin therapy has been demonstrated to improve outcomes in patients with CAD and those with a history of CABG. However, no prospective study to date has evaluated the use of early high-dose statin therapy for the prevention graft disease after CABG. The ACTIVE trial is a randomized double-blind controlled trial comparing early high-dose statin therapy to standard moderate-dose statin therapy for the prevention of saphenous vein graft occlusion following CABG using CT coronary angiography 1 year after surgery.

Competing interests

The authors have no relationships to disclose pertaining to this research.

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. MR is the secondary investigator who helped with subject recruitment and drafting of the manuscript.

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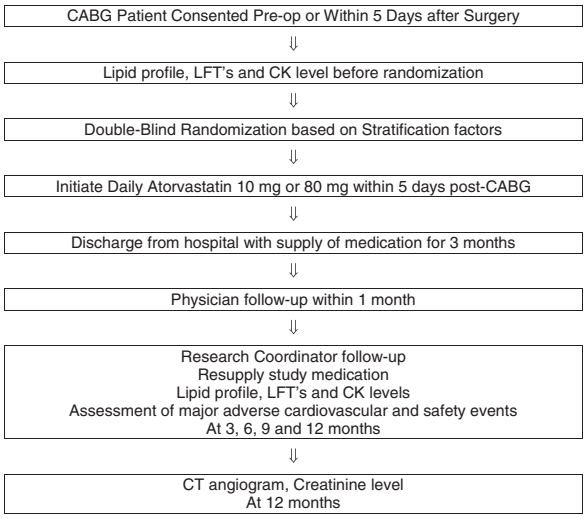
Appendix A. Study inclusion and exclusion criteria.

Inclusion criteria	Reason
- Patients undergoing first-time CABG with at least one saphenous vein graft - On-pump or off-pump CABG - Concurrent valve repair or replacement	- The population of clinical interest

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
- Allergy to statin	- Contraindication to use of statin
- History of severe liver disease	- Contraindication to use of statin
- Pregnancy or seeking pregnancy	- Contraindication to use of statin (teratogen)
- Inability to provide informed consent	- Ineligible for research study enrollment
- Postoperative low cardiac output syndrome requiring > 2 inotropes 48 h after surgery	- Unstable patient unlikely to benefit from treatment

Appendix B. Trial timeline.



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