

INVESTIGATOR'S ABBREVIATED PROTOCOL

1. TITLE: Prasugrel for prevention of early saphenous vein graft thrombosis

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3. SPONSOR OF THE STUDY: VA Merit, VA OR&D

4. IND/ IDE: Not Applicable

5. PURPOSE OF THE STUDY, INCLUDING HYPOTHESIS TO BE TESTED:

Aortocoronary saphenous vein graft failure is common and is associated with high morbidity and mortality. Thrombus formation plays a critical role in early saphenous vein graft occlusion and may predispose to subsequent atherosclerosis formation. Optical coherence tomography is a novel, high-resolution, intravascular imaging technique that can reliably identify thrombus. Based on the findings of earlier VA Cooperative Studies, aspirin significantly reduces the incidence of early saphenous vein graft failure and is currently used in nearly all patients undergoing coronary bypass graft surgery. Administration of clopidogrel for improving early saphenous vein graft patency has provided conflicting results in small randomized studies. Prasugrel is a novel thienopyridine that provides more rapid, consistent, and intense platelet inhibition than clopidogrel. However, in patients who undergo coronary artery bypass graft surgery, it remains unknown whether prasugrel may decrease thrombus formation in saphenous vein grafts during the first postoperative year, and whether this will result in less saphenous vein graft wall thickening, less lipid deposition in the saphenous vein graft wall and fewer clinical events without increasing the risk for severe bleeding.

We hypothesize that in patients undergoing clinically-indicated coronary artery bypass graft surgery, administration of prasugrel starting at dismissal from the index coronary bypass graft surgery hospitalization will result in lower prevalence of thrombus formation in a target SVG, as assessed by optical coherence tomography performed 12 months post surgery compared to placebo, with similar incidence of major bleeding.

6. BACKGROUND AND RESULTS OF PREVIOUS RELATED RESEARCH:

Saphenous vein graft failure

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the US population and is highly prevalent among veterans. Obstructive CAD often requires coronary revascularization, which can be achieved either with percutaneous coronary intervention (PCI) or with coronary artery bypass graft surgery (CABG). In spite of a decline in surgical volume over time,¹ CABG is still one of the most frequently performed surgical procedures: during 2006, 444,000 (14.9 per 10,000 population) CABG operations were performed in nonfederal USA hospitals that participated in the National Hospital Discharge Survey.²

First used by Rene Favaloro in 1968, saphenous vein bypass grafts (SVGs) continue to be used in almost all CABG operations today for several reasons: first, because of their relatively large diameter and wall characteristics, they are technically easy to use; second, they are plentiful, and therefore can be used to perform multiple grafts; third, they are long and can reach any coronary artery; and fourth, they are easily harvested.³ However, SVG have high rates of both early and late failure.

Early SVG failure occurred in 46% of 1929 patients in the Project of Ex-vivo Vein Graft Engineering via Transfection IV (PREVENT IV) trial⁴ and in 29-37% of 2203 patients included in the Randomized On/Off Bypass (ROOBY) Study.⁵ In the PREVENT IV trial, the composite of death, myocardial infarction, or coronary revascularization occurred more frequently among patients who developed early SVG failure compared with those who did not [adjusted hazard ratio (HR) 1.79, 95% confidence intervals (CI) 1.40-2.28; P<0.001] (Figure 1).⁶

Early SVG failure may also predispose to late (>1 year) SVG failure, which occurred in 39% of SVGs at 10-years in three VA Cooperative Studies (#207/297/364) (Figure 2)⁷ and in 50% of SVGs at \geq 15 years in another study of 1,388 patients.⁸ As treatment of occluded⁹ or severely stenosed¹⁰ SVGs is challenging and costly, prevention of early

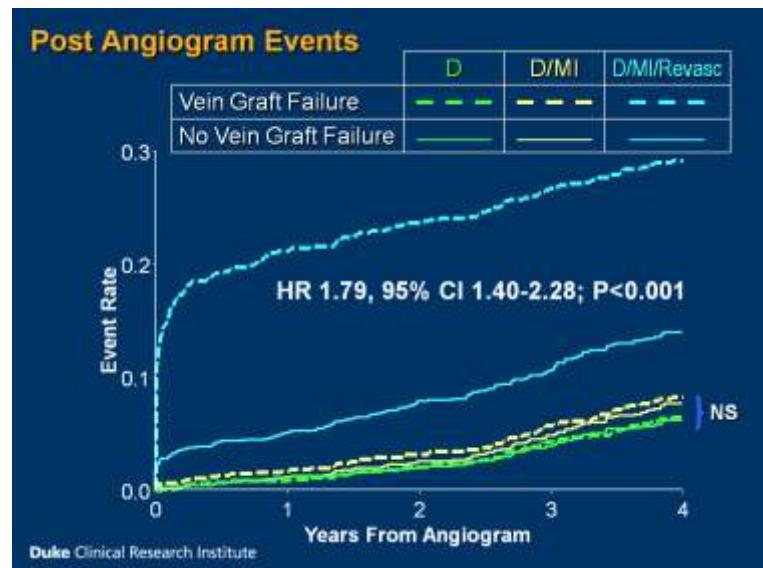
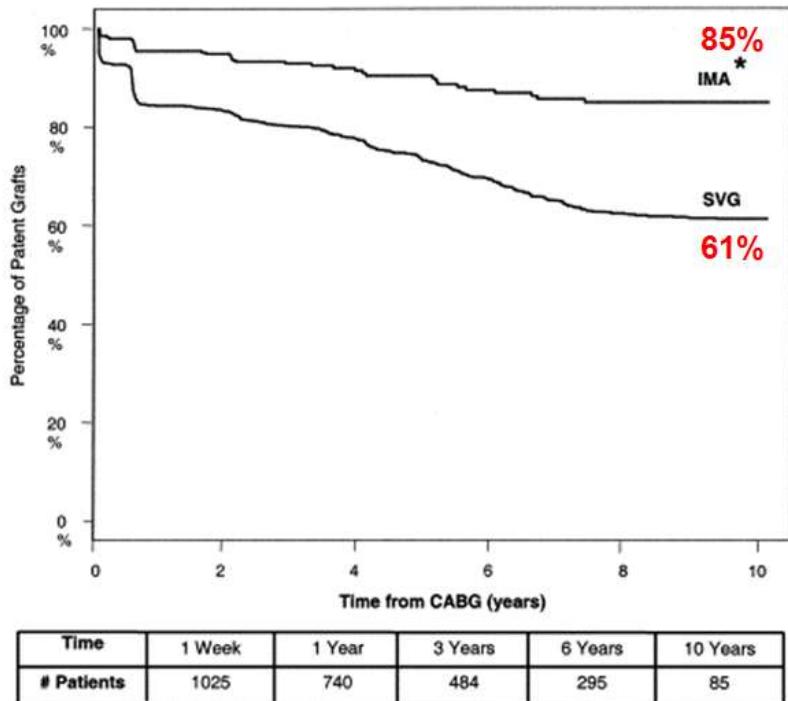


Figure 1. Impact of early SVG failure on subsequent clinical outcomes in the PREVENT IV trial. Patients with early SVG failure had significantly higher risk driven mainly by significant increase in the need for repeat coronary revascularization (D=death, MI=myocardial infarction, Revasc=coronary revascularization)



Time	1 Week	1 Year	3 Years	6 Years	10 Years
# Patients	1025	740	484	295	85

Figure 2. Saphenous vein graft (SVG) and internal mammary artery (IMA) patency rates after CABG in VA Cooperative Studies #207/297/364.

SVG failure is critically important.

Mechanisms leading to saphenous vein graft failure

SVG failure is the result of 3 consecutive and inter-related processes: thrombosis, intimal hyperplasia, and atherosclerosis (Figure 3).^{11, 12} Immediately post CABG thrombus forms in SVGs due to endothelial disruption during harvesting and implantation. If the SVGs remain patent during this period, they develop a platelet-mediated progressive thickening of the vessel wall, which involves smooth muscle cell proliferation and extracellular matrix protein synthesis. Atherosclerosis subsequently develops on the ground of intimal hyperplasia, leading to decreased antegrade flow or eventually SVG occlusion.

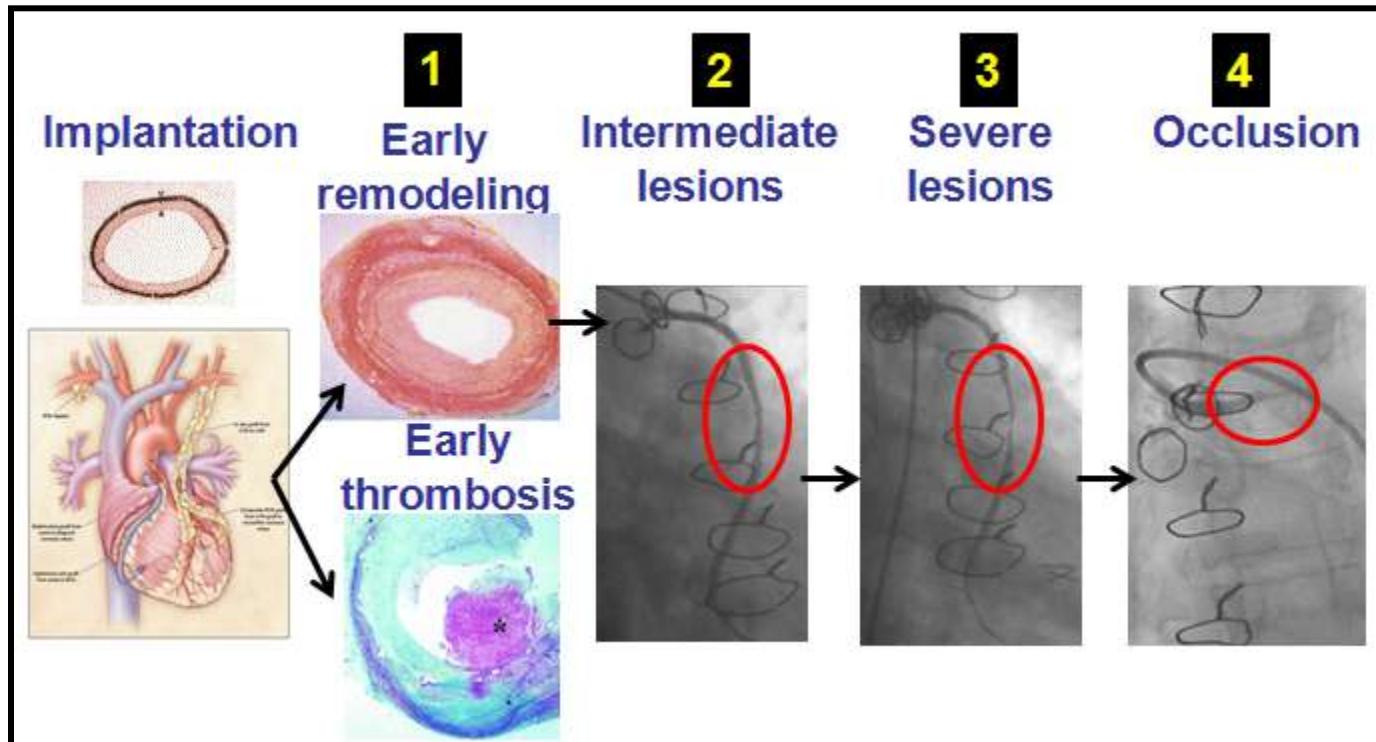


Figure 3. Evolution of saphenous vein graft lesion development. After coronary artery bypass SVGs either occlude early or develop intimal thickening (panel 1), which forms the ground for moderate lesion development (panel 2). Moderate SVG lesions have high rates of progression to severe, symptom-causing lesions (panel 3), and eventually occlusion (panel 4).

SVG harvesting during CABG can cause significant injury, both at the time of removal from the leg and during SVG flushing to prepare the conduit for grafting.¹³ SVG wall injury may predispose to intraluminal platelet thrombus formation, which was observed in 68% of SVGs examined by OCT immediately post harvesting (Figure 4).¹³ Several factors may affect the severity of SVG injury, such as the mode of harvesting (endoscopic vs. open), manual high-pressure intraluminal distension, and the presence of baseline SVG disease. Lack

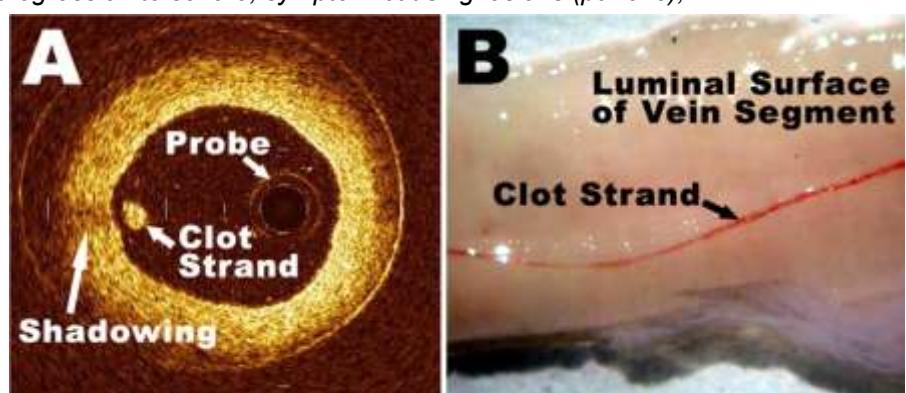


Figure 4. Identification of intraluminal thrombus formation in SVGs immediately after harvesting using optical coherence tomography (panel A) or by direct visualization (panel B).

of heparinization during SVG harvesting was associated with a trend for higher SVG occlusion rates one week post CABG, highlighting the risk for early SVG thrombosis.¹⁴

Several other factors are associated with decreased SVG patency, such as multiple distal SVG anastomoses¹⁵ and off-pump surgery,⁵ that is why SVGs with multiple anastomosis will be excluded from the present study; nearly all coronary bypass graft surgeries are performed on-pump at our institution.

Platelet thrombus formation is critical for promoting subsequent SVG neointima hyperplasia formation.¹⁶ Administration of antiplatelet agents, such as clopidogrel has been shown to decrease intimal proliferation in animal models.^{17, 18}

SVG atherosclerosis forms on the ground of intimal hyperplasia, likely due to a combination of lipid accumulation and thrombus formation.¹⁹ SVG atherosclerosis is usually diffuse, concentric, and friable with a poorly developed or absent fibrous cap and little evidence of calcification, whereas native vessel atheroma is proximal, focal, eccentric, and nonfriable with a well-developed fibrous cap and frequent calcification.¹¹ Histologically, SVG atheromas tend to have more foam cells and inflammatory cells, including multinucleate giant cells, than native coronary atheromas.¹¹ SVGs have a more powerful system of lipid biosynthesis and uptake, that may in part account for the accelerated formation of SVG atherosclerosis and forms the basis of using aggressive lipid lowering therapies to prevent SVG failure.¹¹

In summary thrombus formation occurs frequently during the early period post implantation and plays a critical role both in early SVG occlusion and in the formation of intimal hyperplasia and subsequent SVG atherosclerosis. Therefore, strategies that can decrease early SVG thrombus formation could be beneficial in preventing SVG atherosclerosis development and SVG failure.

Current therapies for SVG failure prevention

At present, the only treatments proven to prevent SVG failure are aspirin and lipid-lowering agents, mainly statins.^{11, 20}

Aspirin significantly reduces the rates of graft occlusion and clinical complications after CABG.²¹ In a meta-analysis from the Antiplatelet Trialists' Collaboration, low-dose aspirin was associated with improved graft patency, as assessed by coronary angiography, at one year after surgery.²¹ The pooled odds reduction for SVG closure was 41 percent (8 percent absolute risk reduction) with low-dose aspirin (75 to 325 mg/day) compared to placebo or control therapy. The benefit was similar to that seen with higher and more gastrotoxic doses of aspirin. Aspirin should be started either preoperative or within 6 hours from CABG²² and continued indefinitely.

Lipid lowering therapy can significantly reduce atherosclerosis risk in a variety of high and low-risk populations. Four trials have specifically examined the role of lipid-lowering therapy in SVGs: (1) the Post-Coronary Artery Bypass Graft (POST-CABG)^{23, 24} trial evaluated lovastatin and if needed, cholestyramine; (2) the Lopid Coronary Angiography Trial (LOCAT)²⁵ evaluated gemfibrozil; (3) the Cholesterol Lowering Atherosclerotic Study (CLAS)²⁶ evaluated colestipol and niacin; and (4) the study by Makuuchi et al evaluated pravastatin vs placebo.²⁷ The first 3 trials showed reduction in the

angiographic progression of SVG disease. The POST-CABG and the CLAS trials also demonstrated a reduction in clinical events.

Although administration of aspirin and statins is the current standard of care for preventing early SVG failure, 29-46% of patients experience SVG failure during the first year post CABG.^{4, 5} Therefore, additional therapies are needed to further decrease the SVG failure risk of those patients.

Investigative therapies for early SVG failure prevention

Several therapies are currently being evaluated to prevent early SVG failure. Those therapies address different stages of the SVG disease process, starting at the time of CABG surgery and continuing through the initial year post implantation.

Intraoperative treatments that are under investigation include: (a) bathing of SVGs before implantation in short oligomers of L-arginine that can cross the membrane of the endothelial cells comprising the vessel wall and are cleaved inside the endothelial cells to provide an effective intracellular source of monomeric L-arginine. The delivery of L-arginine results in increased nitric oxide release leading to reduced intimal hyperplasia (NCT00264706 and NCT01313533); (b) bathing of SVGs in peptides or small molecules, such as novel anti-c-myc antisense drug (AVI-5126, NCT00451256). However the results of the PREVENT IV trial that evaluated pre-implantation bathing of SVGs in edifoligide (e2F decoy) did not show any benefit at 12-18 month follow-up angiography⁴; (c) endoscopic saphenous vein harvesting to minimize vessel trauma (NCT01121341); (d) intra-operative imaging of SVGs (with fluorescence angiography in the GRIIP trial (NCT00187421) or with standard angiography in a hybrid catheterization laboratory/operating room²⁸) with immediate surgical or percutaneous treatment of suboptimal grafts (12% of total grafts in one study²⁸); (e) use of SVG sheaths (such as the eSVS mesh, NCT00777777) that may minimize intimal hyperplasia by providing external SVG support; and (f) use of the “no touch” SVG harvesting technique, that aims to minimize SVG trauma (Improving the Results of Heart Bypass Surgery Using New Approaches to Surgery and Medication – SUPERIOR SVG - NCT01047449).

Treatments for the **first year after CABG** that are currently under evaluation include (a) P2Y12 inhibitors such as ticagrelor (NCT01373411), (b) fish oil (as part of the SUPERIOR SVG trial); and (c) monthly infusion of a recombinant human monoclonal antibody against P-selectin during the first 8 months post CABG (NCT01245634). Another study (NCT00481806) is attempting to evaluate the role of thrombin in angiographic SVG occlusion during the first year post CABG.

In summary there are multiple clinical trials evaluating different options for optimizing early SVG patency, highlighting the large clinical need for improvements in this area, that has not changed for several years.³

Thienopyridine administration for early SVG failure prevention

Five studies evaluating thienopyridines for the prevention of early SVG failure have been published to date with conflicting results (Table 1).

Limet et al randomized 173 patients to ticlopidine vs. placebo and performed graft angiography at 3 time points (10, 180, and 360 days).²⁹ Graft patency was higher in the ticlopidine group at all time points.

Two Chinese studies have been published (the first author is Gao in both studies):

Gao et al randomized 197 patients to aspirin + clopidogrel vs. aspirin alone. Using computed tomography they reported similar 1 and 12-month SVG patency rate (98.1% and 98.2% at 1 month and 93.5% and 96.3% at 12 months for aspirin and the combination, respectively, p=non-significant).³⁰

Gao et al randomized 249-patients to aspirin + clopidogrel vs. aspirin alone. Using computed tomography they reported higher 3-month SVG patency rate in patients receiving clopidogrel (91.6% vs. 85.7%, p=0.043).³¹

In contrast, the Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) trial randomized 113 patients to aspirin + clopidogrel vs. aspirin + placebo for 1 year. Follow-up angiography and IVUS evaluation showed no difference in 12-month SVG patency (95% in both groups, p=1.0) or in SVG intimal area hyperplasia ($4.5 \pm 2.1 \text{ mm}^2$ vs. $4.1 \pm 2.0 \text{ mm}^2$, p=0.44).¹²

Finally, the Preoperative Aspirin and Postoperative Antiplatelets in Coronary Artery Bypass Grafting (PAPA-CABG) study randomized 100 patients undergoing CABG to placebo or clopidogrel for 30 days. Patients subsequently underwent computed tomography for bypass graft patency evaluation.³² Overall, similar proportion of patients in the placebo and clopidogrel group had at least one SVG occlusion (23.1% vs. 17.5%, p=0.54), but radial artery occlusion occurred less frequently in the clopidogrel group (43.8% vs. 10.5%, p=0.05). Although more potent antiplatelet therapy could increase the risk of bleeding, no significant difference in bleeding was observed in the above studies, yet these studies were underpowered to detect such differences.

Table 1. Studies assessing the effect of thienopyridine administration post CABG on bypass graft patency.

Study	Thienopyridine	N	Time of assessment	Primary endpoint	Findings
Limet et al ²⁹	ticlopidine	173	10, 180, and 360 days	Graft patency, as assessed by coronary angiography	Higher graft patency in the ticlopidine group at day 10 (84.4% vs. 66.7%, p < 0.05), day 180 (74.4% vs. 52.3%, p < 0.05) and day 360 (75.0% vs. 52.5%, p < 0.05).
Gao et al ³⁰	clopidogrel	197	1 and 12 months	SVG patency, as assessed by computed tomography	Similar SVG patency in both study groups.
Gao et al ³¹	clopidogrel	249	3 months	SVG patency, as assessed by computed tomography	Higher SVG patency in clopidogrel group: 91.6% vs. 85.7%, p=0.043

CASCADE ¹²	clopidogrel	113	12 months	SVG intimal area at follow-up IVUS	4.5±2.1 mm ² in placebo vs. 4.1±2.0 mm ² in clopidogrel, p=0.44
PAPA CABG ³³	clopidogrel	100	30 days	SVG occlusion, as assessed by computed tomography	23.1% in placebo vs. 17.5% in clopidogrel groups had ≥1 occluded graft (p=0.54). Radial graft occlusion was lower in the clopidogrel arm (43.8% vs. 10.5%, p=0.05).

In addition to the above studies an analysis of the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, showed that patients who underwent CABG had a trend for lower incidence of the primary endpoint (composite of cardiovascular death, myocardial infarction, or stroke) at 12 months [14.5% for clopidogrel 16.2% for placebo; relative risk (RR), 0.89; 95% CI, 0.71 to 1.11].³²

In summary 2 of the 5 published trials demonstrated benefit with thienopyridine on bypass graft patency and 3 did not. There are multiple possible explanations for these conflicting results. One explanation is that SVG thrombus is not important for maintaining early SVG patency, however this would contradict studies showing association of baseline SVG thrombus with subsequent SVG failure.¹⁴ A second possible explanation is that clopidogrel does not provide adequate platelet inhibition to successfully prevent SVG thrombus formation. Several studies have demonstrated variable antiplatelet response to clopidogrel depending on genetic factors and concomitant medication administration.³⁴ A third possible explanation is that the surrogate endpoint used in the CASCADE trial (intimal hyperplasia) may not be the best surrogate endpoint, and surrogate endpoints that directly assess SVG thrombus (such as OCT) may be more accurate.

7. Definition of the Population to Which the Study is Directed, with Justification:

Study subjects will be recruited from the group of patients who are referred for coronary artery bypass graft surgery the Dallas VA Medical Center. The study we propose is significant because: (a) it would affect many veterans, (b) the consequences of early SVG failure are grave, (c) treatment of severe/total SVGs lesions is challenging, and (d) outcomes after treatment of severe/total SVG lesions are poor.

- (a) CABG is one of the most commonly performed operations with nearly a half million operations performed annually in the US.² Early SVG graft failure is common with 29%-46% of patients undergoing CABG developing failure of at least one SVG during the first postoperative year.^{4, 5}

(b) Early SVG failure is associated with significantly higher rates of death, myocardial infarction, or coronary revascularization.⁶

(c) Treatment options for severe SVG lesions or SVG occlusion are limited. Although percutaneous coronary intervention is currently the preferred treatment for severe SVG lesions,⁵⁰ it is limited by high-rates of peri-procedural myocardial infarction (approximately 10%, even when embolic protection devices are used⁵¹) and by high rates of in-stent restenosis, requiring repeat procedures,⁵² which may be reduced by drug-eluting stent implantation.¹⁰ Repeat CABG is technically difficult, has higher mortality compared to initial CABG, and provides less symptomatic improvement.⁸ Percutaneous coronary intervention of a native coronary artery instead of the diseased SVG is an option, but outcomes were similar to SVG interventions in a series of 142 patients from our institution.⁵³ We recently proposed retrograde percutaneous coronary intervention of native coronary artery chronic total occlusions to treat acutely thrombosed SVGs, however this approach is technically demanding and its long term outcomes are unknown.⁵⁴

(d) Clinical outcomes after SVG interventions are poor,⁵³ especially if SVGs are occluded at presentation. We recently reviewed the outcomes of 34 consecutive patients undergoing percutaneous intervention for acute SVG occlusion at our institution and found 86% procedural success compared to 99% success in native coronary artery lesions.⁹ At 1 and 3 years, mortality was 8% and 42%, an acute coronary syndrome occurred in 15% and 41%, and repeat coronary revascularization was required in 28% and 38%, respectively.⁹ Approximately half of the deaths were cardiac, and the remainder were non-cardiac (cancer, infection, stroke), which is likely explained by their advanced age and multiple comorbidities.

In summary, early SVG failure is common and carries significant morbidity and mortality. If prasugrel can prevent early SVG failure, it could significantly improve the quality and duration of life of patients undergoing CABG, reduce the need for repeat revascularization procedures, and potentially reduce their healthcare costs.

8. SUBJECT SELECTION, INCLUSION AND EXCLUSION CRITERIA:

Patients undergoing clinically-indicated CABG will be identified by a study investigator or coordinator and will be screened for eligibility for the study using the following criteria:

Inclusion criteria:

1. Age 18 years or greater
2. Willing and able to give informed consent. The patients must be able to comply with study procedures and follow-up.
3. Undergoing clinically-indicated coronary artery bypass graft surgery

Exclusion criteria:

1. Known allergy to aspirin or prasugrel
2. Need for concomitant cardiac procedure, such as valve repair or replacement
3. Increased risk of bleeding [need for warfarin or oral Xa inhibitor or thrombin inhibitor administration, recent (within 30 days) major bleed, known bleeding diathesis or coagulation disorder]
4. Positive pregnancy test or breast-feeding
5. Coexisting conditions that limit life expectancy to less than 12 months or that could affect a patient's compliance with the protocol
6. Serum creatinine > 2.5 mg/dL
7. Severe peripheral arterial disease limiting vascular access
8. Prior stroke or transient ischemic attack
9. Weight <60 kg or age >75 years
10. Multiple distal SVG anastomoses
11. Postoperative complications prolonging hospitalization (including, but not limited to bleeding, prolonged intubation, infection, deep venous thrombosis or pulmonary embolism)

9. NUMBER OF SUBJECTS IN THE STUDY:

Approximately 120 patients will be randomized into this study at the Dallas VA Medical Center.

10. JUSTIFICATION FOR THE USE OF SPECIAL SUBJECT POPULATIONS:

Not applicable.

11. STUDY DESIGN:

The primary efficacy objective is to compare the prevalence of SVG thrombus as detected by optical coherence tomography of a target SVG between patients receiving prasugrel vs. placebo. We hypothesize that prasugrel will be superior to placebo in reducing the prevalence of SVG thrombus at 12-month follow-up OCT imaging.

The primary safety endpoint is the incidence of severe bleeding as defined using the GUSTO study criteria.⁶⁷ We hypothesize that patients receiving prasugrel will have similar incidence of severe bleeding compared to patients receiving placebo during the 12-month study period.

The secondary endpoints will be: (1) incidence of angiographic SVG failure (defined as $\geq 75\%$ SVG diameter stenosis in at least one SVG); the total and normalized total SVG atheroma volume within at least 40 mm of the target SVG, as assessed by intravascular ultrasonography; the lipid core burden index of the target SVG, as assessed by near-infrared intracoronary spectroscopy; and (2) the incidence of major adverse cardiac events and moderate bleeding during the 12-month study period.

The proposed study is a phase 3, single-center, randomized, double-blind, controlled, parallel-group study of prasugrel vs. matching placebo in patients with recent CABG, starting at the time of hospital dismissal from CABG (Figure 13). All patients will be receiving aspirin, as per standard current practice.

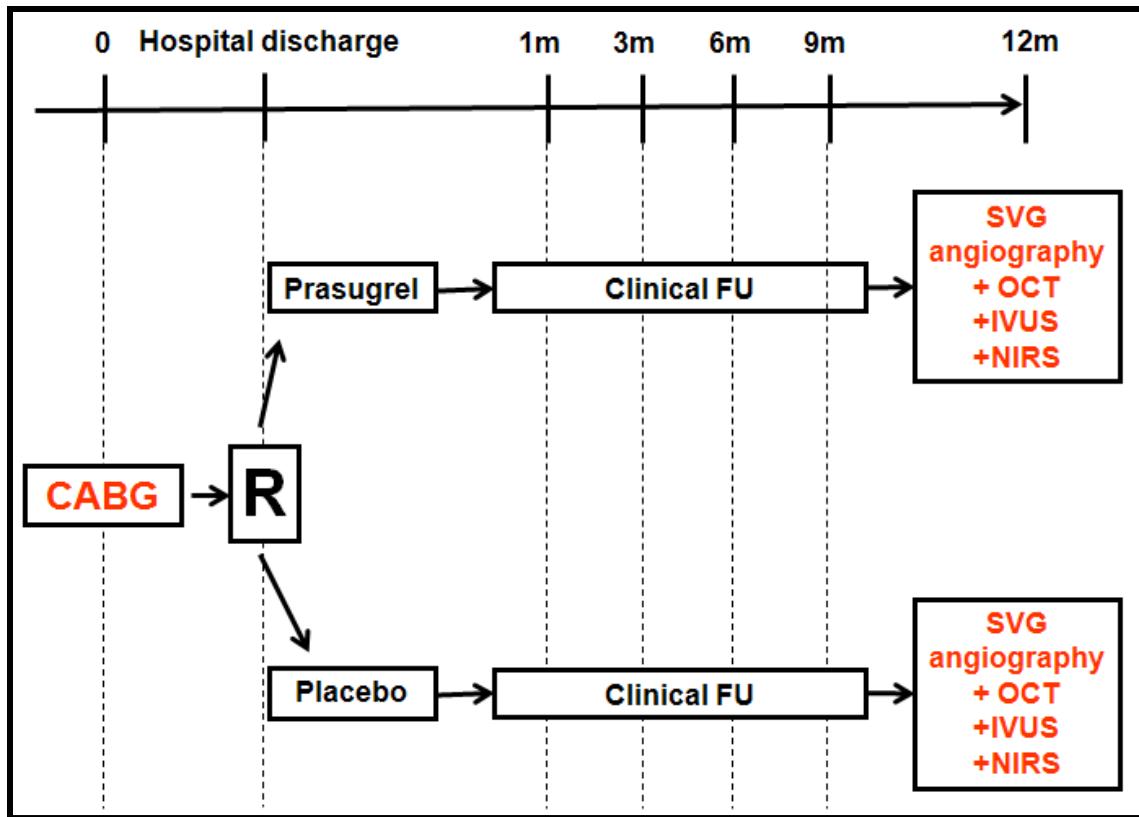


Figure 13: Flowchart of the proposed study design.

CABG = coronary artery bypass graft surgery; OCT = optical coherence tomography; IVUS = intravascular ultrasound; NIRS = near-infrared spectroscopy; R = randomization; m = month; FU = follow-up.

12. DESCRIPTION OF PROCEDURES TO BE PERFORMED:

The study design will be explained to the patients and if they agree to participate they will be asked to sign an informed consent form and they will receive a copy of the consent form. They will subsequently be randomized to prasugrel or placebo, as described below.

Randomization and Treatment

Randomization will be performed based on computer-generated random numbers, and will be blocked with block sizes of 4-10, varying randomly. Subjects will be assigned on a 1:1 basis to prasugrel (Effient®, Daiichi Sankyo and Eli Lilly) at a dose of 10 mg daily or matching placebo. The patients and study coordinators will be blinded to the study medication. Angiographic, OCT, IVUS, NIRS and angiographic analyses will also be done blinded to study-arm allocation. Breaking the blind will be possible for any patient who develops a complication or whose clinical care requires knowledge of the study group allocation.

Patients randomized to the treatment arm will receive prasugrel at a dose of 10 mg daily. Patients randomized to placebo will receive one placebo tablet. To minimize the potential for side effects during the study period patients with an increased risk of bleeding [need for warfarin or oral Xa inhibitor or thrombin inhibitor administration, recent (within 30 days) major bleed, known bleeding diathesis or coagulation disorder], will be excluded from the present study.

To minimize the possibility of study medication discontinuation, adherence with the study medication will be assessed during every follow-up visit. Patients will be asked to return all unused medications and study containers. The number of tables issued minus the number of tablets returned will be used to calculate the number of tablets taken. From this information compliance will be calculated as: (number of capsules dispensed – number of capsules returned) / (number of days between visits x number of tablets per daily dose). Patients with <80% compliance with the study medication will be counseled on the importance of taking their medications.

Catheterization, OCT, IVUS, and NIRS

One SVG will be examined in each patient. The target intermediate SVG lesion will be selected by the interventional cardiologist performing the procedure as the longest and least-angulated SVG amenable to intravascular imaging. After intragraft administration of 200 µg of nitroglycerin, an OCT catheter (DragonFly, St Jude Medical, Minneapolis, Minnesota) will be advanced 40-50 mm distal to the SVG proximal anastomosis and will be pulled back proximal to the lesion using a motorized system at a speed of 20 mm/sec. The OCT images will be written on CD-R or DVD for subsequent off-line analysis. Subsequently, a 45-MHz, 3.2F, rotational IVUS catheter (Revolution, Volcano therapeutics, Rancho Cordova, California, USA) will be advanced into the target SVG and the transducer will be advanced as distal as possible within the SVG and will then be pulled back to the SVG aortic ostium using a motorized pull-back system at a speed of 0.5 mm/s. During pullback, gray-scale IVUS will be recorded at a rate of 30 frames per second. The gray-scale IVUS movie will be written on CD-R or DVD for subsequent off-line analysis. Similarly, a 3.2-F near-infrared spectroscopy catheter (Lipiscan IVUS, InfraReDx, Burlington, Massachusetts) will be advanced into the target SVG and positioned to the same location where the IVUS catheter was previously placed, if feasible. The catheter will then be pulled back to the aortic ostium using a motorized pull-back system at a speed of 0.5 cm/s. A chemogram of the artery will be obtained, as shown in Figures 10-12. The near-infrared spectroscopy data will also be recorded in CD-R or DVD for subsequent analysis.

Examination of the target SVG lesion with angiography, OCT, IVUS, and NIRS will be obtained at 12 months post CABG. If the patient undergoes clinically-indicated graft angiography before the 12-month planned angiography, then: (a) if ≥ 10 months have elapsed from enrollment in the study, then angiography, OCT, IVUS, and NIRS of a target SVG will be performed; or (b) if <10 months have elapsed from enrollment, then prasugrel will be continued and the patient will be asked to return for the planned 12-month angiography, OCT, IVUS and NIRS.

Follow-Up: Study procedures and follow-up assessments are summarized in the below table 2.

Table 2. Schedule of observations and laboratory assessments.

Test	Treatment period						Post-Treatment Follow-up Contact (30 days after 12 month visit – Phone FU)
	0	1m +/- 5 days	3m +/- 10 days (phone FU)	6m +/- 10 days	9m +/- 10 days (phone FU)	12m +/- 30 days	
Inclusion/Exclusion criteria reviewed	X						
Informed consent	X						
Medical history	X	X	X	X	X	X	X
Physical examination/ Vital Signs	X	X		X		X	
Medication adherence		X	X	X	X	X	
Electrocardiogram	X					X	
SVG angiography, OCT, IVUS and NIRS						X	

FU=follow-up; SVG=saphenous vein graft; IVUS=intravascular ultrasonography; NIRS = near-infrared spectroscopy; OCT = optical coherence tomography

13. ANTICIPATED DATA AND DATA ANALYSIS:

Expected treatment effect

A recent study demonstrated the presence of thrombus in 25% of SVGs examined early post CABG.⁴⁷ Given the potent antiplatelet effect of prasugrel, we anticipate 80% reduction in the prevalence of thrombus in SVGs, as assessed by OCT.

Sample size calculation

Assuming that thrombus will be detected by OCT in 25% of patients in the placebo group vs. 5% of patients in the prasugrel group (80% relative reduction), the sample size required to detect the specified difference with 80% power and a 2-sided α

level of .05 is 48 patients per group, which was increased to 60 patients to allow for 20% dropout.

Assuming 48 patients are evaluable in each group, the power of the study assuming a prevalence of thrombus by OCT in the control arm of 20%, 25%, and 30% will be 67%, 80%, and 89%, respectively.

Enrolling 40 patients per year for three consecutive years will require enrollment of 25 % of the eligible patients at our institution. Enrollment rate in the SOS trial which also required angiographic and IVUS follow-up⁶² was 56%, suggesting that enrollment of the projected number of patients is feasible in our setting.

Statistical Analysis of primary endpoints

All endpoints (primary and secondary) will be analyzed with an intent-to-treat approach.

The prevalence of thrombus within the target SVG at 12-month OCT imaging (primary efficacy endpoint) will be analyzed using the Fisher's exact test. In view of the relatively small sample size of the trial, multivariable logistic regression analyses will be performed to adjust the findings for any potential differences in the baseline characteristics of the two study groups, which are known to influence the occurrence of SVG failure. Such characteristics are: patient age, prior myocardial infarction; total cholesterol and HDL-cholesterol levels; minimum graft diameter; mean arterial pressure; ejection fraction; male gender; and current smoking.⁶⁹ The significant characteristics will be incorporated in the calculation of an adjusted odds ratio representing the association between treatment and the prevalence of thrombus, along with 95% confidence intervals. Because off-pump and endoscopic SVG harvesting may be associated with higher rates of SVG failure, randomization will be stratified by (a) on vs. off pump and (b) endoscopic vs. open harvesting.

The time elapsed to the incidence of severe bleeding, defined using the GUSTO criteria⁶⁷ (primary safety endpoint) will evaluated using Kaplan-Meier survival curves and compared between the 2 study groups using the log-rank test.

Statistical Analysis of secondary endpoints:

The differences in angiographic SVG failure, in total and normalized total SVG atheroma volume and in lipid core burden index at 12-month SVG imaging will be compared between the 2 study groups using Fisher's exact test. A logistic regression model will be developed to evaluate the treatment effect on this outcome adjusting for patient age, prior myocardial infarction; total cholesterol and HDL-cholesterol levels; minimum graft diameter; mean arterial pressure; ejection fraction; male gender; and current smoking.⁶⁹

The incidence of major adverse cardiovascular events (composite of death, acute coronary syndrome, and coronary revascularization) at 12 months will be compared between the two study groups using the chi-square test. Kaplan-Meier survival curves and the log-rank test will be used to compare time-to-event of major adverse cardiac events in the two study groups.

All tests will be two-sided. The critical level for the primary and four secondary outcomes will be 0.05. No adjustments will be made for multiple secondary endpoints

14. PROVISIONS FOR MANAGING ADVERSE REACTIONS:

For safety monitoring, any emergency adverse event resulting from participation in the study will be treated at the Dallas VA Medical Center. Dr. Brilakis will evaluate all adverse events and determine the appropriate course of action.

If a patient develops severe bleeding during the study period, prasugrel will be temporarily held and will be discontinued if the patient is considered to be at increased risk for recurrent bleeding. If a patient develops an indication for receiving oral anticoagulation therapy with warfarin or dabigatran during his or her participation in the study, prasugrel administration will be discontinued to minimize the risk of bleeding.

If any subjects are hospitalized for an acute coronary syndrome or undergo coronary angiography at an outside hospital, the hospitalization records will be obtained and reviewed by the clinical events committee. The Universal definition of myocardial infarction will be used for diagnosing myocardial infarction. Bleeding will be assessed with the use of the GUSTO criteria.⁶⁷ Severe bleeding will be defined as fatal bleeding, intracranial hemorrhage, or bleeding causing hemodynamic compromise requiring blood or fluid replacement, inotropes, or surgery.⁶⁷ The frequencies of moderate bleeding, defined as bleeding requiring transfusion not characterized as severe, and moderate/severe and severe bleeding will also be analyzed. Information on (surgical or percutaneous) coronary revascularization will also be collected. Data will be entered on paper-based case report forms and will be double-entered into a secure, password protected database, accessible only by study personnel. Subjects will be identified by a unique study number in the database.

Additionally a Data Safety Monitoring Board will be appointed to review the study periodically (every 12 months, or sooner if required).

15. RISK/ BENEFIT ASSESSMENT:

Although participation in our study carries some risk (related to administration of prasugrel and to invasive follow-up SVG imaging) we will make every effort to minimize it. To minimize the risk associated with prasugrel, patients at high risk for adverse reactions (patients at increased risk of bleeding, patients receiving oral anticoagulants, patients with prior stroke or transient ischemic attack and patients with weight <60 kg or age >75 years) will be excluded from the study. Also patients will be monitored closely with clinic visits or phone follow-up, at 1, 3, 6, 9, and 12 months from enrollment. To minimize the risk from cardiac catheterization and invasive SVG assessment, patients at high risk for complications, such as patients with peripheral vascular disease and renal failure, will be excluded. All angiographic SVG imaging procedures will be performed by experienced, high-volume, interventional cardiologists.

Relevance to Veterans health (Potential Benefit)

Ischemic heart disease is the leading cause of death in men over 40 years of age. The predominantly male, older VA population with its high incidence of hyperlipidemia, hypercholesterolemia, hypertension and cigarette smoking represents a highly susceptible population for this disease.⁵⁵ Frequently the preferred or only possible revascularization treatment for ischemic heart disease is coronary artery bypass graft surgery. Every year, about 5,300 coronary artery bypass procedures are performed in the VA system alone with a total budget of approximately \$222,600,000 per year (\$42,000 per operation),

according to VA Decision Support System (DSS) data. Veterans are at particular risk for early SVG failure, as they often have advanced diffuse coronary artery disease and rapid SVG atherosclerosis progression^{9, 10, 53} and would greatly benefit from successful completion of the proposed study.

16. DATA SAFETY MONITORING PLAN:

A Data and Safety Monitoring Board (DSMB) will be appointed to periodically review the conduct of the proposed trial for safety. The committee members will include cardiologists with experience in clinical research who will not be participating in the trial as investigators. Potential financial or intellectual conflicts of interest will be assessed prior to appointing the members. The DSMB will meet prior to the enrollment of the first subject to review the trial protocol, informed consent documents and plans for safety and data monitoring of the study. The DSMB will determine the risks and benefits to research subjects, protection and safety of the subjects and to offer suggestions for improving the study design. In addition, the DSMB will determine which data will be required for periodic review. The DSMB will meet every 12 months to: determine adherence to study plan; review interim analysis, if applicable, and determine specific data to be analyzed; review protocol violations and deviations to assess adequacy of study; ensure documentation of informed consent; review enrollment followed eligibility criteria, enrollment numbers, visit compliance, or screening failure information; discuss investigator or key personnel changes; review completeness and quality of data collection forms; evaluate the aggregate analysis of adverse events/serious adverse events; review vital signs, clinical tests, etc.; and review confidentiality. At the end of each meeting the DSMB will give a recommendation to continue the trial unchanged, modify the protocols and/or consent form, or terminate the trial.

17. PROCESS FOR OBTAINING INFORMED CONSENT AND PROTECTING SUBJECT PRIVACY:

Before the subject undergoes procedures specific to the protocol, the informed consent and HIPAA authorization will be signed and dated by the subject and the member of the study team performing the Informed Consent procedures. Following referral and notification that a patient meets initial pre-screening criteria, the PI and/ member of the study team will present the option to participate in the research study to the patient and any family/ friend that the patient wishes to include. Study subjects will be recruited by study staff (PI, co-investigator, research nurse/coordinator) from patients who present for Coronary Artery Bypass Surgery once it is deemed appropriate to approach patient per good clinical practice guidelines. If the patient expresses interest, then the informed consent, HIPAA authorization (including risks and benefits) will be discussed in detail and an opportunity will be provided to ask questions. Patient will also be provided the opportunity to discuss with family/ friend, as he/she deems fit. After all required signatures have been obtained; a copy of the consent and HIPAA authorization will be provided to the subject and scanned into the subject's medical record.

18. DOCUMENTATION OF INFORMED CONSENT:

Following the study subjects' enrollment a research enrollment note documenting the procedure of informed consent will be entered in CPRS by a member of the research team. Notes will include a brief description of the study, procedures for obtaining consent and HIPAA authorization, study personnel and contact numbers. A copy of the signed informed consent and HIPAA authorization form will be provided to the research office for scanning into the patient's records.

19. PAYMENT TO SUBJECTS FOR THEIR PARTICIPATION:

Study participants will be paid \$50 for 1 month and 6 month, and \$200 for 12 month follow-up visits, to assist with the cost of transportation.

20. PROVISIONS FOR DATA STORAGE AND CONFIDENTIALITY:

Confidentiality of subject data will be maintained in accordance with VA, IRB and HIPAA regulations. Physician investigators, study coordinators and study team members will have access to the subjects' medical records and the results of all examinations undertaken.

In accordance with HIPAA, the consent form and HIPAA authorization describes to the subject what protected health information will be obtained and/or stored and for what purpose, as well as a list of who may have access to this data, including outside agencies. All records will be maintained in a locked cabinet in the research team's locked office in the CRU. Computerized data will be de-identified and stored on a password protected computer in a locked office of the research team. Additionally patient logs and identifiable computerized data will be stored on the study team's limited access shared research folder located on the secure VA server.

In accordance with VA guidelines, all records of this research study will continue to be securely maintained in accordance with VHA Record Control Schedule. The records will be kept in a locked file cabinet or locked room with limited access. If the PI leaves the VA facility, the research records will be retained by the institution.

21. PROVISIONS FOR STORAGE/ ANALYSIS OF RESEARCH SPECIMENS:

Not Applicable.

22. DISSEMINATION OF RESEARCH RESULTS

The results from this research will be published in medical journals and presented at medical meetings.

23. MULTI-CENTER RESEARCH.

Not applicable.

REFERENCES, APPENDICES and TABLES:

Please see attached Sponsor's Protocol.