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Circulation

IN DEPTH

Saphenous Vein Graft Failure

From Pathophysiology to Prevention and Treatment Strategies

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ABSTRACT: Saphenous vein grafts (SVGs) remain the most frequently used conduits in coronary artery bypass graft surgery (CABG). Despite advances in surgical techniques and pharmacotherapy, SVG failure rates remain high, often leading to repeat coronary revascularization. The no-touch SVG harvesting technique (minimal graft manipulation with preservation of vasa vasorum and nerves) reduces the risk of SVG failure, whereas the effect of the off-pump technique on SVG patency remains unclear. Use of buffered storage solutions, intraoperative graft flow measurement, careful selection of the target vessels, and physiological assessment of the native coronary circulation before CABG may also reduce the incidence of SVG failure. Perioperative aspirin and high-intensity statin administration are the cornerstones of secondary prevention after CABG. Dual antiplatelet therapy is recommended for off-pump CABG and in patients with a recent acute coronary syndrome. Intermediate (30%–60%) SVG stenoses often progress rapidly. Stenting of intermediate SVG stenoses failed to improve outcomes; hence, treatment focuses on strict control of coronary artery disease risk factors. Redo CABG is associated with higher perioperative mortality compared with percutaneous coronary intervention (PCI); hence, the latter is preferred for most patients requiring repeat revascularization after CABG. SVG PCI is limited by high rates of no-reflow and a high incidence of restenosis during follow-up. Drug-eluting and bare metal stents provide similar long-term outcomes in SVG PCI. Embolic protection devices reduce no-reflow and should be used when feasible. PCI of the corresponding native coronary artery is associated with better short- and long-term outcomes and is preferred over SVG PCI, if technically feasible.

Key Words: coronary artery bypass graft surgery ■ embolic protection devices ■ no-reflow ■ percutaneous coronary intervention ■ prevention ■ saphenous vein grafts

Dr David C. Sabiston, Jr, was the first physician to use a saphenous vein graft (SVG) to revascularize the right coronary artery in 1962 at Johns Hopkins University. René Favaloro standardized the surgical technique of using SVGs for coronary artery bypass graft surgery (CABG), earning the title of "Father of CABG." More than 50 years later, and despite the limitations of SVGs, they remain the most frequently used conduits in conjunction with the left internal mammary artery (LIMA). Multiple arterial grafts are used in <10% of CABG operations currently performed in the United States.

SVGs have high failure rates, with 3% to 12% occluding before hospital discharge, 8% to 25% failing at 1 year, and only 50% to 60% remaining patent after a decade.[1–4] Advances in surgical techniques and pharmacotherapy have improved mid- and long-term SVG patency rates, with recent studies reporting comparable patency of composite grafts with arterial grafts at 5 years[5] and 8-year SVG patency as high as 91%.[6] Despite these advances, ≈13% of patients who undergo CABG require repeat revascularization within 10 years, ≈18% of all percutaneous coronary interventions (PCIs) are performed in patients with previous CABG, and ≈6% of all PCIs are performed on SVGs, illustrating the frequent need for repeat revascularization after CABG.[7,8]

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AHB	autologous heparinized blood
BARC	Bleeding Academic Research Consortium
BMS	bare metal stent
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CTA	computed tomography angiography
CTO	chronic total occlusion
GALA	glutathione-ascorbic L-arginine
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
ELCA	excimer laser coronary angioplasty
EPD	embolic protection devices
EVH	endoscopic vein harvesting
FFR	fractional flow reserve
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
IMA	internal mammary artery
IVUS	intravascular ultrasound
LAD	left anterior descending coronary artery
LIMA	left internal mammary artery
MACE	major adverse cardiovascular events
MACCE	major adverse cardiocerebral events
MI	myocardial infarction
MSCTA	multislice computed tomography angiography
NO	nitric oxide
OCT	optical coherence tomography
NS	normal saline
PI	pulsatility index
PCI	percutaneous coronary intervention
RCT	randomized controlled trial
SMC	smooth muscle cell
SVG	saphenous vein graft
TLR	target lesion revascularization
TTF	transient-time flow
TVR	target vessel revascularization

In this article, we review the natural history of the SVGs, followed by discussion of prevention and treatment strategies for each stage of SVG failure according to time from CABG: (1) preoperative and perioperative strategies, (2) early post-CABG period, (3) intermediate SVG lesions, (4) severe SVG stenoses, and (5) acute and chronic total SVG occlusions (Figure 1).

PATHOPHYSIOLOGY OF SVG FAILURE

Three pathophysiologic processes lead to SVG failure: thrombosis and technical failure is the predominant mechanism within the first week and during the first month after CABG, followed by intimal hyperplasia from 1 month to 1 year, and atherosclerosis beyond 1 year.

Early failure is attributed to technical (ie, graft trauma during harvesting, anastomotic deficiencies), conduit-related (ie, mismatch in conduit size or preexisting graft pathology), or extrinsic factors (ie, hypercoagulability) causing acute thrombosis. Mechanical forces and ischemia-reperfusion injury during harvesting and storage result in endothelial denudation and smooth muscle cell (SMC) damage. De-endothelialization leads to exposure of the extracellular matrix and activation of extrinsic coagulation cascade by the tissue factor. Reduced bioavailability of prostacycline and nitric oxide (NO) lead to vasoconstriction and stasis, which further promotes fibrin accumulation, adherence of activated platelets and leukocytes on the luminal surface, and thrombus formation.

SVG intimal hyperplasia is an adaptive mechanism to high arterial pressure, a process called "arterialization," and occurs within months after CABG. It can cause mild lumen reduction but rarely leads to significant early stenosis. Activated platelets secrete multiple cytokines (ie, interleukin-1, interleukin-6) and growth factors (ie, platelet derived growth factor, transforming growth factor beta) that promote SMC proliferation. In parallel, coagulation activation leads to thrombin formation and eventually deposition of polymerized fibrin. Thrombin stimulates SMC proliferation both directly and indirectly through PDGF secretion from platelets. Neo-endothelium begins to form from the edges of the injury zone over a layer of platelets and fibrin. Approximately 4 days after graft insertion, SMC proliferation reaches a peak, and the SMCs of the medial layer undergo phenotypic modulation from a quiescent contractile state to a synthetic stage, similar to fibroblasts, migrating to the intima. Further thickening of the intima takes place by secretion of extracellular matrix, composed of elastin, collagen, glycoproteins, and proteoglycans. High proliferative adventitial fibroblasts migrate to the intima and differentiate into myofibroblasts, contributing to intimal thickening. The aforementioned processes start initially at the anastomotic sites, expanding over time throughout the entire SVG. Innate immune system cells, such as mast cells and natural killer cells, also participate in development of intimal hyperplasia.

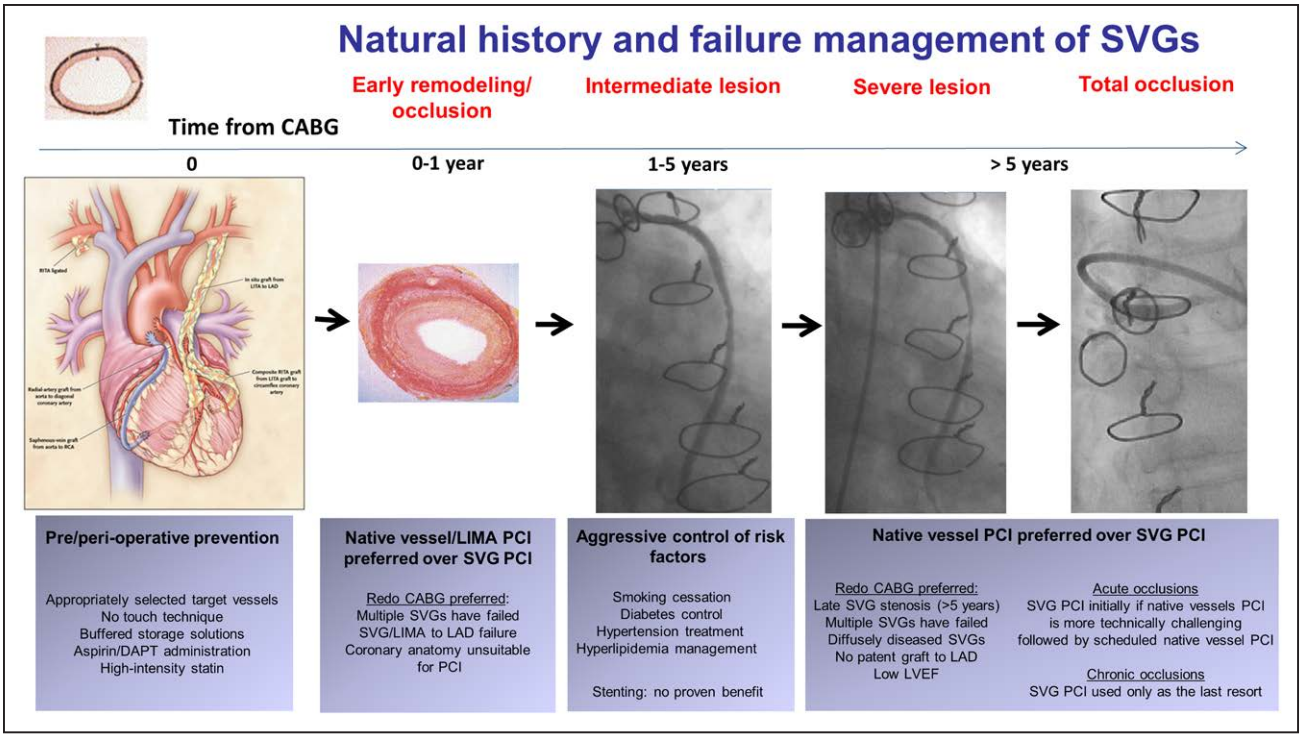

Figure 1. Natural history and failure management of saphenous vein grafts.
The timeline of the natural history of saphenous vein grafts is an approximation, because SVGs may occlude early after CABG or remain patent many years after CABG. CABG indicates coronary artery bypass graft surgery; DAT, dual antiplatelet therapy; LAD, left anterior descending coronary artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and SVG, saphenous vein graft.

Intimal hyperplasia forms the ground for atherosclerosis development, which can lead to late SVG failure. SVG atherosclerosis progresses at a faster pace compared with native coronary artery atherosclerosis. SVG atherosclerosis is often concentric and diffuse, with a less well-defined or even absent fibrous cap compared with native vessel atherosclerosis, and is more prone to rupture.[9] Atherosclerotic changes are identified as early as 1 year after CABG and are initially characterized by foam-cell accumulation followed by development of a necrotic core, typically observed 2 to 5 years after surgery, often forming intermediate SVG lesions. After this period, the necrotic core expands through intraplaque hemorrhage from leaky neoangiogenic vessels, which can lead to plaque rupture and thrombus formation, potentially causing SVG occlusion.[9]

PREOPERATIVE AND PERIOPERATIVE STRATEGIES TO PREVENT SVG FAILURE

Target Vessel Diameter, Distal Bed Quality, and Preoperative Lesion Assessment

A disease-free coronary segment should be chosen for the anastomosis. In addition, the more proximal the anastomosis the better the SVG patency, as the vessel is larger, size discrepancy between vessel and conduit is less, and the runoff may be better. Target vessel diameter affects long-term graft patency.[1,10] At 10 years, SVG patency was 88% in vessels >2.0 mm versus 55% in vessels ≤2.0 mm diameter and 80% in SVGs to the left anterior descending coronary artery (LAD).[1]

Target vessel quality also affects graft patency. SVGs to diffusely diseased and calcified arteries with poor distal runoff have higher rates of occlusion. In the PRAGUE-4 trial, grafts anastomosed on collateralized totally occluded coronary arteries other than the LAD had the lowest patency rates.[11] The risk of SVG occlusion was higher for grafts to the right coronary artery or the circumflex compared with grafts to the LAD.[11]

Grafting of nonhemodynamically significant lesions may result in early internal mammary artery (IMA)[12] or SVG[13] failure because of competitive flow. In a study of 164 patients, Botman et al reported a higher 12-month occlusion rate for SVGs anastomosed to native vessels with fractional flow reserve (FFR) >0.75 versus <0.75 (20% versus 5.9%).[13] Toth et al reported that patients who underwent FFR–guided CABG (intermediate stenoses with FFR ≤0.80 were grafted, whereas intermediate stenoses with FFR >0.80 were deferred) were less likely to develop arterial or venous graft occlusion at 36 months (5% versus 21%, P=0.031) compared with patients who underwent angiography-guided CABG.[14]

Pharmacotherapy

Antiplatelet Therapy

The effect of aspirin on graft patency after CABG has been studied since the 1980s. Perioperative aspirin administration was associated with better survival; hence, aspirin remains essential for patients undergoing CABG. The optimal timing and dose of aspirin remain uncertain. Goldman et al found that preoperative aspirin 325 mg the night before surgery was associated with increased bleeding complications and offered no additional benefit in early SVG patency compared with starting aspirin 6 hours after CABG through a nasogastric tube.[15] Wu et al reported lower SVG failure rates as assessed by computed tomography angiography (CTA) 5 days after CABG (98.2% versus 96.1%, P=0.02) among off-pump patients with CABG who continued aspirin (100 mg) preoperatively compared with patients who stopped aspirin at least 5 days before the operation.[16] Fremes et al examined the effect of antiplatelet and anticoagulant therapy on SVG patency in a meta-analysis of 17 randomized trials. Aspirin significantly reduced graft occlusion compared with placebo (aspirin with or without dipyridamole versus placebo: odds ratio [OR], 0.60 [95% CI, 0.51–0.71]; P<0.0001). A low (100 mg) to medium (325 mg) dose of daily aspirin was more effective and safer than a high dose (975 mg) with the ideal time for aspirin initiation being within 6 hours after CABG, whereas preoperative administration provided no additional benefit.[17] In a meta-analysis of 5 randomized controlled trials (RCTs), medium-dose aspirin (300–325 mg) was associated with a trend toward lower graft occlusion rates compared with low-dose aspirin (50–100 mg; relative risk, 0.74 [95% CI, 0.52–1.06]; P=0.10), likely because of resistance to the antiplatelet effect of aspirin in the postoperative period.[18] Deng et al showed that discontinuation of aspirin <24 hours before CABG was associated with lower 30-day mortality on multivariable analysis (OR, 0.34 [95% CI, 0.2–0.82]).[19] In addition, mortality was significantly lower with aspirin 81 mg (1.4%), compared with aspirin 325 mg (2.9%) or none (3.9%) (P<0.01). In contrast, a recent RCT found no difference in the incidence of death, thrombotic complications, or bleeding at 30 days between administration of 100 mg of aspirin and placebo preoperatively.[20] Although both American Heart Association Scientific Statement and European guidelines propose that aspirin should be administered throughout the perioperative period (preoperatively and within 6 hours according to the American guidelines), the former favor the use of a higher aspirin dose (325 mg daily) rather than a lower aspirin dose (81 mg daily) when it is used as the sole antiplatelet therapy, presumably to prevent aspirin resistance (class IIa, level of evidence A, although it is acknowledged that the benefits are not well established), whereas the latter recommend a low-dose daily regimen of aspirin (class I, level of evidence C).[21,22]

Clopidogrel is an irreversible P2Y12 inhibitor that can reduce the risk of ischemic events compared with aspirin in patients with previous cardiac surgery.[23] In a meta-analysis of 25 728 patients, the combination of clopidogrel plus aspirin was associated with lower incidence of early SVG failure (risk ratio, 0.59 [95% CI, 0.43–0.82]; P=0.02) and lower 30-day mortality (0.8% versus 1.9%; P<0.0001) but higher incidence of major bleeding (risk ratio, 1.17 [95% CI, 1.00–1.37]; P=0.05) compared with aspirin alone. Dual antiplatelet therapy (DAPT) appears to be most beneficial in patients undergoing off-pump CABG.[24]

Prasugrel and ticagrelor are faster-acting and more potent P2Y12 inhibitors. Both medications were associated with better survival in patients who presented with acute coronary syndrome (ACS) and subsequently underwent CABG.[25,26] Ticagrelor was recently approved for patients with stable coronary artery disease (CAD), including those with previous CABG, in addition to aspirin.[27] The DACAB trial (Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery) showed that ticagrelor administration in addition to aspirin, but not ticagrelor monotherapy, improved SVG patency rates after elective CABG (88.7% versus 76.5%, P<0.001 for ticagrelor plus aspirin versus aspirin alone and 82.8% versus 76.5%, P=0.10 for ticagrelor alone versus aspirin alone) at 1 year; 75% of the SVGs in DACAB were placed off-pump; hence, these findings apply mostly to off-pump procedures. In the TiCAB trial (Ticagrelor in Patients Undergoing CABG), administration of ticagrelor monotherapy did not reduce the need for repeat revascularization at 12 months after CABG (4.6% versus 3.3% for ticagrelor and aspirin monotherapy, respectively, P=0.37). Major bleeding events were also similar between the 2 groups (5.8% versus 4%, P=0.24). TiCAB was terminated prematurely and was thus underpowered.[28] RCTs comparing DAPT with antiplatelet monotherapy are summarized in Table 1.[29–36] The Popular CABG trial (Effect of Ticagrelor on Saphenous Vein Graft Patency in Patients Undergoing Coronary Artery Bypass Grafting Surgery) showed no difference in SVG occlusion rate at 1 year with ticagrelor 90 mg twice per day in addition to aspirin 80 mg (10.5% versus 9.1%, P=0.38).[35] The ongoing TARGET trial (Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis; URL: http://www.clinicaltrials.gov. Unique identifier: NCT02053909) is randomizing patients undergoing CABG to either ticagrelor 90 mg twice per day or aspirin 81 mg twice per day. SVG patency will be estimated with CTA 1 and 2 years after CABG. In a meta-analysis of 20 RCTs, the use of DAPT with either aspirin plus ticagrelor (OR, 0.50 [95% CI, 0.31–0.79]) or aspirin plus clopidogrel (OR, 0.60 [95% CI, 0.42–0.86]) reduced SVG failure when compared with aspirin monotherapy with no difference in major bleeding, myocardial infarction (MI), and death.[37]

Table 1. Randomized Controlled Trials of Dual Versus Single Antiplatelet Therapy for Preventing Saphenous Vein Graft Failure

Source	No. of patients	Comparison	Time of administration of P2Y12 inhibitor	Outcomes
Clopidogrel plus aspirin vs aspirin				
Gao et al[30]	249	Aspirin (100 mg) plus clopidogrel (75 mg) vs aspirin (100 mg)	Within 48 h after CABG	SVG patency assessed by MSCTA 3 mo after the operation was higher in the DAPT group (91.6% vs 85.7%, *P*=0.043). Bleeding rates were not reported.
Sun et al[34]	79	Aspirin (81 mg) plus clopidogrel (75 mg) vs aspirin (81 mg)	6–48 h after CABG	No difference in SVG patency as assessed by CTA at 1 mo after CABG between the DAPT and aspirin groups (93.2% vs 93.5%, *P*=0.92). No difference in total bleeding events (14.3% vs 16%, *P*=1.0).
Kulik et al[31]	92	Aspirin (162 mg) plus clopidogrel (75 mg) vs aspirin (162 mg)	On the day of CABG	DAPT did not reduce intimal hyperplasia (4.1±2.0 vs 4.5±2.1 mm^2, *P*=0.44) and did not affect SVG patency (94.3% vs 92.3%, *P*=0.69) compared with monotherapy with aspirin as assessed with IVUS and angiography, 1 y after surgery. Similar major bleeding events (1.8% vs 0%, *P*=0.5).
Mannacio et al[32]	300	Aspirin (100 mg) plus clopidogrel (75 mg) vs aspirin (100 mg)	After CABG	DAPT reduced the rate of SVG occlusion over aspirin alone as assessed by CTA at 1 y (7.4% vs 13.1%, *P*=0.04) in patients undergoing off-pump CABG. No difference in major bleeding (1.3% vs 1.3%, *P*=1.0).
Rafiq et al[33]	165 hypercoagulable patients	Aspirin (75 mg) plus clopidogrel (75 mg) vs aspirin (75 mg)	Day 2 after CABG	Similar rate of stenosed or occluded SVGs (22.7% vs 10.4% for DAPT and aspirin monotherapy, respectively, *P*=0.167) as assessed by MSCTA at 3 mo follow-up. Epistaxis occurred more often with DAPT. There was a trend toward more major bleeding events with DAPT.
Ticagrelor plus aspirin vs ticagrelor vs aspirin				
Zhao et al (DACAB)[36]	461	Ticagrelor (90 mg BID) plus aspirin (100 mg) vs ticagrelor (90 mg BID) vs aspirin (100 mg)	Within 48 h after CABG	Ticagrelor plus aspirin but not ticagrelor alone improved 1-y SVG patency rates after elective CABG (88.7% vs 76.5%, *P*<0.001 for ticagrelor plus aspirin vs aspirin alone and 82.8% vs 76.5%, *P*=0.10 for ticagrelor alone vs aspirin alone) as assessed by MSCTA or coronary angiography. Non–CABG-related bleeding was numerically more common with ticagrelor plus aspirin (30.4%) compared with ticagrelor alone (12.1%) and aspirin alone (9%).
Willemsen et al (Popular CABG)[35]	443	Ticagrelor (90 mg BID) plus aspirin (80 or 100 mg) vs aspirin (80 or 100 mg)	After CABG	SVG occlusion (10.5% vs 9.1%, *P*=0.38) and SVG failure (14.2% vs 11.6%, *P*=0.54) at 1 y was not different between ticagrelor plus aspirin and aspirin alone group. No difference in BARC major (3.6% vs 2.4%, *P*=0.42) and minor (14.2% vs 12.4%, *P*=0.57) bleeding events between the 2 groups.
Prasugrel plus aspirin vs aspirin				
Danek et al[29]	59	Prasugrel (10 mg) plus aspirin vs aspirin alone	After CABG (after discharge)	Thrombus was identified by OCT in 56% vs 50% of patients in the prasugrel plus aspirin vs aspirin-only groups, respectively (*P*=0.78). Angiographic SVG failure was similar between the 2 groups (24% vs 40%, *P*=0.19) at 12 mo. No difference in GUSTO severe (2.4% vs 0%, *P*>0.99) or moderate (0% vs 0%, *P*>0.99) bleeding events.

BARC indicates Bleeding Academic Research Consortium; BID, bis in die (twice a day); CABG, coronary artery bypass graft surgery; CTA, computed tomography angiography; DAPT, dual antiplatelet therapy; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; IVUS, intravascular ultrasound; MSCTA, multislice computed tomography angiography; OCT, optical coherence tomography; and SVG, saphenous vein graft.

A scientific statement from the American Heart Association for secondary prevention after CABG recommends aspirin (81–162 mg) and clopidogrel (75 mg) for 1 year after off-pump CABG to reduce graft occlusion (class I, level of evidence A). Combination therapy with aspirin and clopidogrel for 1 year after on-pump CABG may be considered in patients without recent ACS, but the benefits are not well-established (class IIb, level of evidence A). DAPT with ticagrelor or prasugrel and aspirin is preferred over clopidogrel and aspirin in patients with ACS who undergo CABG (class IIa, level of evidence B).[21] Whether addition of ticagrelor to aspirin improves SVG patency remains controversial given the conflicting results of the DACAB trial (better SVG patency with ticagrelor)[36] and Popular-CABG (similar SVG patency with ticagrelor).[35] The European guidelines do not recommend DAPT in patients with stable CAD after CABG but recommend resumption of DAPT as soon as deemed safe for patients (1) who had ACS and subsequently underwent CABG for up to 12 months if there is no need for concomitant oral anticoagulation or (2) who underwent cardiac surgery after stent implantation (class I, level of evidence B for both indications).[22]

The concept of oral anticoagulation administration to prevent SVG failure has been tested for >40 years.

Whereas Gohlke et al reported higher SVG patency rates with phenprocoumon versus placebo,[38] vitamin K antagonists did not provide benefit over antiplatelet agents in improving SVG patency rates; thus, their administration in patients undergoing CABG is not recommended in the absence of another indication for oral anticoagulation. The effect of rivaroxaban, a novel oral anticoagulant that inhibits factor Xa, on graft patency was evaluated in a substudy of the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies). Rivaroxaban 2.5 mg twice per day plus aspirin 100 mg daily (OR, 1.05 [95% CI, 0.72–1.53]; *P*=0.79) or rivaroxaban 5 mg twice daily alone (OR, 0.82 [95% 0.55–1.22]; *P*=0.32) that was started 4 to 14 days after CABG did not reduce the 1-year incidence of SVG failure compared with aspirin 100 mg daily alone, although the combination of rivaroxaban and aspirin was associated with fewer major adverse events compared with aspirin alone.[39]

Lipid Management

Multiple studies have evaluated the effect of statins on SVG patency (Table 2).[40–43] The ACTIVE trial (Aggressive Cholesterol Therapy to Inhibit Vein Graft Events) randomized 173 patients with previous CABG to 10 mg or 80 mg of atorvastatin daily, showing no difference in SVG occlusion (12.9% versus 11.4%, *P*=0.85).[41] The multicenter, randomized, double-blind StaRT-CABG trial (Statin Recapture Therapy Before Coronary Artery Bypass Grafting; URL: http://www.clinicaltrials.gov. Unique identifier: NCT01715714) is examining the effect of oral statin reload at 12 and 2 hours before CABG on major adverse cardiocerebral events (MACCE) after surgery using the maximum dose of the chronically prescribed statin.

The American Heart Association recommends starting statin therapy in the preoperative period and resuming its use early after the operation (class I, level of evidence A). High-intensity statin therapy (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) should be administered after surgery to all patients with CABG <75 years of age. Moderate-intensity statin is recommended for patients intolerant to high-intensity statin therapy and patients at greater risk for drug-drug interactions (class I, level of evidence A).[21]

Growing evidence supports the benefit of PCSK-9 and ezetimibe administration in patients with previous CABG. In the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the combination of simvastatin and ezetimibe improved outcomes in patients with previous CABG.[44] In a prespecified analysis of the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) that enrolled patients with recent ACS and elevated atherogenic lipoprotein levels despite high-intensity statin therapy, patients with previous CABG who received alirocumab had larger absolute reduction in major adverse cardiovascular events (MACEs) and death.[45] However, neither ezetimibe nor alirocumab has been specifically investigated for SVG failure prevention. Icosapent ethyl, a highly purified omega-3 fatty acid containing only eicosapentaenoic acid, reduced ischemic events in the REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial), which included several patients with previous CABG, leading to a broad label expansion for patients with elevated triglycerides.[46]

No-Touch Technique

In the no-touch technique, the SVG is harvested as a pedicle, preserving the vasa vasorum and nerves in the adventitia; graft distention is also avoided.[47] It has been shown that the no-touch harvesting technique is associated with higher baseline blood flow and pressure-tolerant capacity after nicardipine intraluminal administration during off-pump CABG procedures compared with conventional preparation.[48] The no-touch technique may improve both short- and long-term SVG patency by reducing intimal hyperplasia and atherosclerosis progression.[10,49] Samano et al randomized 54 patients undergoing CABG to either the conventional or the no-

Table 2. Studies Evaluating Statin Therapy for Prevention of Saphenous Vein Graft Failure

Source	No. of patients	Comparison	Outcomes
Post Coronary Artery Bypass Graft Trial Investigators[40]	1351	Lovastatin 40–80 mg vs lovastatin 2.5–5 mg	Higher lovastatin dose was associated with less SVG atherosclerosis progression (27% vs 39%, *P*<0.001) and a lower incidence of new SVG occlusions (10% vs 16%, *P*=0.001) at 4 y.
Makuuchi et al[43]	303	Pravastatin 10–20 mg vs placebo	Although there was no significant difference in the quantitative coronary angiography measurements between the 2 groups, the visually assessed global change score indicated a significant pravastatin-mediated reduction in plaque progression (*P*<0.01).
Kulik et al[42]	92	LDL <100 mg/dL vs LDL >100 mg/dL	12-mo graft patency as assessed by coronary angiography was higher in the LDL <100 mg/dL group (97% vs 83%, *P*=0.03).
Kulik et al[41]	145	Atorvastatin 80 mg vs atorvastatin 10 mg	12-mo graft occlusion did not differ significantly between the 2 groups (13% vs 11% for atorvastatin 10 mg and 80 mg, respectively, *P*=0.85).

LDL indicates low-density lipoprotein; and SVG, saphenous vein graft.

touch technique. After a mean follow-up of 16 years, SVG patency was higher with the no-touch technique (83% versus 64%, *P*=0.03).[50] The SUPERIOR SVG trial (Surgical and Pharmacological Novel Interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting Surgery) randomized 127 patients to the no-touch technique and 123 patients to conventional SVG harvesting. At 12 months after surgery, the primary composite end point of SVG closure or cardiovascular death was similar between the no-touch and conventional techniques (7.8% versus 15%, *P*=0.11), whereas vein harvest site infection was more common in the former. In a meta-analysis of 4 trials, the no-touch technique was associated with a significantly lower 12-month SVG occlusion rate.[51] According to the recent European guidelines on myocardial revascularization, no-touch vein harvesting should be considered when an open technique is used (class IIa, level of evidence B).[22] Two ongoing trials, the IMPROVE-CABG trial (Impact of Perivascular Tissue on Endothelial Function in Coronary Artery Bypass Grafting; URL: http://www.clinicaltrials.gov. Unique identifier: NCT01834846) and the SWEDEGRAFT trial (Clinical Trial on No-Touch Vein Graft [NT-Graft] in Coronary Surgery; URL: http://www.clinicaltrials.gov. Unique identifier: NCT03501303) will give further insights on the outcomes of the no-touch technique compared with conventional harvesting. In the former, graft function will be evaluated by angiography at 6 months and 5 years, whereas in the latter, graft patency will be examined by CTA at 2 years.

Endoscopic Vein Harvesting

Endoscopic vein harvesting (EVH) was developed to reduce the rate of wound infection, pain, and hospital stay length. However, subgroup analysis of the ROOBY trial (Randomized On/Off Bypass) demonstrated worse 1-year graft patency and higher 1-year incidence of revascularization with EVH. Similarly, the PREVENT IV trial (Prevention of Vein Graft Failure Following Coronary Artery Bypass Surgery) showed higher rates of graft failure at 12 to 18 months and death, MI, or repeat revascularization at 3 years with EVH.[2,52] In contrast, 1 single-center RCT and 2 large observational studies showed no effect of EVH on MACE.[53–55] In the REGROUP trial (Randomized Endo-Vein Graft Prospective), 1150 patients were randomized to EVH or open-vein harvesting; the primary composite end point of death from any cause, nonfatal MI, and repeat revascularization at 2.8 years was similar between the 2 groups (13.9% versus 15.5%, *P*=0.47).[56] Outcomes were significantly influenced by operator expertise. The European guidelines recommend EVH, if performed by experienced surgeons, for reducing wound complications (class IIa, level of evidence A).[22]

On-Pump Versus Off-Pump

Earlier RCTs reported higher rates of graft patency for on-pump compared with off-pump techniques.[57,58] The ROOBY trial randomized 2203 patients to off-pump versus on-pump CABG. Follow-up angiography at 12 months demonstrated lower SVG FitzGibbon A patency rates (widely patent graft) in the off-pump group (72.7% versus 80.4%, *P*<0.001).[57] In the PROMISS trial (Prospective Randomized Comparison of Off-Pump and On-Pump Multi-Vessel Coronary Artery Bypass Surgery), SVG patency rates were higher at 5 weeks after surgery in patients who underwent on-pump CABG (95% versus 90%, *P*=0.03), although the advantage of on-pump CABG was lost after adjusting for heparin dose.[58] Two recent RCTs, the CORONARY trial (Coronary Artery Bypass Surgery Off or On Pump Revascularization Study) and the GOP-CABE trial (German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients) showed similar MACE with on- and off-pump CABG.[59,60] In the CRYSSA trial (Prevention of Coronary Artery Bypass Occlusion After Off-Pump Procedures), the combination of aspirin with clopidogrel significantly reduced the 12-month incidence of SVG occlusion compared with aspirin alone in patients who underwent off-pump CABG (7.4% versus 13.1%, *P*=0.04).[32]

In summary, although on-pump CABG has been associated with higher SVG patency rates, there is no difference in subsequent MACE when off-pump CABG is performed by experienced operators. Off-pump coronary anastomoses should be performed using an intracoronary shunt to minimize ischemia and blood loss. The 2018 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization favor off-pump CABG in patients with calcified aorta (class I, level of evidence B) and high-risk patients (class IIa, level of evidence B) if performed by experienced teams.[22]

Intraoperative Graft Storage Solutions

From harvesting until anastomosis, SVGs can be stored in dedicated solutions designed to preserve endothelial integrity. Normal saline (NS) mixed with heparin, and autologous heparinized blood (AHB) are traditionally used for storage. Although the detrimental effects of NS on the endothelium are well known, there are no published RCTs, with most data derived from in vitro studies.[61] Several buffered storage solutions have been developed, such as the University of Wisconsin preservation solution, histidine-tryptophan-ketoglutarate, TiProtec, He solution, and glutathione-ascorbic L-arginine (GALA). These solutions contain ions, antioxidants, and high-molecular-weight molecules that provide better ionic balance and a more physiological pH. In vitro studies showed superior functional and structural preservation with buffered preservation solutions.[61] The GALA solution includes glutathione, ascorbic acid, and L-arginine, which is a substrate

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of NO. It has been associated with greater cell integrity, calcium mobilization, and NO production compared with NA and AHB. Harskamp et al demonstrated lower SVG failure rates with the GALA solution compared with NS (graft-level OR, 0.63; $P<0.001$) or the AHB group (graft-level OR, 0.62; $P<0.001$) with a trend toward lower 5-year MACE.[62] The effect of L-arginine on SVG patency is being assessed in the randomized double-blind Biologically Modified Saphenous Vein Transplants for Improved CABG Outcomes trial (URL: http://www.clinicaltrials.gov. Unique identifier: NCT01313533). The performance of the GALA solution is currently evaluated by a European multicenter registry of patients who have undergone CABG (VASC [Treatment of Vascular Conduits With DuraGraft]; URL: http://www.clinicaltrials.gov. Unique identifier: NCT02922088) and a randomized double-blind multicenter trial (A Study to Evaluate the Use of SOMVC001 [GALA] Vascular Conduit Preservation Solution in Patients Undergoing CABG [STEPS] (GALA); URL: http://www.clinicaltrials.gov. Unique identifiers: NCT02272582/NCT02774824).

Graft Configuration

A SVG can be anastomosed to a single coronary artery or sequentially to >1 vessel. The major advantages of a sequential graft are revascularization of multiple target vessels with a single SVG and greater graft flow because of lower vascular resistance. However, occlusion at the proximal anastomosis may jeopardize flow to multiple coronary branches. The initial enthusiasm for sequential grafting was followed by skepticism after the results of the PREVENT IV trial (Project of Ex Vivo Vein Graft Engineering via Transfection IV), which reported higher 1-year (adjusted OR, 1.24 [95% CI, 1.03–1.48]) and 5-year (hazard ratio, 1.15 [95% CI, 1.00–1.31]) MACE rates for SVGs with multiple distal anastomoses.[63] In contrast, a meta-analysis by Li et al showed that midterm and long-term patency was better with sequential SVGs, and the patency of side-to-side anastomoses was better than end-to-side anastomoses for sequential SVGs.[64] SVGs can also be used as composite grafts: the SVG is anastomosed proximally with an in situ IMA, forming a composite Y-graft. The IMA is then anastomosed with the LAD and the SVG sequentially to other coronary branches. This technique has the theoretical advantage of minimal manipulation of the ascending aorta that is especially beneficial for patients with multivessel CAD and diffuse aortic atherosclerosis. Furthermore, the SVG is exposed to less circulatory stress than a conduit anastomosed to the ascending aorta and is continuously exposed to endothelium-protective substances such as NO released from the IMA. Last, the SVG length needed to reach the target vessel with a sequential anastomosis technique is shorter than the SVG length if the SVG originated from the aorta. However, the SVG can potentially steal flow from the IMA, threatening its patency. Gaudino et al reported that composite LIMA–SVG graft was perfectly patent in only 17 of 25 patients (72%) at a mean of 2.5±1.2 years after surgery,[65] although other studies demonstrated similar patency rates as total arterial composite grafts.[5] The randomized SAVE RITA trial (Saphenous Vein Versus Right Internal Thoracic Artery as a Y-Composite Graft) randomized 224 patients with multivessel CAD to SVG or right internal mammary artery Y-composite grafts from the LIMA, showing similar 5-year occlusion rates (4.3% for SVGs versus 2.4% for right internal mammary artery, $P<0.001$ for noninferiority).[5]

External Venous Support

The effect of external support devices on SVG remodeling was originally investigated >50 years ago. External support decreased vein dilatation and intimal hyperplasia in animal models. Two external stents have been tested in human studies, the eSVS mesh (Kipsbay Medical Inc, Minneapolis, MN) and the VEST device (Vascular Graft Solutions LD, Tel Aviv, Israel); however, they are not used clinically given disappointing clinical data. Two studies are ongoing: the multicenter, dual cohort (randomized and single vessel) eMESH 1 feasibility study (eMESH 1; URL: http://www.clinicaltrials.gov. Unique identifier: NCT01676376) and the VEST III trial (URL: http://www.clinicaltrials.gov. Unique identifier: NCT02511834).

Intraoperative Quality Control

Mean graft flow and pulsatility index (PI; difference between maximum and minimum flow divided by mean flow) assessment by transient-time flow measurement have been associated with SVG failure.[66] SVG flow 30 to 40 mL/min and PI <5 (ideally <3) have been proposed as criteria of optimal grafting.[66] A PI >5 should prompt revision of the anastomosis. The European revascularization guidelines recommend routine intraoperative graft flow measurement (class IIa, level of evidence B).

Preoperative and periprocedural strategies for prevention of SVG failure are summarized in Table 3.

MANAGEMENT OF EARLY POST-CABG SVG FAILURE

Approximately 3% to 12% of SVGs fail before hospital discharge.[67] Occlusion because of acute graft thrombosis, anastomotic stenosis, graft kinking or overstretching, and postoperative graft spasm are the most common causes of early graft failure. Routine coronary angiography after completion of CABG before chest closure revealed defects in 12% of (both arterial and vein) grafts that was repaired by a minor adjustment of the graft,

Table 3. Periprocedural Strategies to Reduce Saphenous Vein Graft Failure

Appropriately selected target vessel (>2 mm diameter with significant stenoses).
Grafting of functionally significant lesions only and of vessels with good distal targets.
Disease-free coronary segment at the anastomosis.
Buffered solutions for graft storage.
No-touch technique for graft harvesting.
Intraoperative graft flow measurement.
Perioperative aspirin administration (81–325 mg).
Dual antiplatelet therapy administration to patients undergoing off-pump coronary artery bypass grafting and in those with recent acute coronary syndrome. For patients with acute coronary syndrome, ticagrelor or prasugrel are preferred. Dual antiplatelet therapy may also be considered for on-pump coronary artery bypass grafting.
High-intensity statin administration before and early after coronary artery bypass grafting.

open chest PCI, or traditional surgical revision.[4] Clinically manifested early postoperative graft failure is associated with high mortality (≈15%) and should be treated with surgical revision or immediate PCI.

Differentiation between early graft failure and periprocedural (type 5) MI related to a native coronary artery can be challenging. Electrocardiography and imaging modalities cannot reliably identify early graft failure, with coronary angiography being mandatory for distinguishing graft-related and non–graft-related type 5 MI.[67] Perioperative cardiac troponin I elevation after CABG can help identify patients with early graft failure: cardiac troponin I >45× upper reference limit at 12 hours and >70× upper reference limit at 24 hours have been proposed as cutoff limits.[67] Emergent coronary angiography is proposed in patients with clear signs of acute myocardial ischemia, unexplained hemodynamic compromise immediately after surgery or low cardiac output syndrome, recurrent ventricular arrhythmias, persistent ischemic electrocardiographic changes indicating large area of risk, new ischemic wall motion abnormalities, and large cardiac troponin I elevation.[67] Coronary angiography and PCI are strongly indicated in cases of postoperative cardiogenic shock. PCI of occluded grafts may be associated with increased risk of perforation at the anastomotic sites. Redo CABG is generally preferred if the coronary anatomy is not suitable for PCI, in the presence of severe ischemia (ie, failure of the graft revascularizing the LAD territory or occlusion of several important grafts), and in cases of failure of LIMA artery or Y-graft to the left coronary arteries.[22,67]

Although PCI is preferred for most patients, the decision for performing reintervention and the choice of modality (PCI versus CABG) should be individualized after evaluation by a multidisciplinary heart team taking into consideration the feasibility of revascularization, area at risk, comorbidities, and clinical status (class I, level of evidence C).[22]

TREATMENT OF INTERMEDIATE SVG LESIONS

Intermediate SVG lesions (30% to 60% diameter stenosis) are found in 21% to 34% of patients with previous CABG.[68] In contrast with intermediate native coronary artery stenoses that progress slowly, intermediate SVG stenoses have high rates of progression to severe lesions or occlusion, frequently leading to ACS.

The VELETI pilot study (Moderate Vein Graft Lesion Stenting With the Taxus Stent and Intravascular Ultrasound) randomized 57 patients with intermediate SVG lesions (30% to 60% diameter stenosis) to stenting with a paclitaxel-eluting stent or no stenting. After 5 years, MACE related to the target SVG lesion tended to be lower in the paclitaxel-eluting stent group (17% versus 33%, P=0.146) because of lower target lesion revascularization (TLR, 13% versus 33%, P=0.072).[69] In the VELETI II trial, which included 125 patients after a median follow-up of 3.4 years, the incidence of MACE related to the target SVG lesion was not significantly different between drug-eluting stents (DES) and medically treated patients (10% versus 17%, P=0.21). The results were attributed to late (>2 year) restenosis after SVG stenting that resulted in loss of the early beneficial effect of stenting.[70]

Patients with intermediate SVG lesions are currently treated medically with control of diabetes, smoking cessation, and aggressive lipid lowering. Although mean low-density lipoprotein level was <70 mg/dL in VELETI II, SVG failure rates were high, suggesting that even more strict lipid control may be necessary. The ALPINE-SVG trial (Atherosclerosis Lesion Progression Intervention Using Niacin Extended Release in Saphenous Vein Grafts) examined the effect of extended-release niacin versus placebo on intermediate (30% to 60%) SVG lesions. It was terminated prematurely after randomizing 19 patients to each group and showed no significant difference in change of percent atheroma volume.[71]

TREATMENT OF LATE SVG FAILURE AND SEVERE SVG STENOSES

Reintervention is often needed after CABG because of bypass graft lesion development or progression of native atherosclerosis. SVG lesions are most often treated with PCI that carries 2 major limitations: (1) distal embolization and no-reflow in the acute phase, and (2) high rates of restenosis and SVG disease progression during follow-up.[72]

Modality of Revascularization, Selection of Target Vessel

Redo CABG is infrequently performed, because patients who undergo redo CABG are older and have more co-

morbidities and higher mortality than patients who undergo initial CABG. In an analysis from the National Inpatient Sample, redo CABG was associated with higher in-hospital MACCE (2.2% versus 14%, $P<0.001$), in-hospital all-cause mortality (0.9% versus 4.2%, $P<0.001$), stroke (0.4% versus 3.7%, $P<0.001$), and all-cause bleeding (0.6% versus 2%, $P<0.001$) compared with PCI.[73] The frequency of redo CABG in the United States increased between 2010 and 2016 (1.2% to 2.2% of all CABG surgeries), but in-hospital mortality did not change, although redo CABG was performed in sicker patients with more comorbidities.[74]

In the patient choice subgroup of the AWESOME registry (Angina With Extremely Serious Operative Mortality Evaluation), patients with previous CABG with medically refractory myocardial ischemia plus 1 more high-risk factor selected redo CABG or PCI. The 36-month survival was higher in the PCI group (86% versus 65%, $P<0.01$).[75] Harskamp et al reported higher target vessel revascularization (TVR, 31% versus 8%, $P=0.009$) and TLR (21% versus 3%, $P=0.008$) and similar composite of all-cause death, MI, or TVR (58% versus 51%, $P=0.51$) with PCI versus redo CABG during a median follow-up of 3.9 years. Most (81%) patients with PCI received bare metal stents (BMSs).[76]

PCI is, therefore, preferred in patients with previous CABG requiring revascularization, with redo CABG performed in patients unsuitable for PCI, such as patients with extensively diseased or occluded bypass grafts and diffuse native vessel disease, especially in the absence of a patent IMA to the LAD.[22] IMA should be the conduit of choice during reoperation if it has not been used previously. Additional factors that favor redo CABG include reduced ejection fraction, failure of multiple SVGs, and late (>5 years) SVG stenosis. Factors that favor PCI include poor targets for grafting (see "Graft Configuration"), old age, ACS, diabetes, dementia, malignancy, and collagen disorders.[73]

In cases of SVG failure, PCI can be performed to either the culprit SVG or the corresponding native vessel. Although no RCTs have compared the outcomes of these strategies, observational studies have shown better short- and long-term outcomes with native vessel PCI.[7,8] In the 2018 ESC/EACTS guidelines on myocardial revascularization, PCI to a native vessel is preferred over bypass graft PCI (class IIa, level of evidence C). Native vessel recanalization is not always feasible, because native vessel lesions are often complex, with chronic total occlusions (CTOs) encountered in up to 89% of patients with previous CABG, in part because of acceleration of native coronary atherosclerosis after CABG.[77] Specialized equipment and expertise are required for such interventions; hence, ad hoc PCI of the native coronary artery lesion in the setting of acute SVG failure causing ACS is not always feasible. A strategy of staged revascularization has been proposed for such cases: the culprit SVG lesion is treated first, followed by PCI of the corresponding native coronary artery weeks or months later.[78] SVGs can be used for retrograde crossing of native coronary artery CTOs with high success rates (Figure 2).[79] The ongoing PROCTOR RCT (Percutaneous Coronary Intervention of Native Coronary Artery Versus Venous Bypass Graft in Patients With Prior CABG; URL: http://www.clinicaltrials.gov. Unique identifier: NCT03805048) is evaluating the clinical and angiographic outcomes of native vessel PCI compared with SVG PCI in patients with a failing SVG and a clinical indication for revascularization. A practical algorithm for the management of patients with late SVG failure is illustrated in Figure 3.[72]

As continued flow through the SVG after PCI of the corresponding native coronary artery lesion may lead to stent thrombosis because of competitive flow, SVG occlusion (with coiling or an Amplatzer vascular plug) is often performed with favorable outcomes.[80]

Balloon Angioplasty Versus BMS Versus DES

Although BMS implantation did not reduce angiographic restenosis compared with balloon angioplasty, it reduced MACE and TVR rates; thus, stent implantation is the standard of care for SVG PCI.[81] Seven RCTs have compared the outcomes of BMS versus DES in SVG interventions, with conflicting findings (Table 4). The most recent RCT, the DIVA trial (Drug-Eluting Stents Versus Bare Metal Stents in Saphenous Vein Graft Angioplasty), which used contemporary second-generation DES in most (88%) patients randomized to DES, reported similar target vessel failure rates with DES versus BMS (37% versus 34%, $P=0.44$) during a median follow-up of 2.7 years.[82] A meta-analysis of 6 RCTs showed similar cardiovascular mortality (risk ratio [RR], 1.00 [0.64–1.57], $P=0.99$), all-cause mortality (RR, 1.11 [0.77–1.62], $P=0.57$), MI (RR, 0.74 [0.48–1.16], $P=0.19$), stent thrombosis (RR, 1.06 [0.42–2.65], $P=0.90$), and TVR (RR, 0.73 [0.48–1.11], $P=0.14$) in patients who received DES versus BMS in SVG lesions.[83]

Technical Aspects of SVG PCI and Periprocedural Pharmacotherapy

SVG lesions have high plaque burden predisposing to distal embolism of friable atheromatous material during PCI. The incidence of no-reflow during SVG PCI varies from 3.4% to 18.5% but is substantially higher than that of native coronary artery PCI.[7] Compared with patients who had good antegrade flow after SVG PCI, patients with no-reflow had higher risk of MI (14% versus 55%, $P=0.036$) and death (13% versus 52%, $P=0.039$) during 5-year follow-up.[84] Multiple strategies have been developed for the prevention of no-reflow and periprocedural MI.

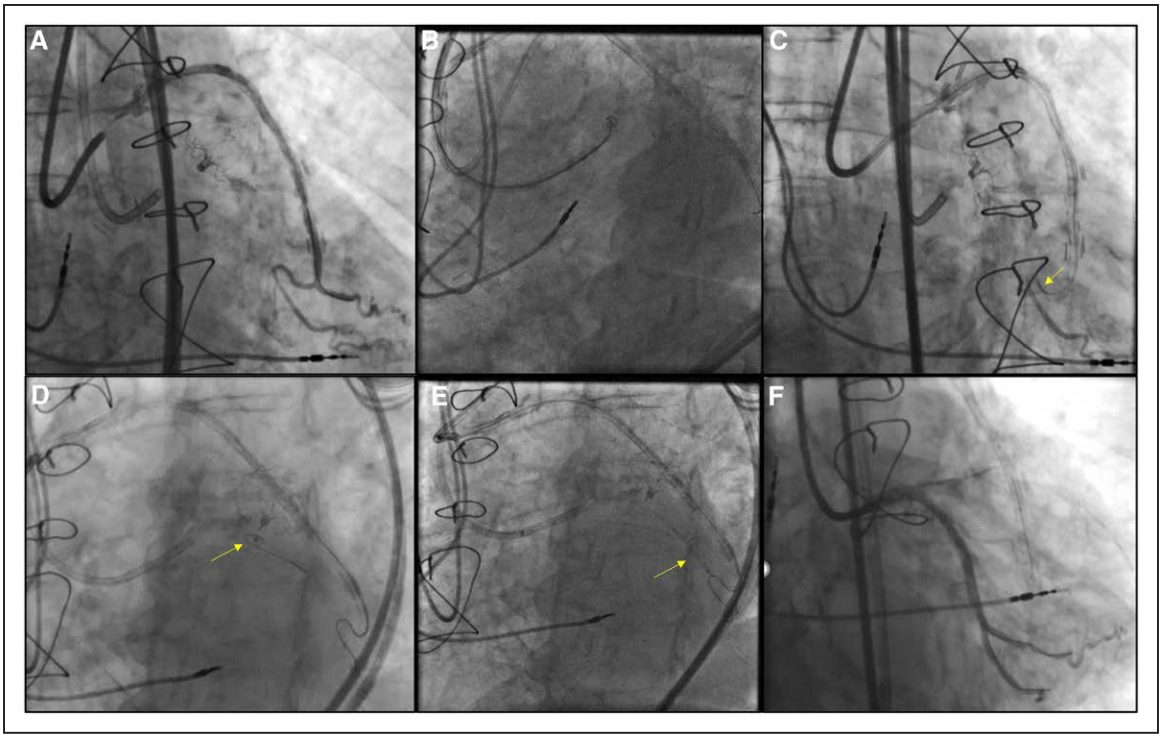

Figure 2. Chronic total occlusion percutaneous coronary intervention in a patient with prior coronary artery bypass graft surgery. **A**, An 85-year-old woman with coronary artery bypass graft surgery 20 years previously, presented with recurrent failure of a saphenous vein graft (SVG) to the first obtuse marginal branch, requiring multiple percutaneous coronary interventions (PCIs). Engagement of the SVG was challenging because of protrusion of a previous stent into the aorta. The left main had an ostial chronic total occlusion. A decision was made to attempt left main and circumflex PCI. **B**, Antegrade wire escalation failed. **C**, A guidewire and Caravel microcatheter was advanced retrogradely to the first obtuse marginal branch (arrow). **D**, Guide catheter extension reverse controlled antegrade and retrograde tracking was performed following by externalization of a retrograde guide wire. **E**, After predilatation, the circumflex and left main were successfully stented. **F**, Successful restoration of Thrombolysis in Myocardial Infarction (TIMI) III flow to the left main and first obtuse marginal.

Embolic Protection Devices

Embolic protection devices (EPDs) are the only prevention strategy for no-reflow evaluated in RCTs (Figure 4). Only 2 EPDs are currently commercially available in the United States: the FilterWireEZ (Boston Scientific, Natick, MA) and the SpiderFx (Medtronic, Santa Rosa, CA). Both filters were compared in RCTs with each other and with the GuardWire, a distal EPD, which had been shown to reduce MI and no-reflow in SVG interventions.[85] In the

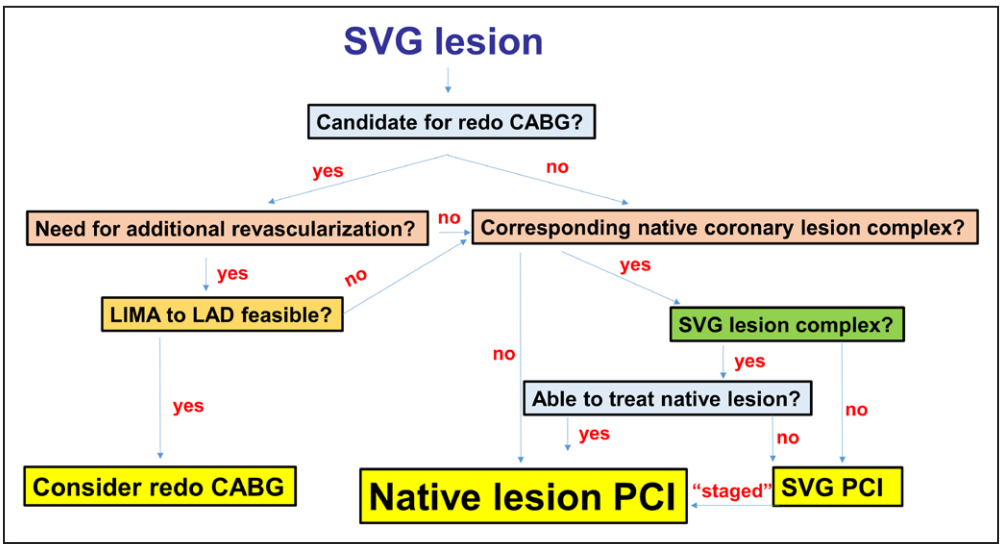

Figure 3. How to manage late SVG failure.
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Table 4. Randomized Controlled Trials Comparing Drug-Eluting Stents With Bare Metal Stents in Patients Undergoing Saphenous Vein Graft Interventions

Name of study	Year published	No. of patients	Primary end point	Event rate (%)		*P* value
				Drug-eluting stent	Bare metal stent	
RRISC	2006	75	6-mo angiographic restenosis	13.6	32.6	0.031
DELAYED RRISC	2007	75	Major adverse cardiac events (all-cause mortality, MI, TVR) at 32 mo	58	41	0.130
BASKET*	2020	47	Major adverse cardiac events (cardiac death, MI, symptom-driven TVR) at 18 mo	21	62	0.007
SOS	2009	80	12-mo angiographic restenosis	9	51	<0.001
SOS (long-term follow-up)	2010	80	Target vessel failure at 35 mo	34	72	0.001
ISAR-CABG	2011	610	12-mo composite of death, MI, and target lesion revascularization	15	22	0.02
ISAR-CABG (5-y outcomes)	2018	610	60-mo composite of death, MI, and target lesion revascularization	55.5	53.6	0.89
BASKET-SAVAGE	2016	173	36-mo composite of cardiac death, MI, and TVR	12.4	29.8	0.0012
ADEPT	2018	57	Late lumen loss at 6 mo	0.47±0.95 mm	0.53±1.09 mm	0.86
DIVA	2018	597	2.7-y median follow-up—composite of cardiac death, target vessel MI, and TVR	37	34	0.44

ADEPT indicates Comparison between the STENTYS self-apposing bare metal and paclitaxel-eluting coronary stents for the treatment of saphenous vein grafts; BASKET, Bare-Metal Stents for Saphenous Vein Graft Interventions; BASKET-SAVAGE, Study to Test the Efficacy and Safety of Drug Eluting vs. Bare-Metal Stents for Saphenous Vein Graft Interventions; DELAYED RRISC, Death and Events at Long-Term Follow-Up Analysis: Extended Duration of the Reduction of Restenosis in Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent; DIVA, Drug-Eluting Stents Versus Bare Metal Stents in Saphenous Vein Graft Angioplasty; ISAR-CABG, Efficacy Study of Drug-Eluting and Bare Metal Stents in Bypass Graft Lesions; MI, myocardial infarction; RRISC, Reduction of Restenosis in Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent; SOS, Stenting of Saphenous Vein Grafts; and TVR, target vessel revascularization.

*The BASKET trial was not exclusively dedicated to saphenous vein graft interventions.

FIRE RCT (FilterWire EX Randomized Evaluation), which included 651 patients undergoing SVG-PCI, the FilterWire was noninferior to the GuardWire with respect to 30-day MACE rates (9.9% of FilterWire EX group versus 11.6% of GuardWire group, *P*=0.0008 for noninferiority).[86] Likewise, the SpiderFX filter was compared with the FilterWire and GuardWire in 700 patients in the SPIDER RCT (Saphenous Vein Graft Protection in a Distal Embolic Protection Randomized Trial) and had similar 30-day MACE rates (9.1% versus 8.4%; *P*=0.01 for noninferiority).[87] The 2018 ESC/EACTS guidelines on myocardial revascularization[22] downgraded the indication of EPD use in SVG PCI to class IIa, level of evidence B, on the basis of observational studies.[88] Although the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (SCAI) guidelines give a class I (level of evidence B) recommendation for the use of EPDs in SVG PCI when technically feasible, EPDs remain underused. They were used in 21% of the SVG PCIs in the United States, likely because of technical difficulties, risk of injury to the distal vessel, and additional time and cost.[89]

Periprocedural Pharmacotherapy

Several medications have been used for the prevention and treatment of no reflow. High doses of intragraft adenosine (2000–4000 μg), nitroprusside (50–1000 μg), and calcium channel blockers may prevent and reverse slow flow and no reflow. In the randomized, controlled VAPOR trial (Vasodilator Prevention of No-Reflow), intragraft verapamil reduced no-reflow rates versus placebo (0% versus 33%, *P*=0.016).[90] In a study by Fischell et al, pretreatment with intragraft nicardipine (200–300 μg) resulted in a low incidence of no/slow-reflow (2.4%) and in-hospital MACE (4.4%).[91] Nicardipine is often preferred over other vasodilators because it has prolonged duration of action and less hypotensive effect.[72] Vasodilators can be used as adjunct of or substitute for EPD, if EPDs cannot be used. Glycoprotein IIb/IIIa receptor inhibitors have been associated with higher mortality in SVG PCI and should not be routinely used.[92]

Excimer Laser Coronary Angioplasty

Excimer laser coronary angioplasty (ELCA) may result in "vaporization" of thrombus and plaque components, potentially reducing the risk for distal embolization, but also carries the potential risk of vessel dissection and perforation, especially in angulated SVGs.

In the CORAL trial (Coronary Graft Results Following Atherectomy With Laser), 98 consecutive nonrandomized patients with stenotic SVGs underwent atherectomy with use of excimer laser without EPD use. Patients included in the CORAL registry had a slightly higher, but not statistically significantly, rate of no reflow (5.1% versus 3%, *P*=0.37) compared with the patients included in the EPD group of SAFER (Saphenous Vein Graft Angioplasty Free of Emboli Randomized

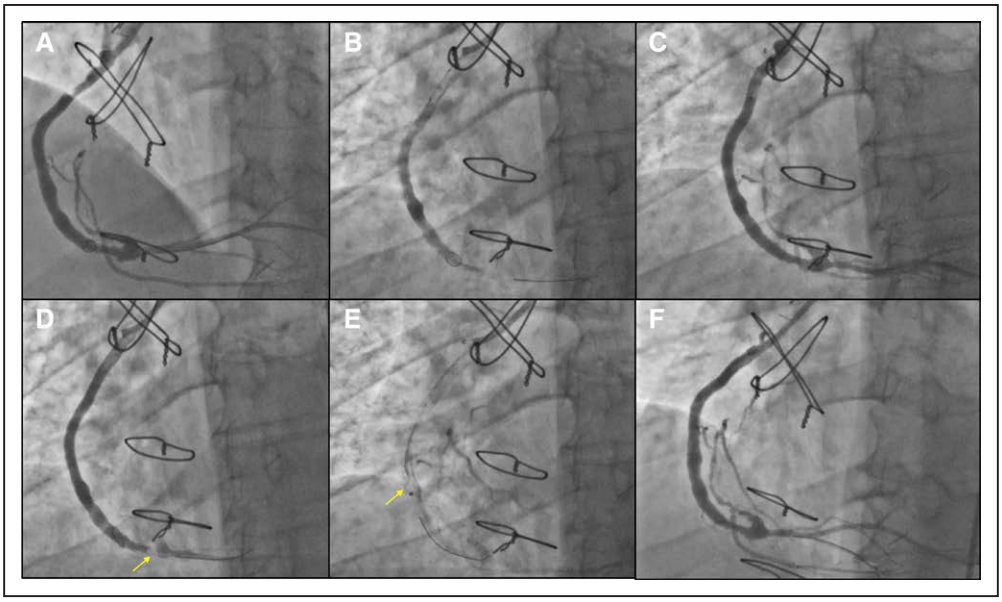

Figure 4. Utilization of embolic protection devices in saphenous vein graft interventions.
A, A 60-year-old patient presented with unstable angina caused by a lesion in the proximal segment of an 11-year-old saphenous vein graft. **B**, A FilterWire was advanced at the distal part of the graft, followed by dilation with a 3.0 × 12 mm balloon that caused slow-flow. **C**, After FilterWire removal, Thrombolysis in Myocardial Infarction (TIMI) III flow was restored. However, the proximal graft lesion required further treatment. **D,** A second FilterWire was placed. A 3.5 × 23 mm drug-eluting stent was deployed at 16 atmospheres, resulting in debris migration that was captured by the FilterWire (arrow). **E**, The second FilterWire was removed, and aspiration was performed with an Export catheter (arrow). **F**, Final result with TIMI III flow in the target saphenous vein graft.

Trial).[86,93] In a prospective case-control registry, ELCA was compared with FilterWireEZ and the SpiderFx in patients with a non–ST-segment–elevation acute coronary event undergoing SVG PCI. ELCA was associated with a lower incidence of angiographic microvascular obstruction (13% versus 32%, *P*=0.09) and type IVa MI (21% versus 49%, *P*=0.04) compared with EPDs.[94]

Randomized trials of ELCA in SVG PCI are missing. ELCA has been approved by the US Food and Drug Administration for the treatment of multifocal, thrombotic SVG lesions, but there are no guideline recommendations for its use in SVG PCI.

Direct Stenting and Stent Size

Direct stenting could trap debris, reduce distal embolization from repeated balloon inflations, and cause less extensive SVG injury that predisposes to subsequent stent thrombosis/restenosis. Iakovou et al reported that aggressive stent expansion in SVG lesions was associated with higher incidence of MI (26% versus 8%, *P*=0.003) and similar TVR (31% versus 26%, *P*=0.3) at 1 year.[95] In a study by Leborgne et al of 527 patients who underwent SVG PCI, direct stenting was associated with lower Creatine Kinase MB release (9.5% versus 19.6%, *P*<0.01) and lower TLR at 1 year (OR, 0.47; *P*=0.01) compared with conventional angioplasty.[96] In a substudy of the DIVA trial, compared with the stent-only group, patients in the stent-balloon group were more likely to have definite stent thrombosis (1% versus 5%, *P*=0.009), definite/probable stent thrombosis (5% versus 11%, *P*=0.009), and target vessel MI (8% versus 14%, *P*=0.023).[97] Undersized stents have also been used to reduce distal embolization. Hong et al demonstrated that the use of undersized DES in SVG lesions was associated with lower risk of creatine kinase-MB elevation after PCI with similar 1-year TLR and TVR.[98]

LATE SVG FAILURE: MANAGEMENT OF ACUTE AND CHRONIC TOTAL SVG OCCLUSIONS

PCI of acutely occluded SVGs has poor outcomes. In 2 large cohort studies of patients with acute MI, restoration of Thrombolysis in Myocardial Infarction (TIMI) III flow flow rates were lower for acutely occluded SVGs compared with native vessels (70.2% versus 95%, *P*=0.03 and 80.7% versus 93.6%, *P*=0.0001).[99,100] In-hospital mortality was higher among patients who underwent SVG PCI in both studies. Although the outcomes of SVG PCI remain suboptimal, recanalization of the corresponding native vessel can be technically challenging and carries risk of complications; thus, a strategy of staged revascularization is appealing.[78]

SVG CTO PCI has been associated with low success and high repeat revascularization rates and should be avoided according to the ACCF/AHA/SCAI 2011 guidelines (class III harm, level of evidence C).[90] However, in highly selected cases with no other options, PCI of SVG CTOs may provide clinical benefit. In a study of

28 SVG CTO PCIs in 27 patients, technical success was 79%, with 2 intraprocedural Q-wave MIs (7%). After a mean follow-up of 596±429 days, 81% of patients who underwent successful PCI had angina relief with acceptable TVR rate (9.5%).[101]

Chronically totally occluded SVGs can be used as retrograde conduits for the revascularization of native vessel CTOs. In a recent study, technical success (77% versus 87%, for occluded and patent SVGs respectively, P=0.11) and in-hospital MACE (6.4% versus 8.4%, P=0.1) were similar in cases where occluded SVGs were used for retrograde crossing compared with cases where retrograde crossing was performed through patent SVGs.[79]

CONCLUSIONS

SVGs remain the most commonly used grafts during CABG. Despite advances in surgical techniques and pharmacotherapy, SVG failure rates are high, often requiring subsequent interventions. SVG PCI is challenging. Periprocedural complications and restenosis remain higher compared with native coronary artery PCI, emphasizing the importance of prevention and favoring PCI of the corresponding native vessel if technically feasible. Newer potent antiplatelet agents and lipid-lowering agents may delay the rapid progression of SVG atherosclerosis and reduce SVG failure rates.

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