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REVIEW

Management and Prevention of Saphenous Vein Graft Failure: A Review

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ABSTRACT

Coronary artery bypass grafting (CABG) remains a vital treatment for patients with multivessel coronary artery disease (CAD), especially diabetics. The long-term benefit of the internal thoracic artery graft is well established and remains the gold standard for revascularization of severe CAD. It is not always possible to achieve complete revascularization through arterial grafts, necessitating the use of saphenous vein grafts (SVG). Unfortunately, SVGs do not have the same longevity, and their failure is associated with significant adverse cardiac outcomes and mortality. This paper reviews the pathogenesis of SVG failure, highlighting the difference between early, intermediate, and late failure. It also addresses the different surgical techniques that affect the incidence of SVG failure, as well as the medical and percutaneous prevention and treatment options in contemporary practice.

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INTRODUCTION

Coronary artery bypass grafting (CABG) remains the gold standard treatment for revascularization of complex multivessel coronary artery disease (CAD) and has proven long-term survival benefits [1, 2] especially in patients with diabetes [3–5]. Despite increasing advances in percutaneous coronary intervention (PCI), over 400,000 patients per year in the US still undergo CABG [6]. The main shortcoming of CABG is saphenous vein graft (SVG) failure, which is associated with adverse cardiac events, such as recurrent angina, need for repeated coronary revascularization, myocardial infarction, and death [7, 8].

The use of an internal thoracic artery (ITA) graft has proven prognostic benefits [9] with its patency at 10 years having been quoted as 85–91% [9, 10]. In comparison, rates of SVG failure at 1-year post surgery have been quoted at between 10% and 25% [10, 11]. From 1 to 5 years a further 5% to 10% SVGs will close, and from years 6 to 10 an additional 20–25% will fail, [12] meaning that at 10 years SVG patency rates are approximately 50%, with only half of these atherosclerosis free [13].

Greater use of multiple arterial grafts during CABG has repeatedly been shown to improve

event-free survival of patients undergoing multivessel coronary artery bypass grafting [14–19] including the use of the radial artery as a second arterial graft [20, 21]. Despite this data and support from guideline recommendations, the use of multiple arterial grafts during surgical revascularization has not translated into clinical practice. Only 9% of CABG in North America is performed with multiple arterial grafting [22], meaning the SVG is still the most commonly used conduit in conventional CABG in North America. Interesting a recent RCT comparing single and bilateral internal-thoracic-artery in 3102 patients with there being no difference in mortality or the rates of cardiovascular events at 5 years of follow-up. There were more sternal wound complications with bilateral internal thoracic artery grafting than with single internal thoracic artery grafting. [23].

Treatment of occluded SVGs is challenging, and thus preventing their obstruction is of utmost importance [24]. Here we discuss the known pathogenesis of SVG failure and critically review the medical treatments for prevention of SVG failure.

This article does not contain any new studies with human or animal subjects performed by any of the authors.

PATHOGENESIS

SVG failure can be divided conceptually into three phases: early, intermediate, and late [25]. Early failure (less than 1 month) is primarily due to technical failure or thrombosis, generally at the site of anastomosis. Several predisposing factors can trigger this through graft endothelial injury. Initial harvesting of the vein disrupts the vasa vasorum and adventitia causing hypoxia in the vessel wall, promoting platelet adhesion and thrombosis [26]. Intraoperative assessment of graft integrity by high pressure distension can further stress the wall [27, 28] exposing the media to proinflammatory and procoagulant reactions, even before graft aortocoronary implantation [29, 30]. Implantation exposes the vein to arterial pressure increasing venous diameter, turbulent blood flow and shear stress [27], which further damages the endothelial layer causing decreased levels of nitric oxide, promoting vasospasm and reducing vessel patency [31].

Intermediate (1 month–1 year) graft failure is caused primarily by progressive neointimal hyperplasia secondary to exposure to arterial pressure and is thought to affect all SVGs to varying degrees [32]. Arterial blood flow damages the endothelium resulting in release of growth factors and cytokines causing platelets and activated macrophages migration, and proliferation of smooth muscle cells. The migrated smooth muscle cells release extracellular matrix resulting in a reduction in intimal cellularity [33]. Reduced levels of endothelial nitric oxide, prostaglandins and adenosine, further contribute to smooth muscle proliferation [34–36]. Over time continued smooth muscle cell and fibroblast migration and proliferation cause extracellular matrix deposition and fibrotic change leading to development of neointimal hyperplasia, which results in luminal loss and a predisposition towards graft atherosclerosis [37].

Late (beyond 1 year) graft failure is primarily due to progressive atherosclerosis, which occurs over the already injured endothelium. Compared to native coronary artery atheroma, SVG atherosclerosis is more diffuse and concentric, yet less calcified [25]. In addition, SVG are not capable of positive remodelling [38], meaning long-term atherosclerotic lesions are often complicated by aneurysmal dilatation and associated with risk of thrombosis [39]. SVG atherosclerosis occurs at two main sites, aorto-ostial or the main shaft of the graft, with shaft lesions associated with increased rates of death and myocardial infarction, having higher rates of plaque rupture and no-reflow [40, 41].

FACTORS PREDISPOSING TO SVG FAILURE

Factors linked to SVG failure include patient-related, graft related and surgical related. Patient-related include age, female gender, left ventricular dysfunction, renal insufficiency,

diabetes, as well as atherosclerotic risk factors [13, 42–45]. The graft-related factors include the coronary flow and the specific artery grafted. Reduced flow has been associated with greater neointimal proliferation in SVG and failure [46] and is dependent on inflow, graft diameter, presence of any focal stenoses and the size of the distal perfusion bed. SVGs to the left anterior descending artery have the best patency, followed by those to diagonals, circumflex branches, and the posterior descending artery, with grafts to the main right coronary artery least likely to have long term patency [47, 48].

Surgical factors that predispose patients to thrombosis include graft kinking, size mismatch between the graft and artery, poor distal runoff, and small target vessel diameter. Several surgical techniques have been shown to influence SVG patency.

No Touch Technique

Intra-operative manual disruption, as well as the use of hydrostatic dilatation can promote endothelium thrombus within the graft [49]. Souza et al. in 1996 developed the "no-touch" SVG harvesting, which involved removing the pedicled SVG with the perivascular tissue intact, thus avoiding direct contact and thus manual distension of the vein. This demonstrated improved graft patency and less neointimal hyperplasia compared with the standard harvesting technique [50, 51]. More recent randomised work has suggested that compared with conventional harvesting, the use of no touch harvesting, results in less intra-operative vascular smooth muscle cell activation, suggesting less likelihood of developing neointimal hyperplasia [52]. Other studies have even suggested that the use of no touch harvesting confers a significantly higher long term (>15 years) patency than conventional technique [53].

On-Pump and Off-Pump Surgery

A number of studies have compared on-pump and off-pump CABG in terms of clinical outcomes and graft patency. Off-pump CABG involves surgery without a heart–lung machine or cardioplegia. In contrast during on-pump surgery the heart is motionless and empty, and the veins are unpressurized and contracted, which may create a more favourable condition for vascular anastomoses. Although several small initial studies found that after 1 year there was no difference in graft patency or clinical outcomes [54–57], the larger randomized on/off bypass (ROOBY) trial suggested the off-pump group had worse 1-year composite outcomes (9.9% vs. 7.4%, $P = 0.04$) and poorer graft patency (82.6% vs. 87.8%, $P < 0.01$) [58]. These results have also been reported in other randomized studies [59, 60], as well as meta-analyses [61, 62]. The poorer graft patency rates in off pump CABG could be explained by a relative hypercoaguability compared with on-pump surgery, as cardiopulmonary bypass induces platelet dysfunction and coagulopathy which may be desirable in promoting SVG patency. Mannacio et al. conducted a single-centre prospective RCT study which randomized 300 patients undergoing off-pump CABG to either aspirin 100 mg ($n = 150$) or aspirin 100 mg plus clopidogrel ($n = 150$). Graft patency was assessed by CTA. DAPT use was associated with a reduced SVG occlusion rate (7.4% vs. 13.1%; $P = 0.04$) [115]. Current guidelines recommend 1 year of DAPT after off pump CABG to improve SVG patency [170].

Sequential and Composite Grafting

The most basic SVG configuration is a single graft, which is composed of a single distal anastomosis for every proximal anastomosis. In contrast, sequential and composite grafting involves more than one distal anastomosis for every proximal anastomosis allowing for more complete revascularisation. The sequential anastomosis was first described by both Flemma and Bartley [63, 64] which, was initially termed the "snake" operation [65] with longitudinal side-to-side "snaking" grafts between recipient arteries. The major advantage of the sequential anastomosis is the larger combined perfusion bed resulting in lower coronary vascular resistance and thus higher flow velocity compared

to single grafts [65, 66]. The composite graft has either a Y- or T-end-to-side graft constructed to allow perfusion of more than one distal target using a single graft. Composite grafts were first described in arterial grafts [67], but may also be constructed with SVG. The composite graft anastomosis must be performed accurately as an error can potentially threaten both distal outflows. Furthermore, there is risk of steal from one territory to another in the case of unbalanced flows.

The use of grafts with multiple distal anastomoses allows for a more complete revascularization in patients with multi-vessel CAD by using the limited SVG material more efficiently. Initially the use of multiple distal target SVGs was met with optimism, with early data suggesting that clinical outcomes were comparable or better than single distal target SVGs [63, 65, 66]. However, more recent larger data has suggested that patients who received a composite SVG were more likely to have graft failure and had a trend towards increased death, MI, or repeat revascularization in the 5 years after surgery [68]. This is particularly true in diabetics where both the end-to-side and side--to-side anastomosis may insert into a poor-quality target vessel [69, 70].

Compression Therapy

The luminal diameter of SVG are generally much larger than the coronary artery to which they insert, potentially creating a mismatch in blood flow. This can result in stasis and abnormal flow currents within the vein, damaging the vessel and potentially leading to thrombus formation. In addition, because veins lack the muscular wall that is seen in arteries, exposure to arterial pressure damages SVG resulting in further dilation and neointimal hyperplasia. External compression of SVGs prevents dilation and promotes down-sizing, which has been shown to encourage more arterial like healing and help reduce intimal hyperplasia [71, 72]. External compression can be achieved by a support device implanted during surgery. The eSVS® mesh (Kips Bay Medical, Inc., Minneapolis, MN, USA) is a flexible extravascular nickel-titanium mesh, with early work suggesting that it reinforces SVGs; improving healing with less endothelial injury and neointimal hyperplasia formation compared to unsupported grafts [71, 72]. Recent non-randomised studies have suggested a clinical benefit. Genoni et al. reported safe application of the device in 20 patients who received the mesh supporting the SVG to the right coronary artery only. The patency of the grafts was assessed after 5 days by computerized tomography angiography (CTA), with a 95% success rate [73]. Klima et al. reported the 7-month follow-up in 12 patients who received an on-pump non-sequential eSVS® mesh. The CTA patency rate was 92% [74]. Inderbitzin et al. reported the 1-year follow-up in 19 of 22 surviving patients who had received the mesh with overall 1-year CTA patency rate of 21 eSVS® meshed SVGs being 76% [75]. Larger randomised studies with longer term follow-up are needed however before more widespread clinical adoption of such devices.

ASSESSMENT FOR SVG PATENCY

Routine assessment for SVG failure is not recommended by current guidelines, and thus rates of occlusion are only studied in clinical trials or in clinically driven follow-up. Assessment of SVG patency is generally performed via invasive coronary angiography (ICA), which in addition to being more technically difficult compared to native coronaries, also has rates of complications three times higher [76]. More recently, the use of coronary CTA has shown much promise in this regard (Fig. 1). Studies from over a decade ago show that evaluation of coronary bypass grafts by CTA is highly accurate in predicting the findings seen on ICA [77–80] with a meta-analysis, of 16- and 64-slice CTAs quoting a sensitivity of 98% and specificity of 97% for graft stenosis or occlusion [81]. Newer generation of CT scanners undoubtedly increase diagnostic accuracy, with the use of CTA for post CABG assessment now recommended in clinical guidelines [82]. Limitations of CTA assessment including artifact from surgical clips and difficulty in assessing distal anastomoses

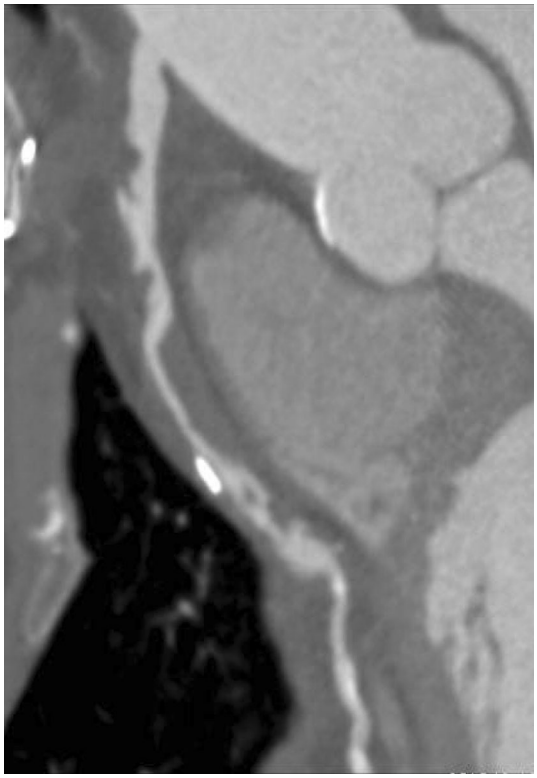

Fig. 1 Spiral thrombus within SVG graft

inserted into heavily calcified native vessels [83].

MEDICAL MANAGEMENT FOR PREVENTION OF SVG FAILURE

Hypercoagulable states post CABG increase thrombosis and lower overall graft patency rates [84], thus necessitating the need for therapy aimed at reducing thrombotic risk. There have been several studies that have assessed the use of various pharmacologic agents.

Aspirin

Very early studies assessing the use of aspirin (acetylsalicylic acid) for SVG patency were not encouraging. Pantley et al. in 1979 assessed 50 patients who were randomized to 24 controls, 13 receiving dual antiplatelet therapy (DAPT) with aspirin and dipyridamole, and 13 receiving warfarin [85]. Treatment began on the third post-operative day. Six months after surgery, all patients underwent ICA to assess graft patency. Twenty-seven of 33 grafts (82%) with DAPT and 29 of 37 grafts (78%) with warfarin ($P < 0.5$) were patent. The overall conclusion was that postoperative treatment either with DAPT or with warfarin failed to improve the patency. McEnany et al. in 1982 randomized trial compared warfarin, aspirin, and placebo treatment in post-CABG patients [86]. From an initial group of 216 patients, SVG patency was determined in 111 patients (220 grafts) from 1 to 47 months postoperatively. There was a trend toward better cumulative graft patency in patients given warfarin, but the results did not achieve statistical significance. In 1984 Chesebro et al. compared the combination of aspirin and dipyridamole to placebo in 407 patients with treatment beginning as early as 7 h post--surgery [87]. ICA at 1 month showed SVG patency significantly higher in the antiplatelet therapy cohort (98% vs. 90%, aspirin and dipyridamole vs placebo; $P < 0.0001$). Longer term follow-up of the same study also showed a significant difference in patency (89% vs. 77%, aspirin and dipyridamole vs placebo; $P < 0.0001$), suggesting that DAPT prevented late SVG occlusions in those patients whose grafts had been patent at 1 month (6% vs. 14% late occlusion rate, aspirin and dipyridamole vs. placebo; $P = 0.02$) [32]. The Veterans Administration Cooperative Study compared the use of different aspirin regimens in 772 CABG patients [88]. They administered either (1) aspirin, 325 mg daily, (2) aspirin, 325 mg three times daily, (3) aspirin plus dipyridamole (325 mg and 75 mg, three times daily), (4) sulfinpyrazone (267 mg three times daily), or (5) placebo (three times daily). Medications were taken to for 1 year. At 60 days post-surgery, 555 patients (1781 grafts) had undergone ICA, illustrating the following graft patency rates: aspirin once daily 93.5%; aspirin three times daily 92.3%; aspirin and dipyridamole three times daily 91.9%; sulfinpyrazone 90.2%. All aspirin-containing therapeutic regimens improved ($P < 0.05$) graft patency compared with placebo (85.2%). Operative mortality was 2.3%, without significant differences among treatment groups. Overall conclusions were early SVG patency was

improved after CABG with all aspirin-containing drug regimens.

In addition to graft patency, the use of aspirin has also been shown to reduce in-hospital mortality without an associated increase in hemorrhage-related risks [89–91]. Consequently, its use before CABG surgery is recommended in both European and American Guidelines [92, 93].

Clopidogrel

Clopidogrel is a thienopyridine-class antiplatelet that inhibits the platelet $P2Y_{12}$ adenosine diphosphate receptor and has been the mainstay of DAPT therapy for over 10 years. The benefit of DAPT in acute coronary syndrome (ACS) is well established [100–102], with National guidelines recommend their use on presentation [99, 103, 104, 107]. This has been reflected in clinical practice with the Global Registry of Acute Coronary Events (GRACE) and GRACE2 registries reporting a significant increase in early use in patients with ACS [94, 105, 106]. This is despite the fact that 7–11% of ACS patients will subsequently require CABG [94, 95] and pre-surgery use of DAPT is associated with increased risk of postoperative death, reoperations for bleeding, blood loss, and need of blood transfusions [96]. Consequently, for ACS patients who subsequently need CABG, it is recommended to stop the second antiplatelet agent 5–7 days prior to CABG if possible [97–99]. It is recommended that DAPT should be restarted after CABG when safe [99, 104, 107]. However, the risk of bleeding remains, leading to variability in DAPT resumption post CABG [108–110].

There is a paucity of evidence in the literature directly comparing aspirin alone to DAPT with clopidogrel to improve SVG patency. Gao et al. [111] used a weekly alternating scheme in a prospective non-randomized cohort, and assigned 102 patients to clopidogrel 75 mg daily and 95 patients to clopidogrel 75 mg plus aspirin 100 mg daily after CABG. No significant difference in SVG patency as assessed by CTA was seen at 1 month or 1 year (1 month: 98.1% vs. 98.2%, $P = 0.73$; 1 year: 93.5% vs. 96.3%, $P = 0.25$, clopidogrel vs. clopidogrel plus aspirin). Sun et al. used partial blinding to compare postoperative clopidogrel 75 mg and aspirin 81 mg daily with aspirin 81 mg alone among 100 patients undergoing on-pump CABG [112]. Graft patency was assessed by CTA, for 79 patients at 1 month. There was no difference in SVG patency either among all grafts (92.9% vs. 95%, aspirin vs aspirin and clopidogrel; $P = 0.43$) or SVG alone (93.2% vs. 93.5%, aspirin vs. aspirin and clopidogrel; $P = 0.92$). Gao et al. in a RCT randomized 249 patients to either clopidogrel 75 mg plus aspirin 100 mg daily or aspirin 100 mg alone starting within 48 h of surgery [113]. No blinding or placebo control was used in this trial. SVG patency by CTA was assessed in 90% of patients at 3 months, with patency higher in the DAPT group compared to aspirin alone (85.7% vs. 91.6%, $P = 0.04$). The Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) trial was a randomized, double-blind, placebo-controlled trial comparing aspirin 162 mg alone with DAPT using aspirin 162 mg and clopidogrel 75 mg [114]. The 113 patients underwent ICA and intravascular ultrasound (IVUS) at 1 year after surgery to assess for intimal hyperplasia. The use of DAPT did not significantly reduce the development of intimal hyperplasia compared with aspirin alone. Overall graft patency (95.2% vs. 95.5%, DAPT vs. aspirin alone; $P = 0.90$) and SVG patency (94.3% vs. 93.2%, $P = 0.69$) were not significantly different. Mannacio et al. conducted a single-centre prospective RCT study which randomized 300 patients undergoing off-pump CABG to either aspirin 100 mg ($n = 150$) or aspirin 100 mg plus clopidogrel ($n = 150$). Graft patency was assessed by CTA. DAPT use was associated with a reduced SVG occlusion rate (7.4% vs. 13.1%; $P = 0.04$) [115]. In 2017 Rafiq et al. reported a randomized trial comparing DAPT to aspirin monotherapy in hypercoaguable patients undergoing CABG and found no difference in SVG patency rates at 3 months [116] Based on this evidence current guidelines recommend 1 year of DAPT after CABG in patients presenting with ACS or who undergo off pump surgery, however the benefits of routine DAPT after CABG have not been well established [117].

Anticoagulant Therapy

Little is known about the use of an oral anticoagulant to prevent SVG failure and improving clinical outcomes. It has been suggested that patients taking warfarin who undergo CABG have no higher rate of bleeding compared to controls, [118] and warfarin administration concomitantly with an antiplatelet agent dramatically reduces the incidence of ischemic stroke associated with postoperative atrial fibrillation [119]. Most trials assessing the use of anticoagulants to prevent SVG failure in CABG are old, have small numbers and were in direct comparison to antiplatelet therapy [85, 86, 120–122]. However, Gohlke et al. [123] randomized 89 patients to a vitamin K antagonist, (starting on the seventh postoperative day) and 84 patients to no anticoagulation. ICA follow-up found graft patency after surgery was 90.4% in the treatment group and 84.6% in the control group ($P < 0.015$). The Post Coronary Artery Bypass Graft Trial was a two-by-two factorial design which assigned 1351 CABG patients to aggressive or moderate treatment to lower LDL cholesterol levels and to treatment with warfarin or placebo [124]. Angiographic follow up at 4 years showed no improvement in graft patency between the warfarin and placebo groups, although aggressive lowering of cholesterol did reduce the progression of atherosclerosis. Other trials also did not show any clinical advantage of warfarin over antiplatelets [125] and consequently the use of anticoagulants post CABG is not supported in guidelines [117] (Table 1).

Ticagrelor/Prasugrel

The evidence supporting newer, more potent antiplatelet agents comes from two main studies, PLATO and TRITON-TIMI 38 [102, 126]. The PLATO study was a large randomized trial comparing DAPT with ticagrelor as opposed to clopidogrel, concluding that in ACS patients, ticagrelor significantly improved clinical outcomes without an increase in the rate of overall major bleeding [102]. In PLATO, 1584 patients (12%) underwent CABG. "Major Fatal/Life-Threatening" bleeding was approximately 42% in both treatment groups. Fatal CABG bleeding occurred uncommonly, six patients in each treatment group (0.8% and 0.7% of CABG patients on ticagrelor and clopidogrel, respectively). Further subgroup-analysis in the PLATO study showed that the use of ticagrelor compared to clopidogrel was associated with better clinical outcomes both in ACS patients with prior CABG and those who underwent redo CABG [102, 127, 128]. In TRITON-TIMI 38 patients that underwent CABG after presenting with ACS also had a significantly reduced all-cause mortality with prasugrel compared with clopidogrel (2.31% vs. 8.67% adjusted odds ratio: 0.26; $P = 0.025$) in the short term, although there was an increase in observed bleeding, platelet transfusion, and surgical re-exploration for bleeding in patients randomized to receive prasugrel [126]. A recent retrospective observational study compared the use of dual antiplatelet therapy with aspirin and ticagrelor ($n = 1266$) or clopidogrel ($n = 978$) in ACS patients who underwent CABG [129]. The incidence of CABG-related major bleeding was high when ticagrelor/clopidogrel was discontinued <24 h before surgery. Discontinuation 3 days before surgery, as opposed to 5 days, did not increase the incidence of major bleeding complications with ticagrelor, but increased the risk with clopidogrel. The overall risk of major CABG-related bleeding complications was lower with ticagrelor than with clopidogrel [12.9 vs. 17.6%, adjusted OR 0.72 (95% CI 0.56–0.92), $P = 0.012$]. Based on these data current guidelines support DAPT after CABG in patients presenting with ACS with either clopidogrel, prasugrel or ticagrelor (preferred over clopidogrel) [117].

Lipid Lowering Therapy

As with native coronary arteries, SVG atherosclerosis correlates with serum lipid levels with the use of statins seemingly slowing disease progression. The lipid lowering aspect of the Post Coronary Artery Bypass Trial involved randomization to either aggressive or moderate cholesterol management [123]. ICA at 4 years

Table 1 Medical intervention for SVG patency

Author	Comparison	Design	Result
Anticoagulant vs antiplatelet			
Pantely et al. (1979) [85]	Aspirin/dipyridamole vs. oral anticoagulant	Randomised. SVG patency assessed by ICA	No difference in graft patency
McEnany et al. (1982) [86]	Aspirin vs. oral anticoagulant vs. placebo	Randomised. SVG patency assessed by ICA	No difference in graft patency
van der Meer et al. (1993) [122]	Aspirin vs. aspirin/dipyridamole vs. oral anticoagulant	Randomised. SVG patency assessed by ICA	No difference in graft patency
Anticoagulant vs placebo			
Gohlke et al. (1981) [123]	Phenoprocoumon vs. placebo	Randomised. SVG patency assessed by ICA	Higher patency rates with oral anticoagulant
Post Coronary Artery Bypass Graft Trial Investigators. (1997) [124]	Wafarin vs. placebo	2 × 2 multifactorial. Randomised. SVG patency assessed by ICA	Warfarin did not reduce the progression of atherosclerosis in SVGs
Antiplatelet vs placebo			
Chesebro et al. (1984) [32]	Aspirin/dipyridamole vs. placebo	Randomised. SVG patency assessed by ICA	Higher patency rates with DAPT
Goldman et al. (1989) [88]	Aspirin vs. aspirin/dipyridamole vs sulfinpyrazone vs placebo	Randomised. SVG patency assessed by ICA	Higher patency rates with aspirin
Aspirin vs DAPT with clopidogrel			
Gao et al. (2009) [111]	Clopidogrel vs. aspirin/clopidogrel	Non randomised. SVG patency assessed by CTA	No difference in graft patency
Kulik et al. (2010) [114]	Aspirin vs. aspirin/clopidogrel	Randomised. SVG patency assessed by ICA	No differences
Gao et al. (2010) [113]	Aspirin vs. aspirin/clopidogrel	Randomised. SVG patency assessed by CTA	Higher patency rates with DAPT
Sun et al. (2010) [112]	Aspirin vs. aspirin/clopidogrel	Randomised. SVG patency assessed by CTA	Higher patency rates with DAPT
Mannacio et al. (2012) [115]	Aspirin vs. aspirin/clopidogrel in off pump CABG	Randomised. SVG patency assessed by CTA	Higher patency rates with DAPT
Aspirin vs. DAPT with newer antiplatelets[a]			

Table 1 continued

Author	Comparison	Design	Result
Held et al. (2011) [127]	Aspirin and clopidogrel vs. aspirin and ticagrelor	CABG subgroup of PLATO trial to assess bleeding and clinical outcomes	Reduction in total and CV mortality without excess risk of bleeding with ticagrelor
Smith et al. (2012) [126]	Aspirin and clopidogrel vs. aspirin and prasugrel	CABG subgroup of TRITON TIMI-38 trial to assess bleeding and clinical outcomes	Higher bleeding but lower rate of death with prasugrel
Hansson et al. (2016) [129]	Aspirin and clopidogrel vs. aspirin and ticagrelor	Retrospective observational to assess bleeding	Lower bleeding complications with ticagrelor
Lipid lowering therapy			
Post Coronary Artery Bypass Graft Trial Investigators. (1997) [124]	Lovastatin 2.5–5 mg vs. lovastatin 40–80 mg	2 × 2 multifactorial RCT to assess SVG patency with angio	Higher patency rates with higher statins
Makuuchi et al. (2005) [131]	Pravastatin vs. placebo	Randomised. SVG patency assessed by ICA	Higher patency rates with higher statins
Kulik et al. (2011) [132]	LDL levels <100 mg/dL compared to levels >100 mg/dL	Non-randomised post hoc analysis of statin use in CASCADE trial	Higher patency rates with LDL <100 mg/dL

[a] Clinical studies only—none on SVG patency

highlighted that aggressive cholesterol treatment improved SVG patency (occlusion rates of 10% vs. 21%, $P < 0.0001$). Longer term follow up showed aggressive management was associated with a significant reduction in repeat revascularization and adverse cardiovascular events [130]. Makuuchi et al. randomly assigned 303 post CABG patients to either pravastatin or control. ICA were obtained at baseline and at the end of 5-year follow-up in 182 (60%) patients [131]. Although there was no significant difference in the quantitative ICA measurements between the two groups, a global change score indicated a significant pravastatin-mediated reduction in plaque progression ($P < 0.01$). A post hoc analysis of The CASCADE study assessed the impact of statin therapy on graft patency and neointimal hyperplasia, comparing these to different levels of LDL [132]. Twelve-month graft patency was higher for patients with LDL levels <100 mg/dL (96.5%) compared with levels >100 mg/dL (83.3%, $P = 0.03$). However, no improvement in graft patency was noted with further LDL reduction to less than 70 mg/dL ($P = 1.00$). In addition, consistent statin use throughout the trial period was independently associated with less SVG neointimal hyperplasia documented by IVUS at 12 months ($P = 0.04$).

A recent meta-analysis of eight studies and 6645 patients post CABG showed that aggressive statin therapy, compared to moderate statin therapy, decreased graft atherosclerotic progression by 39% with associated clinical benefits of reduced myocardial infarction [95% CI 0.66–0.95; risk ratio (RR) = 0.80; and 95% CI 0.66–0.85; RR = 0.75] and lower risk of cardiac death (95% CI 0.64–1.08; RR = 0.83) [133]. Other lipid lowering drugs have also been shown to have clinical benefits post CABG

[134–137]. However, statins have both cholesterol lowering and anti-inflammatory properties. Their anti-inflammatory effect reduces vascular oxidative stress and improves nitric oxide bioavailability, thus reducing vascular thrombosis and improving SVG patency [138–140]. In addition, hyperlipidemia has also been identified as one of the most potent risks of increasing intimal proliferation and subsequent fibrous hyperplasia [8]. As such the early use of statins is recommended in all CABG patients unless contraindicated [141].

Gene Therapy

Gene therapy in a relatively new approach to preventing SVG failure and its use is still in the developmental stage. The aim is to inhibit the cellular proliferation that causes intimal hyperplasia thus preventing SVG failure. Bypass grafting presents an ideal opportunity for gene therapy, as SVGs can be treated ex vivo, thus maximizing gene delivery, minimizing the potential for systemic toxicity, and targeting the pathogenesis of vein graft disease at its onset [142]. Initial optimism was seen after PREVENT II, a phase IIb trial of 200 patients undergoing CABG, randomized patients to either placebo or edifoligide, a transcription factor decoy that modulates smooth muscle cell proliferation. The treatment group demonstrated a 30% relative reduction in SVG critical stenosis by ICA and a 30% reduction in total wall volume by intravascular ultrasound [143]. This was then followed by the much larger trial PREVENT IV in which 3014 patients undergoing CABG were enrolled [144]. Harvested SVG were randomly assigned to ex vivo treatment with edifoligide, or saline solution placebo before grafting. At follow-up ICA 12–18 months after the operation, there was no difference in the rate of graft occlusion (41.8% in the edifoligide group vs. 41.7% in the placebo group; $P = 0.97$) or the primary end-point of death and SVG occlusion, or the composite clinical end-point of death, MI or revascularization. Currently gene therapy remains an area of research, but has no role in improving SVG patency.

INTERVENTION FOR GRAFT FAILURE

PCI on CABG grafts comprises an important subset of interventional cardiology cases, with approximately 5.7% of all PCIs between 2004 and 2009 being SVG PCI [145]. Initial early studies of plain old balloon angioplasty (POBA) on SVGs revealed disheartening results with 46–60% restenosis rates in the first 6 months [146]. The seminal study comparing POBA with bare-metal stents (BMS) was the Saphenous Vein De Novo (SAVED) trial, which compared POBA with BMS in SVG lesions [147]. This demonstrated a higher procedural success rates (97% vs. 86%) with BMS and a better composite outcome of freedom from death, MI, repeat CABG, and target lesion revascularization (TLR) (26% vs. 39%). Similar work also confirmed clinical benefits of BMS compared to POBA with a reduced need for revascularization and significantly higher event-free survival at 1-year follow-up [148]. When drug eluting stents (DES) became available they were also compared to BMS in SVG PCI. The Reduction of Restenosis in Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent (RRISC) trial randomized 75 patients to either sirolimus-eluting stent or BMS, with a 6 months follow-up [149]. The instent late loss and target lesion revascularization rate was significantly reduced (5.3% vs. 21.6%), but there was no difference in death or infarction. The Stenting of Saphenous Vein Grafts (SOS) trial randomized patients to either paclitaxel-eluting stent or BMS and found a significant reduction in the primary end-point, angiographic restenosis at 12 months (9% vs. 51%) as well as target lesion revascularization target vessel failure, with a trend towards lower mortality (5% vs. 12%, hazard ratio: 1.56; 95% CI 0.72–4.11, $P = 0.27$) [147, 150]. The Prospective, Randomized Trial of Drug-Eluting Stents Versus Bare Metal Stents for the Reduction of Restenosis in Bypass Grafts (ISAR-CABG) randomized 610 patients with diseased SVGs to DES or BMS, finding that there was a lower rate of the primary endpoint (combined incidence of death, MI, and target lesion revascularisation at 1 year) with DES, driven mostly by reduction in target lesion revascularization (7.2% vs.

13.1%), with no differences in mortality [151]. This theme of improved efficacy with DES over BMS, but without mortality benefit has been also published in meta-analyses, [152, 153] and in real-world situations [154, 155]. The introduction of 2nd generation DES compared to 1st generation, has also not improved mortality outcomes [156–158] but longer term follow up from larger studies is needed.

After graft failure redo CABG is another revascularization option, although it is associated with substantial risk. Such patients are older, have more comorbidities, more extensive CAD, and reentry of the sternum can be problematic when patent grafts, the aorta, or the right ventricle have adhered to the sternum [159]. It is associated with higher mortality compared with primary CABG, with intraoperative mortality rates are 5.8–9.6% [160]. Other major complications quoted include stroke (1.4–3.2%), non-fatal MI (3.0–9.6%), and post-operative bleeding (2.7–4.4%) [160, 161].

Patients with prior CABG presenting with ACS have a worse prognosis compared to those without [162–164]. Medical management of such patients has also been showed to be inferior to PCI [165, 166]. Studies comparing redo CABG and PCI are limited. Early work suggested that the use of POBA vs. redo CABG had equivalent 1 and 6 year mortality rates, although POBA had higher a revascularization need [167]. The AWESOME trial randomized ischemic patients with prior history of CABG to redo CABG or PCI finding that in hospital mortality was significantly higher in the CABG arm [168, 169]. Retrospective observational studies have suggested long term mortality of redo CABG vs PCI is similar [170–172] although this data does not account for contemporary PCI practice.

HYBRID REVASCULARIZATION

Noting the superior patency rates of internal mammary arterial grafts compared to SVG, as well as the possibility of performing LIMA-LAD bypass grafting via a minimally invasive approach, some investigators have hypothesized that a hybrid revascularization strategy involving contemporary coronary stents as well as a LIMA graft may be superior to conventional CABG. Several reports involving small series of patients have been published [173, 174]. The largest of these was a single center experience of 117 patients which reported 1 year freedom from major adverse events of 85.5% [175]. To date, no randomized controlled trial has been performed comparing hybrid revascularization to conventional CABG.

CONCLUSIONS

CABG remains a vital treatment for patients with multivessel CAD, especially in diabetics. Unfortunately, SVG failure limits the long-term benefits of the procedure. In this paper, we review the pathogenesis of and the differences between early, intermediate and late SVG failure. We also address the different surgical techniques and medical options used to preventing neointimal hyperplasia and SVG failure, as well as reviewing the literature regarding novel treatments and PCI in SVGs. Prevention of SVG failure is multifactorial and begins from the moment the grafts have been harvested. It is important for all physicians to recognize the impermanence of SVG and appropriate medical management is essential in maintaining graft patency.

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