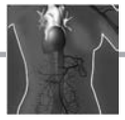
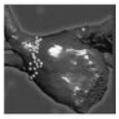
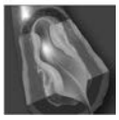

Advances in vein graft intervention

While saphenous vein grafts continue to serve as the most common conduit in coronary artery bypass surgery, within the first decade approximately 50% will have developed significant disease. Percutaneous coronary intervention is often undertaken in patients with saphenous vein graft disease as an alternative to reoperation, but is associated with an increased risk of distal embolization, no-reflow, periprocedural myocardial infarction, and late restenosis. Evidence-based clinical trials have established the routine use of stents and distal protection devices as the standard of care for vein graft intervention. Nevertheless, questions persist as to the safety and efficacy of drug-eluting stents in vein grafts given that randomized trial data is minimal and contradictory. This review will examine the evolutionary advances and current status of interventional techniques in treating this problematic disease.

KEYWORDS: distal protection ■ no-reflow ■ percutaneous coronary intervention ■ restenosis ■ saphenous vein bypass graft ■ stent

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Coronary artery bypass grafting (CABG) for selected high-risk patients with coronary artery disease (CAD) is associated with lower morbidity and mortality than medical management [1]. Whereas saphenous vein grafting is a beneficial operation, it remains associated with a high incidence of accelerated atherosclerosis. Approximately 12–26% of saphenous vein grafts (SVGs) occlude within the first year of surgery, followed by a 3–5% incidence of occlusion per year [2,3]. No more than 50–60% remain functional after 10 years postsurgery [4,5].

The long-term need for repeat revascularization is common in patients with a SVG; 5-, 10- and 12-year freedom from either reoperation or angioplasty is 96, 81 and 69%, respectively [6]. Angina recurs in up to 20% of patients during the first year after CABG and in 4% of patients annually during the subsequent 5 years. Treatment of recurrent ischemia after bypass graft surgery creates a challenging technical and clinical dilemma.

There are significant sequelae associated with degenerative SVG disease. Revascularization options include native vessel or vein graft percutaneous intervention, and repeat CABG. Both surgery and angioplasty have limitations, and are linked with suboptimal outcomes. Compared with the initial surgery, reoperation carries a high mortality rate of 3–7% and a 4–11.5% risk of perioperative myocardial infarction (MI) [7,8]. Furthermore, most patients with SVG disease are older, with depressed left ventricular function and multiple comorbidities. This augments the risk of perioperative morbidity and mortality associated with a repeat CABG [8,9]. The AWESOME trial suggested that percutaneous intervention may be a preferred revascularization strategy over repeat surgery for SVG disease, given the survival advantage in the former group [10].

The purpose of this paper is to review the pathogenesis, preventative strategies and the percutaneous approach to vein graft disease. Particular focus will be made on the current approaches of drug-eluting stent (DES) use and distal embolization protection devices.

Historical background

While SVGs are feasible conduits for coronary artery targets, 10-year patency rates are significantly lower than with internal mammary artery grafts. The Coronary Artery Surgery Study (CASS) registry of patients who had undergone first-time coronary artery bypass over 15 years demonstrated that patients with internal mammary artery grafts have a relative mortality risk of 0.73 compared with vein grafts [11]. Nevertheless, the functional patency and long-term clinical outcomes of SVGs are similar to other alternatives such as the radial or right internal thoracic artery when used as a second graft [12]. Graft patency does not vary by coronary system, with all arteries equally involved [4,5,13]. Moreover, atherosclerosis in grafts does not appear to be related to patient age or sex, but is instead associated with abnormalities of cholesterol lipoprotein fractions [14]. It has been

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proposed that vasospasm of vein grafts with release of serotonin may be the basis for the occlusion, followed by increased platelet aggregation at the lesion site. The dominant process is thought to be due to atherosclerotic obstruction occurring on a foundation of neointimal hyperplasia [15]. Reduced neutrophil adhesion to the endothelium of the internal mammary artery is due to enhanced release of nitric oxide, owing to its longer patency [16].

Saphenous vein graft stenosis is comprised of three distinct but inter-related pathological phases depicted as early, intermediate and late: thrombosis, intimal hyperplasia and atherosclerosis [15]. Compared with native vessels, vein grafts are more prone to higher friable plaque burden and thrombus; they are richer in cholesterol than calcium, making distal embolization a considerable concern during manipulation.

Early occlusion occurs during the first month after bypass surgery in 3–12% of vein grafts [5,17]. Zhao *et al.* reported that routine intraoperative angiography after CABG in 796 grafts detected 12% of grafts with significant angiographic defects. Vein harvesting with the attenuation of the activity of thrombomodulin, alterations in the vessel wall, changes in blood rheology and altered flow dynamics result in endothelial disruption with superimposed thrombotic occlusion [18]. To prevent this occurrence, intraoperative graft assessment after harvesting with criteria for graft revision using indocyanine-green fluorescent angiography and transit-time flowmetry have been analyzed to determine whether this would decrease the likelihood of graft occlusion or stenosis. There was no difference with imaging, as the saphenous graft occlusion was high early on in both groups [19].

The intermediate-phase occlusion, from the first month up to 1 year after surgery, occurs in 5–10% of grafts. The most common etiology is marked intimal hyperplasia, the migration of smooth muscle cells into the tunica intima as a response to injury with subsequent increased proliferation. This process is due to a loss of vascular supply, and imposed wall stress with the transfer of a thin-walled vessel from a low-pressure venous system to a high-pressure arterial system. Thrombin is a mediator of the venous bypass graft failure. Functional thrombin receptors are present on the endothelium of smooth muscle cells of the saphenous vein, causing contraction and proliferation. By contrast, in the internal mammary artery, thrombin has a vasodilatory effect [20].

In late occlusion, beyond the first year after bypass surgery, atherosclerosis is the dominant process underlying the attrition of the SVG and the eventual recurrence of ischemic symptoms [15]. An accelerated atheroma typically presents after 3–5 years; it has a thin fibrous cap, causing its friability. Angiographic studies of CABG patients presenting with unstable angina and MI are most often found to be due to graft disease with superimposed thrombus in up to 70–85% of cases [21]. In addition, most SVG lesions are most often located in the mid-body of the graft (38%), followed by proximal (30%), distal (23%) and ostial (<7%) locations [22].

Graft disease prevention

Certain risk factors predispose an individual to increased vein graft disease after coronary bypass-grafting. Independent prognostic factors for atherosclerosis progression include (in the order of importance): graft disease at time of implantation; years post-SVG placement; moderate low-density lipoprotein cholesterol (LDL-C)-lowering strategy; prior MI; high triglyceride level; small minimum graft diameter (<2.0 mm); low high-density lipoprotein cholesterol (HDL-C); high LDL-C; high mean arterial pressure; low ejection fraction; male gender; and current smoking [15,23,24].

Medical therapy for SVG disease prevention has been reviewed (Table 1) [25]. Initiating aspirin therapy at the time of surgery and anti-lipid agents were found to reduce the progression of atherosclerosis and the occurrence of graft occlusion. The use of the ACE inhibitor quinapril for 1-year post-CABG showed a reduction in cardiovascular events in a small, randomized controlled trial [26]. More trials with larger numbers of patients are needed to define its effect. Other medications such as β-blockers [27], calcium channel blockers [28] and warfarin [24] failed to have an effect on major adverse cardiac events (MACE), and graft disease progression [25].

The Antiplatelet Trialists' Collaboration overview of randomized trials of antiplatelet therapy demonstrated that the use of aspirin significantly reduces vascular occlusions, with the absolute reduction being greatest in patients at the highest risk of occlusion [29]. Studies suggest that antiplatelet agents started promptly after CABG improves vein graft patency and reduces the risk of death and ischemic complications [30,31].

Numerous studies have demonstrated the benefit of lipid lowering in CAD [32,33]. Aggressive lipid control with a goal of LDL-C under 100 mg/dl to delay the progression of

atherosclerosis in grafts was studied by the Post Coronary Bypass Trial Investigators in 1351 patients who had undergone CABG up to 11 years previously. Patients were assigned to aggressive or moderate treatment with lovastatin and, if needed, cholestyramine to lower LDL-C levels. The rate of revascularization over the next 4 years was 29% lower in patients with aggressive lipid lowering to a LDL-C level of less than 100 mg/dl. In addition, there was less progression of atherosclerosis (27 vs 39%) [34]. The Lopid Coronary Angiography Trial (LOCAT) corroborated the benefit of aggressive lipid lowering in post-CABG patients with an LDL-C 175 mg/dl or less and HDL-C of 42 mg/dl or less. In patients treated with gemfibrozil, there was reduced progression of new vein graft lesions (2 vs 14%) [35]. Studies assessing the role of fish oils (long-chain polyunsaturated n-3 fatty acids) have yielded conflicting results [36,37].

The PREVENT IV trial studied the reduction of neointimal hyperplasia in *ex vivo* treatment with edifoligide, an E2F transcription factor inhibitor and subsequent gene deactivator. Prior to the trial, this drug demonstrated effective blocking of cellular proliferation. In PREVENT IV, half of the enrolled patients had their veins pressure treated with edifoligide for 10 min prior to implantation. Researchers found no statistical difference between the groups: 45.2% with treated veins versus 46.3% in the control group had at least one vein with more than 75% obstruction. Despite good overall outcomes with CABG, 30% of SVG failed within 12–18 months. In additon, no benefit was observed in death and MI [2].

Graft patency may also be influenced by initial surgical techniques. The Randomized On/Off Bypass (ROOBY) trial randomly assigned 2203 patients scheduled for urgent or elective CABG to undergo either on-pump or off-pump surgery. The end point demonstrated that patients undergoing CABG off-pump surgery had worse clinical outcomes at 1 year. Likewise, follow-up angiograms in 1371 patients demonstrated poorer graft patency at 1 year in off-pump patients than patients who were on-pump during surgery (82.6 vs 87.7%; $p < 0.01$) [3].

Percutaneous coronary intervention

■ Limitations of balloon angioplasty

Percutaneous treatment of vein graft lesions has been attempted since the early days of balloon angioplasty, with less favorable results than in native vessels. The technical and clinical characteristics of balloon angioplasty are different for SVG. Owing to the friable nature of graft atheroma, the effect of balloon dilation is less predictable, and the risk of distal embolization and periprocedural MI is increased [38–40]. Furthermore, the long-term clinical and angiographic results of balloon angioplasty are limited by high occurrence of restenosis. Restenosis in vein grafts following balloon

Table 1. Studies of pharmacotherapy for graft disease prevention.

Study	Pharmacologic treatment	Result	Ref.
Gavaghan *et al.* (1991)	Aspirin	Reduction of SVG stenosis	[30]
Antiplatelet Trialists Collaboration (1994)		Improved graft patency	[29]
Mangano *et al.* (2002)		Reduced risk of death and ischemia	[31]
Post-CABG (1997)	HMG-CoA reductase inhibitors	Less graft progression of atherosclerosis	[34]
Post-CABG follow-up (2000)		Lower revascularization with aggressive therapy	[24]
Frick *et al.*; LOCAT (1997)	Gemfibrozil	Less progression of native coronary atherosclerosis Lower incidence of new lesions in SVG grafts	[35]
Blankenhorn *et al.*; CLAS (1987)	Colestipol/niacin	Fewer lesions in native vessels and grafts	[32] [33]
Cashin-Hemphill *et al.*; CLAS II (1990)		7 years after CABG, repeat revascularization, MI, cardiac death significantly lower	
Oosterga *et al.*; QUO VADIS (2001)	ACE inhibitor	Reduced clinical ischemic events after 1 year	[26]
MACB study group (1995)	β-blocker	No proven benefit	[27]
Gaudino *et al.* (2001)	Calcium-channel blocker	No proven benefit	[28]
Eritsland *et al.* (1996)	Fish oil	No proven benefit	[36]
Boerboom *et al.* (1997)			[37]
Post-CABG (2000)	Warfarin	No effect on disease progression	[24]

ACE: Angiotensin-converting enzyme; CABG: Coronary artery bypass graft; MACB: Metoprolol after cardiac bypass; MI: Myocardial infarction; SVG: Saphenous vein graft.

angioplasty is a function of lesion location: from 40–60% if within the ostium or body of the graft, or lower if performed at the distal anastomosis [38].

The angioplasty of a non-occlusive graft obstruction within the first year of surgery is a relatively low-risk procedure. Complications escalate once the graft age exceeds 3–5 years [39,41,42]. The long-term outcome of 454 patients treated with balloon angioplasty for venous bypass graft lesions reported by Plokker *et al.* demonstrated that only 26% of patients had an event-free survival at 5 years [43]. In addition, 26% died and 48% of patients suffered other MACE (e.g., MI, repeat bypass surgery or angioplasty) [38,43]. Similarly, Keeley *et al.* examined the long-term clinical outcomes of SVGs, reconfirming the concept that balloon angioplasty alone is associated with a high rate of clinical restenosis (43%) [44].

■ Transcatheter debulking strategies

A number of debulking strategies have been developed with the purpose of improving outcomes in SVG stenosis, including directional atherectomy, transluminal extraction and laser angioplasty (Table 2).

The directional atherectomy catheter was designed with a cutting window that could be situated rotationally and longitudinally within an artery for the removal of eccentric plaques [45]. Randomized controlled trials comparing the effectiveness of directional atherectomy to balloon angioplasty in native coronary arteries have shown discouraging results [46,47]. In the CAVEAT II randomized trial, directional atherectomy in vein grafts achieved better initial angiographic results compared with balloon angioplasty, but at the cost of a significantly increased incidence of distal embolization and non-Q-wave MI [48]. At 6 months, there was no significant difference in restenosis.

The transluminal extraction catheter has been used for diffusely degenerated grafts to extract plaque and thrombus by simultaneously cutting and aspirating. Safian *et al.* assessed the transluminal extraction catheter in 146 patients with vein graft disease. In this analysis, 21% of the patients suffered an immediate angiographic complication after transluminal extraction, including distal embolization (11.3%), no reflow (4.4%) and abrupt closure (5%). Restenosis at 6 months was 69%, and complete occlusion occurred in 29% of patients [49]. These 6-month results were reproduced by Meany *et al.* with a 60% angiographic restenosis rate [50].

Excimer laser angioplasty has been widely used in SVG disease, with a particular role in ostial lesions. Although able to ablate plaque and debulk thrombus, its use in vein grafts has been associated with high restenosis and total occlusion rates. Early observations on the efficacy of excimer laser angioplasty in old SVGs reported a 94% success rate, a 1% in-hospital death, 0.6% rate emergency bypass surgery and 2.4% Q-wave MI [51]. Despite the relatively low risk of complications, laser angioplasty in vein grafts was limited by a restenosis rate of 55%. In an observational multicenter study of 106 patients with SVG lesions treated with excimer laser angioplasty, restenosis rates were 52% with a total occlusion rate of 24% at 6 months [52].

Clot removal can be achieved by the Possis AngioJet rheolytic thrombectomy catheter, which uses high-velocity saline jets within the catheter tip to create a Bernoulli effect while pulling the thrombus, which is then evacuated through an exhaust lumen. This device was tested in the Vein Graft AngioJet Study (VeGAS) 2, a randomized comparison of immediate thrombectomy with AngioJet to a prolonged infusion of intracoronary urokinase (a high-risk treatment that is no longer utilized) for the treatment of thrombotic lesions [53]. The AngioJet treatment was associated with greater procedural success (86 vs 72%), fewer bleeding complications (5 vs 12%), a lower incidence of MACE (16 vs 33%), and lower incidence of periprocedural MI (16 vs 33%).

The X-Sizer, a combination of thrombus cutting and vacuum extraction device, has been tested. The X-Tract study compared the X-Sizer with stent implantation to stenting alone and demonstrated no difference in MACE between groups [54]. The use of the device may reduce the extent but not the occurrence of myonecrosis.

Another failed therapy is the coronary thrombolysis device, which uses sonication of obstructing thrombus as an adjunct to percutaneous intervention. When compared with abciximab in the ATLAS trial, there was a significantly higher incidence of adverse clinical events. Not only was angiographic success higher in the abciximab group, but MACE (including MI) was higher in the device group [55].

■ Pharmacologic therapy

Pharmacologic thrombolytic therapies, such as urokinase, are moderately effective in recanalizing venous conduits but are associated with frequent bleeding complications when

administered via a subselective catheter directly into the occluded vein graft [56]. For this reason, urokinase is no longer routinely used.

Although effective in native coronary arteries, antithrombotic pharmacologic therapy with glycoprotein IIb/IIIa inhibitors has not proven helpful in vein graft intervention. Pooled analysis of five randomized trials evaluating the role of glycoprotein IIb/IIIa in percutaneous intervention of SVGs showed a lack of benefit [57]. Platelet aggregation may be less important than particulate embolization in producing ischemic complications in SVGs.

■ ACC/AHA guidelines

In the updated 2007 American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions guidelines for percutaneous intervention in patients with prior CABG, it is a Class I recommendation to perform percutaneous intervention in patients with early ischemia, usually within 30 days following CABG when technically feasible. Distal embolic protection devices should be used with percutaneous intervention of older SVGs when technically feasible [58]. Class II indications for percutaneous intervention of SVG stenosis include patients who present with ischemia due to lesions in graft conduits 1–3 years post-CABG with preserved left ventricular function, disabling angina due to new disease and diseased vein grafts more than 3 years after CABG, with patent internal mammary artery graft [58].

■ Saphenous vein graft stenting

Landmark randomized trials STRESS and BENESTENT demonstrated the superior clinical and angiographic outcome of stent placement over balloon angioplasty in native coronary arteries [59,60]. However, these trials failed to include patients with vein graft lesions. Nonetheless, multiple observational vein graft stent studies demonstrated favorable results with low restenosis rates from 17 to 30% [61–64]. The prospective multicenter Palmaz-Schatz stent registry enrolled 589 patients with 624 focal vein graft lesions [63]. Procedural success was achieved in 98.8%; MI, bypass surgery or death occurred in 2.9%. Stent thrombosis within the first month was diagnosed in 1.4% of patients. Quantitative coronary analysis of the initial 198 patients in the multicenter Palmaz-Schatz stent registry was reported with overall restenosis rates of 34% (22% in new lesions versus 51% in prior angioplasty lesions). Restenosis was also more common in ostial lesions than non-ostial lesions (61 vs 28%) [65]. The use of debulking

Table 2. Atherectomy and thrombectomy devices.

Study	Device	Outcomes	Ref.
Holmes *et al.*; CAVEAT II (1995)	Directional coronary atherectomy	Better initial angiographic success Initial gain in luminal diameter Distal embolization and non-Q-wave MI higher Restenosis similar at 6 months Device unavailable	[48]
Safian *et al.* (1994) Meany *et al.* (1995)	Transluminal extraction catheter	Distal embolization No re-flow Abrupt closure >60% restenosis rate at 6 months Device unavailable	[49] [50]
Bittl *et al.* (1994) Strauss *et al.* (1995)	Excimer laser angioplasty	94% success rate High restenosis: >50% in 6 months	[51] [52]
Kuntz *et al.*; VeGAS 2 trial (2002)	POSSIS angiojet rheolytic thrombectomy	Compared with IC urokinase infusion Higher procedural success Fewer bleeding complications Lower incidence of MACE Lower periprocedural MI	[53]
Stone *et al.*; X-Tract trial (2003)	X-Sizer	Compared with stenting alone No difference in MACE Similar periprocedural MI	[54]
Singh *et al.*; ATLAS trial (2003)	Percutaneous coronary ultrasound device	Compared with abciximab Angiographic success lower Higher MACE Device unavailable	[55]

IC: Intracoronary; MACE: Major adverse cardiac event; MI: Myocardial infarction.

for vein graft aorto–ostial lesions before stent implantation does not improve outcomes compared with stenting alone [66].

The Saphenous Vein De Novo (SAVED) trial established the role of vein graft stenting [67]. This was the first randomized control trial comparing balloon angioplasty with stent implantation for obstructive disease of SVGs. The trial enrolled 220 patients with new vein graft lesions (although the grafts treated were on average 10 years old), and the primary end point was angiographic restenosis at 6 months. Compared with patients assigned to balloon angioplasty, elective stenting of selected SVG lesions with Palmaz-Schatz stents had higher procedural efficacy but more hemorrhagic complications (due to increased anticoagulation used in the trial). Postprocedural minimal luminal diameter was significantly larger (2.81 vs 2.16 mm) reflecting the enhanced acute gain. At 6 months, stenting conferred a significantly larger minimal luminal diameter (1.73 vs 1.49 mm). Freedom from death, MI, repeat bypass, or target lesion revascularization (Figure 1) was significantly better in the stent group (73 vs 58%). However, there was no significant benefit in the rate of angiographic restenosis, which was the primary end point of the study, 36 versus 47% ($p = 0.11$) [67]. Although the primary end point was not statistically different, the SAVED trial was the first study of any coronary intervention resulting in superior angiographic and clinical outcomes compared with balloon angioplasty in SVG disease. The reason for the relatively high restenosis rate in the study may have been due in part to changes in techniques during the time period, when high-pressure stent deployment was evolving. In a substudy analysis, SAVED investigators demonstrated the 6-month minimal luminal diameter to be larger for lesions treated with low-pressure deployment (≤15 atm) than those treated with high-pressure deployment (≥16 atm) [68]. These results suggest that routine high-pressure deployment may have a paradoxical deleterious effect on bare-metal stent (BMS) restenosis in vein grafts.

In the VENESTENT study group, patients with *de novo* lesions in SVGs were randomized to balloon angioplasty or Wiktor I stent implantation. At 6-month, the restenosis was 32.8% in the balloon group and 19.1% in the stent group ($p = 0.069$). At 1-year follow-up target vessel revascularization was 31.4 versus 14.5% ($p < 0.05$). Thus, elective stent implantation in *de novo* SVG lesions is associated with a significant lower target vessel revascularization rate and improved event-free survival at 1-year follow-up compared with balloon angioplasty [69].

■ Acute coronary syndromes

Each year, 3% of patients who have undergone a CABG present with an acute MI, and 30–50% of these presentations are due to an occluded vein graft. In general, data on patients with acute occlusion of SVGs presenting with an acute coronary syndrome and total graft occlusion is limited. Patients treated with thrombolysis in the GUSTO-I trial in patients with STEMI, revascularization with TIMI 3 flow was achieved in only 31.7% of bypass grafts. Likewise, the 30-day mortality in patients with prior CABG was significantly higher [70]. With primary balloon angioplasty, success rates of 85% have been reported [71]. In PAMI-2, compared with native vessels, the SVG reperfusion was achieved in 70.2 versus 94.3% and 6-month mortality was 14.3 versus 4.1% in patients without previous CABG [72]. Patients with STEMI and prior CABG not only have less favorable procedural results, but have a poor longer-term clinical prognosis [73,74].

■ Restenosis pathophysiology

While BMS have decreased the rate of in-stent restenosis, the improvement is relatively modest. The pathophysiology of restenosis after balloon angioplasty consists of a complex interplay between acute vessel recoil, thrombus formation, chronic constrictive remodeling and, neointimal growth [75,76]. Intravascular ultrasound studies in native vessels suggest that the mechanism of restenosis in SVGs after balloon angioplasty is different [77,78]. In native vessels, restenosis after balloon angioplasty is related to a negative vessel remodeling, and to a lesser extent, neointimal hyperplasia and matrix formation. With stent deployment in native vessels, the reduction in restenosis is due to an increase in luminal diameter and reduction in negative remodeling. In stented arteries, late lumen loss and in-stent restenosis are the result of neointimal tissue proliferation, which tends to be distributed over the length of the stent. This holds true for SVGs [79]. Long-term restenosis in SVGs after stent implantation occurs in over 30% of cases, and is due primarily to atherosclerotic plaque or fibromuscular hyperplasia with thrombus formation playing a secondary rather than primary role (as opposed to *de novo* lesions) [80,81]. Thrombi formation

may occur several years after implantation, and restenosis is often observed later in SVGs than in native vessels.

■ Covered stents

Stents covered in an autologous arterial or venous tissue or with polytetrafluoroethylene (PTFE) have been used to seal perforations and exclude aneurysms. The covered stent serves as a barrier to the degenerated vessel wall of SVGs to trap plaque material against the wall to theoretically limit micro-embolization and reduce restenosis by preventing the plaque from obtruding through the stent. In a multicenter registry, the Jostent was associated with in-stent restenosis of approximately 17% and mortality of 7% at 6-month follow-up [82]. Subsequent randomized trials including RECOVERS, STING and BARRICADE have evaluated the role of covered stents in vein grafts. The RECOVERS trial compared the JoMed covered stent to the BMS with no reduction in restenosis but an increase in MI [83]. The STING trial showed similar detriment of covered stents over BMS for restenosis [84]. The BARRICADE trial was terminated early as it demonstrated significantly higher MACE in PTFE-stented patients, and a trend for more total occlusions [85]. Given these sobering results, the use of these devices in vein grafts is not recommended, except for the treatment of coronary perforations and large aneurysms.

Drug-eluting stents

Drug-eluting stents are widely used for reducing the incidence of in-stent restenosis. Currently available drugs, which include the antiproliferative agents paclitaxel, sirolimus, everolimus and zotarolimus, interfere with the cellular microtubular function and/or intimal smooth muscle cell migration, limiting intimal hyperplasia. In native coronary arteries, DES have been shown to reduce the rate of restenosis and target vessel revascularization [86,87]. The high incidence of restenosis with BMS makes DES a logical alternative. The relative safety and efficacy of DES over BMS for percutaneous intervention in patients with SVG stenosis remains uncertain and controversial as the data supporting its use is limited.

■ Nonrandomized studies

Nonrandomized studies suggest that there may be an advantage in immediate- and mid-term outcome in restenosis of patients receiving DES over BMS. Numerous observational single-centered, small sample studies have looked at the use of sirolimus-eluting stents (SES) [88–91], paclitaxel-eluting stents (PES) [92,93], or both [94–106] in SVGs in assessing the frequency of angiographic restenosis and MACE (Table 3). In a study of 61 patients treated with DES, although MACE in the in-hospital setting was similar between the two groups, there was a significantly lower incidence of cumulative MACE at 6-months follow-up. The DES group had a lower incidence of in-segment restenosis and target vessel revascularization [95]. In the study by Lee *et al.*, when compared with BMS, intervention of SVGs with DES was associated with a lower incidence of death, MI, target vessel revascularization and angiographic restenosis [96]. Long-term improvement in MACE with DES use was also observed by Minutello *et al.* [89], and Hoffman *et al.* [92]. By contrast, other studies have reported similar outcomes in vein grafts treated with DES compared with BMS [88,90,94,97,99]. Brodie *et al.* demonstrated a reduction in target vessel revascularization in the treatment of SVGs with DES versus BMS at 9 months. However, the advantage was lost at 2 years [98]. These nonrandomized studies suggest that DES are a viable alternative to BMS for SVG stenosis.

Drug-eluting stents may be the effective option for treating BMS restenosis of SVGs. Prior to the introduction of DES, Waksman *et al.* had demonstrated the beneficial effect of intracoronary brachytherapy with gamma

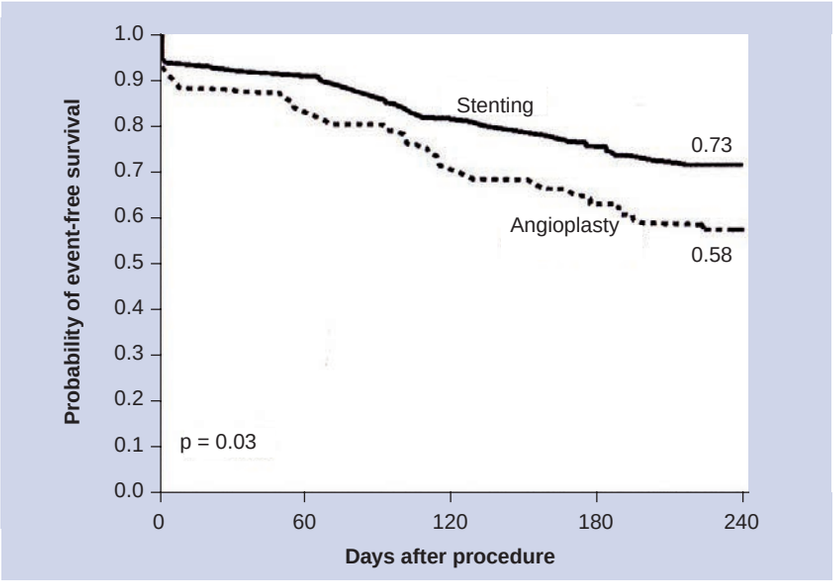


Figure 1. SAVED trial Kaplan–Meier survival curves for freedom from major adverse cardiac events. Event-free survival was significantly higher in patients with vein grafts treated with bare metal stents versus balloon angioplasty. Reproduced with permission from [67].

Table 3. Nonrandomized studies of drug-eluting stents in saphenous vein grafts.

Study	Stent type	Patients (n)	Late follow-up (months)	Death (%)	MI (%)	TLR/(TVR) (%)	MACE (%)	Ref.
Applegate *et al.* (2008)	BMS DES	74 74	24	5.4 6.8	9.5 2.7	(16.2) (9.5)	NR NR	[106]
Assali *et al.* (2008)	BMS DES	68 43	24	4.7 2.9	7 8.8	32.6 (27.9)† 14.7 (10.3)	41.9† 20.6	[105]
Bansal *et al.* (2008)	BMS DES	72 37	33	22.2 18.9	N/A N/A	(41.7) (35.1)	NR NR	[104]
Brodie *et al.* (2009)	BMS DES	343 785	24	14.7† 8.2	11.3 11.9	(16.9) (18.3)	33.8 30.4	[98]
Chu *et al.* (2006)	BMS SES	57 48	12	7.0 6.0	3.5 8.3	7.0 (11.0) 6.0 (13.0)	18.0 21.0	[88]
Ellis *et al.* (2007)	BMS SES	175 175	12	3.6 4.7	N/A N/A	(11.8) (6.8)	NR NR	[90]
Ge *et al.* (2005)	BMS DES	89 61	6	2.2 0	9.0 8.2	19.8 (23.1)† 3.3 (4.9)	28.1† 11.5	[95]
Gioia *et al.* (2008)	BMS DES	106 119	24	6.0 6.0	4.7 6.7	13 (14.0) 13 (14.0)	18.0 19.0	[94]
Hoffman *et al.* (2007)	BMS PES	60 60	6	N/A N/A	N/A N/A	22.0† 6.0	37.0† 15.0	[92]
Jeger *et al.* (2009)	BMS DES	13 34	18	15† 3	0 6	(18.0)† (46.0)	21† 62	[103]
Kaplan *et al.* (2008)	BMS DES	33 37	12	33.3† 10.8	3.0 0	30.3 (33.3)† 5.4 (10.8)	36.4† 10.8	[102]
Lee *et al.* (2005)	BMS DES	84 139	9	4.0† 1.0	20.0† 4.0	(37.0)† (10.0)	37.0† 10.0	[96]
Lozano *et al.* (2009)	BMS DES	113 98	36	13.0 11.0	N/A N/A	13.3 17.3	N/A N/A	[101]
Minutello *et al.* (2007)	BMS SES	50 59	20	12.0 6.8	N/A N/A	(36.0)† (15.3)	50.0 25.4†	[89]
Okabe *et al.* (2008)	BMS DES	344 138	12	12.0 9.0	0.3 1.0	8 (13.0) 9 (20.0)	24.0 29.0	[97]
Ramana *et al.* (2008)	BMS SES	170 141	34	6.0† 12.0	9.0 5.0	7.0 (16.0)† 14.0 (13.0)	28.0 20.0	[91]
van Twisk *et al.* (2008)	BMS DES	128 122	48	27.0 22.5	10.2 5.7	(31.0) (18.4)	53.2 38.5	[100]
Vignali *et al.* (2008)	BMS DES	288 72	12	7.8 3.7	5.2 8.2	8.1 (11.3) 4.3 (8.1)	20.3 17.8	[99]
Wohrle *et al.* (2007)	BMS PES	26 13	12	NR NR	NR NR	NR NR	7.7† 38.5	[93]

†$p < 0.05$.
BMS: Bare metal stent; DES: Drug-eluting stent; MACE: Major adverse cardiac event; MI: Myocardial infarction; N/A: Not applicable; NR: Not reported; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

radiation for BMS restenosis [107]. This group has more recently reported that DES implantation is at least as effective and safe as brachytherapy for the treatment of vein graft in-stent restenosis [108].

Percutaneous intervention on grafts with chronic total occlusions may be feasible in selected patients. Short- and medium-term outcomes of percutaneous intervention on SVG chronic total occlusions (EOS study) using PES demonstrated high success rates and low in-hospital complications. At 1 year, nonetheless, MACE was 25% and graft-free survival free of occlusion and revascularization were only 56% [109]. Meliga *et al.* were able to show more promising results, demonstrating that chronic total occlusions in post-CABG patients treated with either vein graft or native vessel reopening was no different at 3 years, both with similar event-free survival [110].

■ Randomized trials

Although nonrandomized studies suggest that DES are superior to BMS for treatment of SVG disease, there is limited and conflicting randomized controlled trial data (Table 4). The

Reduction in Restenosis in Saphenous Vein Grafts with Cypher (RRISC) was a randomized trial comparing SES and BMS in the treatment of SVG disease with a 6-month follow-up coronary angiography. A total of 75 patients with 96 lesions localized in 80 diseased grafts were included: 38 patients received 60 SES for 47 lesions, whereas 37 patients received 54 BMS for 49 lesions. Results at 6 months showed that the use of SES significantly reduced restenosis compared with BMS (30.6 vs 11.3%). Repeat revascularization procedures were also reduced with SES. Death and MI rates did not differ [111].

The Stenting of Saphenous Vein Graft Trial (SOS) was the first randomized trial to compare PES and BMS in SVG lesions [112]. The primary end point of this 80-patient, 112-lesion study was binary in-segment restenosis at 12-month quantitative coronary angiography. Binary angiographic restenosis occurred in 51% of the BMS lesions versus 9% of PES lesions ($p < 0.0001$). During a 1.5-year mean follow-up, PES was associated with a significantly less target lesion revascularization ratio ($p = 0.003$) and target vessel failure (46 vs 22%; $p = 0.03$). There was a trend towards less MI (31 vs 15%) and no difference in mortality.

Longer-term results from the RRISC trial (DELAYED RRISC) yield conflicting and cautionary findings. The DELAYED RRISC, sought to provide a long-term follow-up of the SES versus BMS in SVGs from the RRISC trial, with extended clinical follow-up to 3 years. Outcomes assessed in this secondary analysis were all-cause mortality, MI and target vessel revascularization. There was an increased risk of mortality: 11 deaths in the SES group versus none in the BMS group ($p < 0.001$). In contrast to the 6-month results, the rates of target vessel revascularization were not statistically different in SES and BMS groups: 34 and 38%, respectively [113].

The conflicting results of these two small studies highlight the relative paucity of randomized trial data on DES in vein grafts. No increased mortality with SES has been observed in large randomized trials in patients with native vessel disease. Therefore, the increased mortality observed in DELAYED RRISC may have been an aberration related to the very small study size. Several of the deaths were noncardiac in nature, also a confounding factor. Conversely, longer-term follow-up of patients in the SOS trial will be necessary to rule out a late catch-up phenomenon with PES stents when used in vein grafts.

Two meta-analyses and one systematic review of DES in SVGs have recently been published. The meta-analysis by Lee *et al.* analyzed 19 published studies comparing DES and BMS in SVG interventions with at least a 6-month follow-up. This included the two randomized trials and 17 registries [114]. Target vessel revascularization and MI were less common in patients who had received a DES than a BMS. There was no difference, however in death or stent thrombosis. Joyal *et al.* correspondingly completed a meta-analysis of 20 studies (18 observational and two randomized control studies) [115]. This analysis concluded that the use of DES is associated with a reduction in overall MACE, death, target vessel revascularization and target lesion revascularization, with no difference in MI between groups.

Lastly, a systematic review of 30 studies, again with the two randomized trials, showed that late loss and binary restenosis was reduced with DES [116]. There was mostly no difference in mortality, MI or stent thrombosis between BMS and DES. In approximately half of the studies, the need for repeat target vessel or lesion revascularization was lower in the DES group [116].

Although overall the data for observational studies imply that the use of DES for stenotic vein grafts have favorable affects on MACE,

Table 4. Randomized studies of drug-eluting stents in saphenous vein grafts.

Study	Stent type	Patients (n)	In-stent restenosis (%)	In-segment restenosis (%)	Late follow-up (months)	Death (%)	MI (%)	TLR/(TVR) (%)	MACE (%)	Ref.
RRISC	BMS	37	30.6†	32.6†	6	0.0	0.0	21.6 (27.0)†	29.7	[111]
	SES	38	11.3	13.6		2.6	2.6	5.3 (5.3)	15.8	
Delayed RRISC‡	BMS	37	NR	NR	32	0	5.0	30.0 (38.0)	41.0	[113]
	SES	38	NR	NR		29.0†	18.0	24.0 (34.0)	58.0	
SOS	BMS	39	51.0†	NR	18	5.0	31.0	28.0 (31.0)†	49.0	[112]
	PES	41	9.0	NR		12.0	15.0	5.0 (15.0)	37.0	

†$p < 0.05$.
‡Delayed RRISC trial is a long-term follow-up of the RRISC trial.
BMS: Bare metal stent; MACE: Major adverse cardiac event; MI: Myocardial infarction; NR: Not reported; PES: Paclitaxel-eluting stent; RRISC: Reduction of Restenosis in Saphenous vein grafts with Cypher sirolimus-eluting stent; SES: Sirolimus-eluting stent; SOS: Stenting of Saphenous Vein grafts; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

these data are observational and the randomized controlled studies are inconclusive. There remains a need for additional multicenter randomized control trials to address the effectiveness and safety of DES for vein graft stenosis. Several such trials are ongoing, including ISAR CABG, BASKET-SAVAGE and DIVA.

■ Disease progression of moderate lesions

The idea of using DES prophylactically in SVGs before the progression to critical stenosis has been entertained. The recently published VELETI study, a study of 57 patients with moderate (30–60%) SVG stenosis who were randomized to either treatment with PES or medical therapy and the outcomes at 1 year were measured using angiographic and intravascular ultrasound (IVUS). Change in minimal lumen diameter was significantly increased in the stent group, as well as percentage of stenosis, which was reduced in the stent group, both were statistically significant. There was lower target SVG revascularization a trend towards lower rate of MACE in the stent group [117]. The 3-year follow-up of the VELETI study showed that there was a reduction of MACE in the group that received a PES.

Distal embolization

Compared with native coronary arteries, vein grafts are commonly larger, less tortuous or calcified and devoid of side branches. This allows for relatively easy access of guide wires and catheters. In spite of this, the friable nature of the stenotic vein graft, older grafts in particular, with superimposed lipid-rich plaques augments the distal atheroembolization risk during percutaneous intervention. The embolization of thrombi and debris distally diminishes flow and is a potential cause of ischemia, myocardial necrosis and slow or no-reflow states [118]. Distal embolization causes an increase in enzyme elevation in 20% of cases after percutaneous intervention, and is associated with significant morbidity and mortality. Microvascular obstruction from smaller particles also results in microinfarcts with an inflammatory response, reduced coronary reserve and left ventricular dysfunction [119]. Risk factors for distal embolization include increasing graft age, long lesions, thrombus formation and larger plaque burden.

In aspirate analyses following SVG interventions with distal balloon occlusions, the histological constituents of the debris were found to be plaques consisting of large, soft, acellular emboli of cholesterol crystals, foam cells, macrophages and collagen, all approximating 80–200 µm in diameter [120]. Not surprisingly, patients who have debris removed have a lower rate of non-Q-wave MI and postprocedural adverse events [22,120]. To reduce periprocedural complications of distal embolization, no-reflow and infarction, these atherothrombotic fragments are contained and retrieved by distal protection devices. Complications are reduced but not eliminated when using distal protein devices when intervening on SVGs. They are most beneficial in older grafts with friable atheroma and are of least benefit in treating in-stent restenosis where the histology of the lesion is composed of neointimal hyperplasia. Nonetheless, embolic protection devices were used in less than 25% of saphenous vein percutaneous interventions in 19,546 patients of the American College of Cardiology-National Cardiovascular Data Registry published in 2007 [121].

■ Diffuse vein graft disease

Intervening on diffusely diseased vein grafts is especially problematic since distal embolization and associated MACE are highly correlated with plaque burden and lesion length; the incidence of MACE is inevitable. The PRIDE study demonstrated that the covariates associated with MACE are longer lesion length, greater angiographically estimated plaque volume and higher SVG degeneration score. Lesion length was the strongest predictor of adverse short-term events, with an increase in MACE observed with increasing lesion lengths [122]. A degeneration score was developed to quantify lumen irregularity and ectasia in SVGs. The score is the ratio of the cumulative length of luminal irregularities or ectasia (>20% of the reference total segment) divided by the length of the entire SVG. If less than 25%, a score of 0 is given; if 26–50%, a score of 1; if 51–75%, a score of 2; and if less than 75%, a degeneration score of 3 is assigned. The angiographic degeneration score is a potent predictor of procedural 30-day MACE [123].

The treatment strategy for patients with diffuse disease of a SVG is controversial. The use of Wallstents, which are self-expanding stents with an elastic wire mesh design, have the advantage of implantation without simultaneous balloon inflation, which may entrap vein graft atheroma and minimize embolization. Choussau *et al.* evaluated the result of less-shortening Wallstent in a series of 126 patients with 13-year-old, diffusely diseased (>20 mm in length) vein

grafts. In-hospital major cardiovascular events were observed in 10.3% of patients and death in 3.2% [124]. In a mean 22-month follow-up in survivors, 11% died, 9.4% sustained a MI and 35% required repeat revascularization. At 3 years, event-free survival was only 43% [124]. Thus, although diffusely degenerated vein graft interventions with self-expanding stents have high initial technical success, the short-term and long-term morbidity and mortality is high.

Embolic protection devices

There are three main types of embolic protection devices in SVG interventions: distal occlusion devices distal filter devices, and proximal occlusion devices. Distal protection devices in clinical use with supporting data include [125,126]:

- Distal balloon occlusion: PercuSurge GuardWire® (Medtronic, Inc., MN, USA) and TriActiv FX system® (Kensey Nash, PA, USA);
- Distal filtration: FilterWire EX/EZ™ (Boston Scientific Corp., MA, USA), Spider/SpiderRX™ (ev3 Inc., MN, USA for carotid artery stenting), Interceptor® (Medtronic Vascular, not commercially available in the USA);
- Proximal occlusion: Proxis® (St Jude Medical, Inc., MN, USA).

Clinical trials have demonstrated the efficacy of these devices (Figure 2).

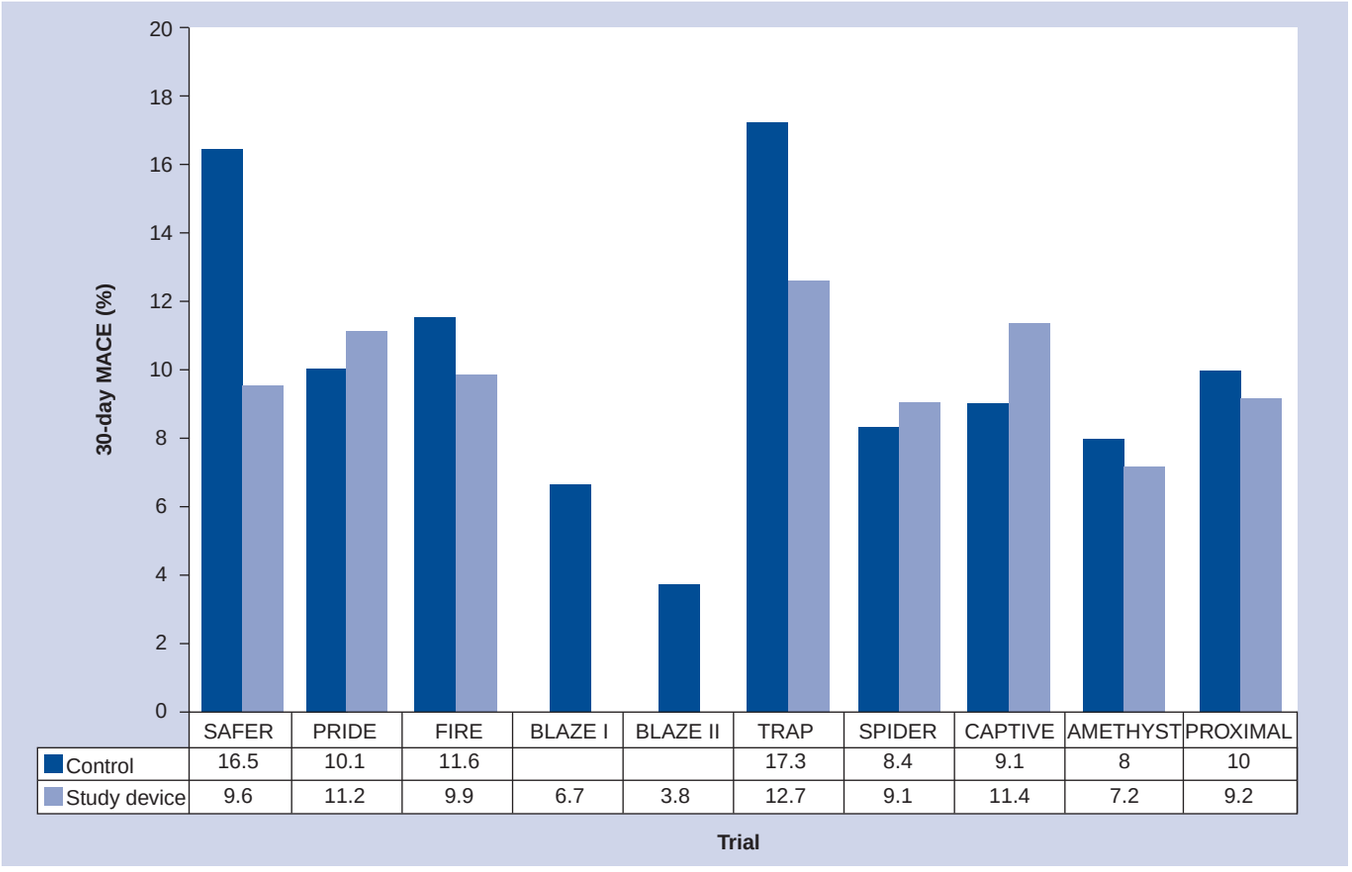
■ Distal occlusion devices

The GuardWire is an occlusion device comprised of a hollow guidewire with a distal low-pressure balloon and an aspiration thrombectomy catheter. The wire is passed through the lesion and the balloon is inflated with saline contrast to occlude outflow. Stent placement is performed in the SVG, an export catheter is advanced and the atherothrombotic debris loosened during revascularization is aspirated before the occlusion balloon is deflated. Conveniently, the wire serves as both guidewire and distal protection device. The disadvantage of distal occlusion devices is the cessation of blood flow distally during balloon inflation, causing myocardial ischemia and inability to opacify the target vessel during the procedure. The first published study to demonstrate the clinical efficacy of an embolic protection device used the AngioGuard Emboli Capture Guidewire with no complications or adverse cardiac events [127]. This was soon followed by the SVG Angioplasty Free of Emboli (SAFE) registry series, a larger study of 105 patients treated with the GuardWire, showing low MACE (5%) and reduction in thrombus burden [128]. The first multicenter randomized trial to assess distal protection devices was the SAFER trial [129]. A total of 801 patients with SVG stenosis were randomly assigned to stent placement over either a GuardWire (n = 406 patients) or a conventional guidewire system. The primary end point (a composite of death, MI, emergency bypass or target lesion revascularization by 30 days) was observed in 16.5% assigned to the control group and 9.6% assigned to the treatment group ($p < 0.01$). The GuardWire was superior with a 50% relative reduction in cumulative 30-day MACE, a 68% relative reduction in mortality and a 49% relative reduction in MI (Figure 3). These results were independent of the use of glycoprotein IIb/IIIa inhibitors. This trial was the first to show that prevention of embolization of atherosclerotic debris by distal protection reduces ischemic complications during vein graft intervention; it established embolic protection as the standard of care for SVG intervention.

The TriActiv Device is a continuous aspiration catheter using carbon dioxide rather than saline for balloon inflation. It was studied in the PRIDE trial, a prospective trial comparing TriActiv and the Guardwire or FilterWire EX system. Although there were more hemorrhagic complications with this device, there was noninferiority to other distal protection devices in terms of cardiac MACE [130]. The follow-up study, ASPIRE (using the TriActiv FX system) showed lower hemorrhagic complications and 30-day MACE (3.2%) compared with the active control group of the PRIDE trial [131]. Neither device is commercially available.

■ Distal filtration devices

In filter systems, the device is advanced past the target lesion in a collapsed state; a retaining sheath is then withdrawn, allowing the filter to open. It remains in its expanded state throughout the procedure collecting debris, after which it is collapsed and retrieved with the retained debris. The advantage of a filter wire is preserved antegrade flow and distal perfusion during the intervention, as well as allowing intermittent contrast injections. Limitations include the delivery sheath size (0.040–0.050 inches), reduced maneuverability of the guidewire, and the possibility of emboli less than 100 µm passing through the filter pore. The FilterWire EX is a filter-based distal protection device consisting of a polyurethane porous



	SAFER	PRIDE	FIRE	BLAZE I	BLAZE II	TRAP	SPIDER	CAPTIVE	AMETHYST	PROXIMAL
Control	16.5	10.1	11.6			17.3	8.4	9.1	8	10
Study device	9.6	11.2	9.9	6.7	3.8	12.7	9.1	11.4	7.2	9.2

Figure 2. 30-day major adverse cardiac event of embolic protection devices for saphenous vein graft interventions, shown in clinical trials. All trials are designed for noninferiority to active controls, except for the SAFER and TRAP, which evaluated the GuardWire® and TRAP device versus no device (p = 0.04 and 0.24, respectively).
MACE: Major adverse cardiac event.

membrane filter attached to a nitinol loop at the distal end of a 0.0014-inch steerable guide wire. The clinical, angiographic and technical factors related to successful stenting of SVGs with the use of the FilterWire EX was initially evaluated by Stone *et al.*, showing a low rate of periprocedural adverse events [132]. The FilterWire EX Randomized Evaluation (FIRE) randomized trial compared the Guard Wire Plus and FilterWire EX system in 651 patients undergoing SVG intervention. The procedural success was equivalent in both. At 30-day MACE was comparable between both groups, occurring in 9.9% of FilterWire EX patients and 11.6% of GuardWire patients (p for superiority = 0.53; p for noninferiority = 0.0008) (Figure 4) [133].

The FilterWire EZ system is the second-generation device featuring a lower profile and a more central suspended loop design that supports the filter, allowing for complete vessel wall apposition in both straight and curved vessels. This updated device was studied in the BLAZE I and BLAZE II clinical registries. The primary objective of these combined clinical registries of 229 SVG patients was to establish the safety and efficacy of the FilterWire EZ System intervention in SVGs. The BLAZE II registry evaluated a smaller device using a protocol similar to the BLAZE clinical registry and FIRE trial except that the vessel size inclusion criteria allowed for reference vessel diameters of 2.25–3.5 mm (compared with 3.5–5.5 mm). Overall, MACE at 30 days was 5.0%, compared with 9.9% in the FIRE trial (p = 0.03) [134].

Among smaller trials of distal filter devices, the SPIDER trial looked at the SpiderRX device; patients were randomized to the Spider/SpiderRX device versus the GuardWire or FilterWire EX/EZ system. In-hospital and 30-day MACE was similar in both groups [135]. The CAPTIVE was a multicenter trial comparing the CardioShield protection device with the GuardWire. The CardioShield was not found to be superior to treatment without a protection device. Furthermore, the investigators were not able to prove noninferiority of this device when compared with the GuardWire [136]. The TRAP trial evaluated the TRAP Vascular Filtration

System; patients were randomly assigned to undergo stenting with or without the TRAP device. The trial terminated early because of poor recruitment once the GuardWire was approved for clinical use. The primary study end point, MACE at 30 days, occurred in 17.3% of controls and 12.7% of patients treated with the TRAP device (p = 0.24) [137]. This trial, along with the SAFER trial, were superiority studies looking at distal protection devices versus no device. Lastly, AMEthyst was a multicenter randomized trial of 797 patients using the Medtronic Interceptor PLUS coronary filtration system for percutaneous intervention of degenerative SVGs compared with approved embolic protection devices. It demonstrated noninferiority when compared with the GuardWire and FilterWire in reducing MACE (8.0 vs 7.3%) [138].

Owing to their simplicity of use and because they allow the percutaneous intervention procedure to be performed in a conventional fashion, distal filter devices have been more widely adopted than balloon occlusion systems. With balloon occlusion, ischemia commonly ensues and therefore balloon inflations, stent deployment and aspiration sequences are undertaken in a hurried fashion. In patients treated with multiple stents or with pre- and post-stenting balloon dilations, these sequences may be required repeatedly. Conversely, porous filters allow continued distal perfusion and intermittent contrast injections to be made. Percutaneous intervention can thus be performed in a routine manner and, once completed, the filter is then removed. Occasionally in patients with diffuse disease and large plaque burden, reduced flow can develop due to debris clogging the filter. In such instances, perfusion can be restored by retrieval of the filter.

■ Proximal occlusion device

Proximal protection devices are balloon occlusion systems that are placed through the guiding catheter and into the graft proximal to the target lesion. Inflation of the proximal balloon creates a stagnant column of blood in the graft with suspended particulate debris that is then aspirated before blood is restored by balloon deflation. The PROXIMAL trial was a randomized, prospective, multicenter trial evaluating 594 patients undergoing stenting of SVGs. It was the first study to compare proximal and distal protection devices in a clinical setting. The test group (n = 294) used the Proxis system when possible (lesions >15 mm from the graft ostium), and a FilterWire or GuardWire when not (lesions located ≤15 mm of the ostium). The control group (n = 300) used a FilterWire or GuardWire when possible and no protection when not. There was no significant difference in the primary end points of death, MI or target vessel revascularization at 30 days (9.2 vs 10%) [22]. The Proxis device is especially useful with distal graft lesions where there is an insufficient landing zone beyond the lesion to park a distal filter or occlusion device.

The introduction of these protection devices has significantly mitigated distal embolization during vein graft intervention. On the other hand, complications related to distal embolization, notably no-flow and myocardial necrosis, while reduced, have hardly been eliminated. Accordingly, additional measures are needed to prevent and treat the problems associated with distal embolization.

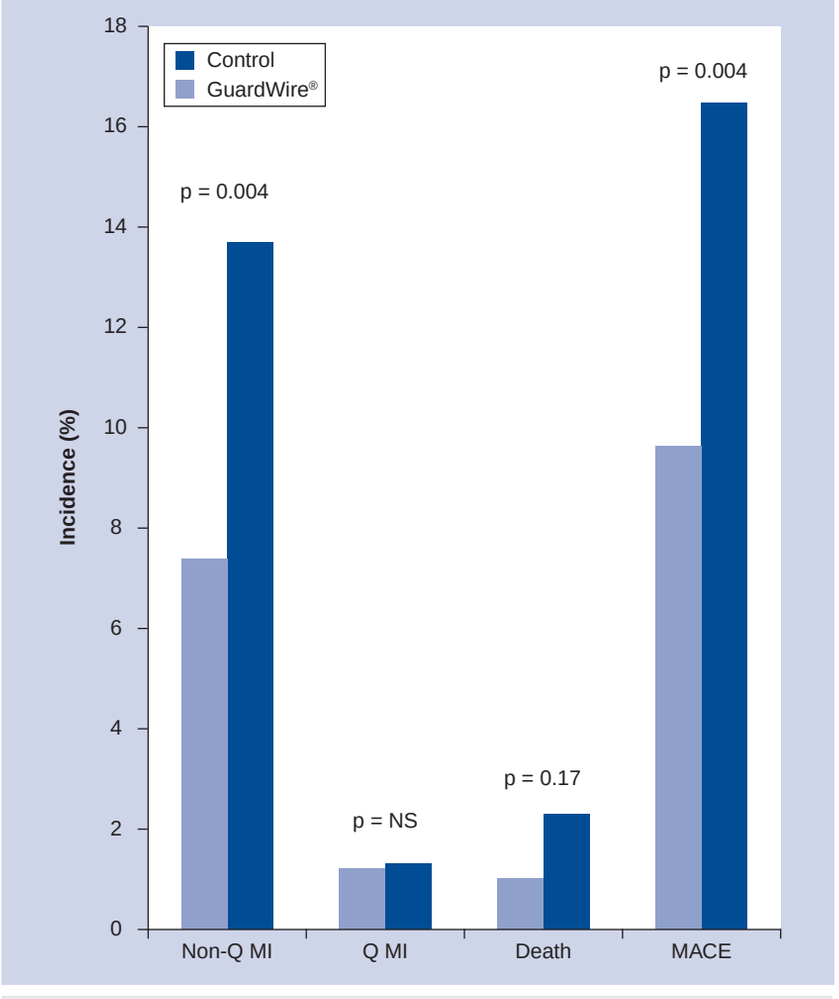


Figure 3. SAFER trial 30-day major adverse cardiac event. There was a significant reduction of overall MACE and non-Q-wave myocardial infarction with the use of the GuardWire® as compared with no embolic protection.
MACE: Major adverse cardiac event; MI: Myocardial infarction.
Adapted from [129].

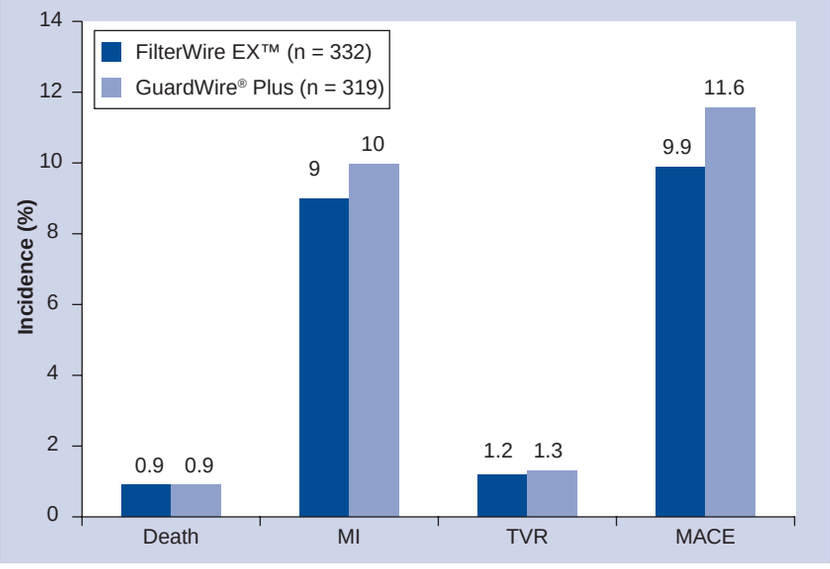


Figure 4. FIRE trial 30-day major adverse cardiac event. There was no difference in clinical outcomes with the use of a FilterWire™ versus the GuardWire®. All p-values were nonsignificant.
MACE: Major adverse cardiac event; MI: Myocardial infarction; TVR: Target vessel revascularization.
Adapted from [133].

■ No reflow

The no-reflow phenomenon is characterized by a reduction in epicardial blood flow in the absence of a residual mechanical coronary obstruction (stenosis, dissection or thrombus) [139]. The development of no-reflow is a significant risk factor for periprocedural MI and death [140]. The pathophysiology of no-reflow is complex involving both distal embolization of particulate debris and microvascular coronary vasospasm. In addition to the distal protection devices described previously, a variety of techniques and pharmacologic strategies have emerged to reduce the complications related to distal embolization and no-reflow.

Observational evidence suggests that the clinical outcomes of patients undergoing bypass graft intervention have improved over time due to an evolution in techniques [141]. The contemporary approach to vein graft percutaneous intervention emphasizes the importance of minimizing the degree of catheter manipulations within the graft, an approach that has been referred to as 'minimally invasive vein graft intervention' [142]. Important related components of the technique include: routine use of direct stenting, limiting the number of pre- and post-stenting balloon inflations, avoiding very high pressure inflations (≥16 atm) whenever possible, refraining from excessive balloon oversizing (which may have a deleterious 'cheese-cutting effect') and restrictive use of atheroablative devices. The importance of avoiding stent overexpansion in treating vein grafts is emphasized by a recent report from the Washington Hospital Center group; a high incidence of creatine kinase MB elevation was observed in patients with graft lesions where deployed stent diameter exceeded the intravascular ultrasound reference vessel diameter [143].

Stent implantation in vein graft lesions leads not only to the release of particulate debris, but also to soluble vasoactive factors including endothelin, serotonin and thromboxane A2 [144,145]. These soluble vasoconstrictive factors undoubtedly contribute to no-reflow, as evidenced by the efficacy of intracoronary vasodilating drugs in treating no-reflow [146,147]. Commonly used agents include calcium-channel blockers, adenosine and nitroprusside [148–153]. In our experience, intracoronary nicardipine has been proven to be particularly useful in managing no-reflow. In the study by Huang *et al.*, no-reflow was successfully reversed by nicardipine in all 23 patients with no-reflow during vein graft intervention [150]. By contrast, intracoronary nitroglycerin is not an effective option for no-reflow [149]. Although nitroglycerin is a potent dilator of veins and epicardial coronary arteries, it is a weak vasodilator of coronary arterioles, which have been implicated in the no-reflow process.

The success of intracoronary vasodilators in treating no-reflow has spurred interest in use of these agents as pretreatment immediately before intervention. Preliminary studies suggest a possible beneficial effect of calcium-channel blockers or nitroprusside when used in this fashion [154–156]. Whether this pharmacologic approach can supplant or supplement conventional distal protection devices requires further investigation.

Conclusion

The percutaneous intervention of SVGs has undergone considerable evolution. Over 400,000 CABG operations are performed annually in the USA, and the saphenous vein is a practical and most used surgical conduit. However, within 10 years of surgery, most venous grafts will develop significant disease. When dealing with vein graft stenosis, the viable alternatives for revascularization include repeat CABG or angioplasty of either the graft or native vessel. Reoperation carries a substantial risk of death and infarction, particularly in patients with advanced age, left ventricular systolic dysfunction and multiple comorbidities. The alternative of percutaneous intervention, which is appealing because it is less invasive, however, is also associated with risk of MI, restenosis and no-reflow due to distal embolization. SVG stenting is preferred over

balloon angioplasty, although the role of DES is still uncertain. Current guidelines give DES use in SVGs a Class IIb recommendation. There are no definite data on DES in SVG percutaneous intervention regarding a decrease in MI or death. Distal protection devices are underutilized despite their proven protective benefits in reducing periprocedural MI. Distal protection should be considered the standard of care for percutaneous intervention in most patients with older vein grafts.

Future perspective

Despite the remarkable technical progress recently achieved, many challenges still remain when intervention is undertaken in aged saphenous vein bypass grafts. In the future, we anticipate further innovative changes and investigations into even more effective therapies for vein graft disease. Improvements in both acute and longer-term outcomes are likely. More widespread utilization of distal protection devices by interventionalists can be anticipated, as next-generation devices offer greater ease of use and greater effectiveness in reducing periprocedural ischemic complications. Synergistic distal protection combining devices and prophylactic use of intracoronary vasodilators may also prove to further reduce the complications related to distal embolization and no-reflow. Future research will also address the long-term outcomes of patients after vein graft interventions. The potential role for prolonged dual antiplatelet therapy will be addressed by ongoing studies. Finally, additional larger multicenter randomized trials are imperative to establish the role of DES in the war again saphenous vein bypass graft disease.

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Executive summary

Historical background

- Saphenous vein graft stenosis is comprised of three pathological phases: early (thrombosis), intermediate (intimal hyperplasia) and late (atherosclerosis).
- Compared with native vessels, vein grafts are more prone to higher friable plaque burden and thrombus.

Graft stenosis prevention

- Aspirin commenced at the time of coronary artery bypass surgery should be continued indefinitely.
- Aggressive lipid-lowering therapy has been found to reduce the progression of atherosclerosis and graft occlusion.

Percutaneous coronary intervention

- Balloon angioplasty is a relatively poor alternative for vein graft disease as it is associated with a high rate of clinical restenosis.
- No percutaneous atherectomy or thrombectomy modality has proven superior to balloon angioplasty in the treatment of obstructed vein grafts, rather most devices are associated with increased distal embolization and/or restenosis.
- The SAVED trial was the first randomized controlled trial comparing balloon angioplasty with bare-metal stent (BMS) implantation for venous graft disease. Patients treated with stents had a lower incidence of major adverse clinical events.

Drug-eluting stents

- Nonrandomized studies have generally reported similar or better outcomes for DES when compared with BMS in diseased saphenous vein grafts.
- Two small, randomized trials have demonstrated lower rates of in-stent restenosis and target vessel revascularization during the first 6–12 months with the use of sirolimus-eluting stents and paclitaxel-eluting stents, compared with BMS.
- The DELAYED RRISC, the long-term evaluation of patients receiving SES, demonstrated an increased incidence of late target vessel revascularization and death. Therefore, the appropriate role of DES in treating vein graft disease remains uncertain and controversial.

Distal embolization

- Embolization devices include distal occlusion, proximal occlusion and distal filtration.
- Embolic protection devices are the only clinical trial-proven therapy for preventing peri-procedural MI in vein graft percutaneous intervention.
- The SAFER trial established the need for embolic protection devices during percutaneous intervention on vein grafts.
- Distal protection devices have been given a Class I indication by the American College of Cardiology and American Heart Association practice guidelines and should therefore be considered standard of care for most patients undergoing vein graft intervention.

No-reflow

- No-reflow is a complex phenomenon caused by distal embolization of atherothrombotic debris with superimposed microvascular spasm.
- A variety of intracoronary vasodilating drugs have been utilized to reverse no-reflow and preliminary data suggests that these agents may also have salutary effects when administered prophylactically before percutaneous intervention.

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