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5

Percutaneous Intervention Post Coronary Artery Graft Surgery in Patients with Saphenous Vein Graft Disease – State of the Art

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1. Introduction

The success of coronary artery bypass grafting, although the gold standard for the treatment of multivessel coronary artery disease is limited by poor long-term vein graft patency. Despite the superiority of arterial graft patency over that of vein grafts, the multivessel nature of coronary artery disease and ready availability of saphenous veins still result in its use in over 70% of coronary artery bypass graft procedures (Murphy & Angelini, 2004). These thin walled grafts promptly begin to fail with intimal hyperplasia, thrombosis and progressive atherosclerosis when exposed to an abrupt increase in wall stress imparted by systemic arterial pressure (Hiscock et al., 2007).

Recurrent ischaemia in patients who have had previous saphenous bypass surgery occurs not only because of attrition of the saphenous vein grafts but also because of progression of coronary artery disease in the native coronary arteries (de Feyter et al., 1993).

During the first year after bypass surgery up to 15% of venous grafts occlude, between 1 and 6 years the graft attrition rate is 1% to 2% per year, and between 6 and 10 years it is 4% per year. By 10 years after surgery only 60% of vein grafts are patent and only 50% of patent vein grafts are free of significant stenosis. In addition, native coronary artery disease progresses in approximately 5% of patients annually (Motwani & Topol, 1998).

Reflecting this graft and native vessel attrition, angina recurs in up to 20% of patients during the first year after saphenous vein grafting and in approximately 4% of patients annually during the ensuing 5 years (Motwani & Topol 1998).

Angiographic studies have shown that 70% to 80% of bypass surgery patients who present with acute coronary syndrome have their culprit lesion located in the saphenous vein graft (Pregowski J et al., 2005).

Further revascularisation, either reoperative bypass surgery or percutaneous intervention, is required in approximately 4% of patients by 5 years, 19% of patients by 10 years, and 31% of patients by 12 years after initial bypass surgery.

Both surgical and percutaneous forms of repeat revascularisation have considerable limitations. As compared with initial surgery, reoperation carries a higher mortality rate (3%

to 7%) with a high rate of perioperative myocardial infarction (4% to 11.5%). Coronary atheroembolism from diseased vein grafts is a major cause of the morbidity and mortality associated with reoperation. Redo surgery is also associated with less complete relief of angina and with reduction in saphenous vein graft patency as compared with initial bypass surgery. As increasing numbers of patients undergo second and third reoperations, the perioperative morbidity and mortality escalates further and the clinical benefit diminishes (Motwani & Topol, 1998). Thus, currently percutaneous coronary intervention is the preferred treatment for saphenous vein graft lesions (Vermeersh et al., 2006).

Percutaneous treatment of soft and friable, degenerated saphenous vein graft lesions provides unique challenges to the interventionalist due to the tendency for distal embolisation to result in slow or no-reflow phenomena with peri-procedural myocardial infarction and the relatively frequent association of superimposed thrombus on critical graft stenoses. This has sprawled a number of pharmaceutical and device-based approaches that may afford distal protection during percutaneous intervention. Nonetheless, there remains a disappointingly high long-term recurrence rate due to restenosis and the emergence of new lesions resulting in target vessel failure (Hiscock et al., 2007).

2. Mechanisms of saphenous vein graft ischaemia

The mechanisms of saphenous vein graft related ischaemia vary with the time that has elapsed since the surgery.

Early, 1-year and late graft failure may be due to thrombosis, fibrointimal hyperplasia and atherosclerosis respectively. There is general agreement that vein graft atherosclerosis differs from arterial lesions in terms of temporal and histological changes. Vein graft atherosclerosis is more rapid, with diffuse concentric changes and a less noticeable fibrous cap, making venous plaques more vulnerable to rupture and subsequent thrombus formation (Hassantash et al., 2008).

2.1 Early postoperative ischaemia (<1month)

The most common cause of ischaemia within hours or days of surgery is acute vein graft thrombosis (60%) (Nguyen T et al., 2004), possibly attributed to harvesting and handling of the vein, to failure of surgical techniques at sites of anastomosis such as surgical failure to carry the graft distal to obstructive points indicated by angiography (Vlodaver & Edwards, 1973) or to poor distal runoff due to severely diseased native arteries (de Feyter et al., 1993). Other causes are incomplete surgical revascularisation (10%), kinked grafts, and focal stenosis distal to the insertion site and at the proximal or distal anastomotic sites, spasm or injury, insertion of graft to a vein causing AV fistulae, or bypass of the wrong vessel. The patients at increased risk for early postoperative ischaemia include those undergoing technically demanding minimally invasive and “off bypass” techniques. (Nguyen T et al., 2004)

2.2 Early postoperative ischaemia (1 month -1 year)

Recurrent angina between 1 month and 1 year after the surgery is most often due to perianastomotic stenosis, graft occlusion or mid saphenous vein graft stenosis from

fibrointimal hyperplasia (Nguyen T et al., 2004). These occlusions are predominantly focal, not associated with diffuse vein graft disease, and usually the thrombotic component of the occlusion is not extensive (de Feyter et al., 1993). Recurrence of angina at about 3 months postoperatively is highly suggestive of a distal graft anastomotic lesion and should, in most cases lead to evaluation for percutaneous coronary intervention. (Nguyen T et al., 2004)

2.3 Late postoperative ischaemia (>3 years after surgery)

At this stage, the most common cause of ischaemia is due to formation in vein grafts of new atherosclerotic plaque, which contains foam cells, cholesterol crystals, blood elements, and necrotic debris as in native vessels, however, these plaques have less fibrocollagenous tissue and calcification, so they are softer, more friable, of larger size, and frequently associated with thrombus. (Nguyen T et al., 2004)

3. Selection of revascularisation strategy in patients who experience recurrence of ischaemia after coronary artery bypass surgery

The optimal revascularization strategy in patients with symptomatic multivessel coronary artery disease and previous coronary artery bypass grafting remains unknown.

Brener et al evaluated 2191 consecutive patients with previous coronary artery bypass graft surgery undergoing isolated, non-emergency multivessel revascularization (1487 with reoperation and 704 with percutaneous coronary intervention) between 1 January 1995 and 31 December 2000. The analysis concentrated on the independent predictors of the revascularization method, as well as on long-term mortality and its predictors, after calculating a propensity score for the method of revascularization.

These authors concluded that in the absence of a dedicated, randomized controlled trial to guide multivessel revascularization in post-coronary artery bypass graft patients, clinical practice appears to favour reoperation over percutaneous coronary intervention for patients at higher risk, with fewer functional grafts, more chronic total occlusions, and impaired systolic function, whereas percutaneous coronary intervention is favoured in those with patent left internal mammary artery and amenable anatomy.

In their study long-term mortality was mostly affected by age and ejection fraction, while the choice of revascularization had a modest impact. Percutaneous coronary intervention appeared to be related to a slight excess in long-term mortality (despite better 30-day outcome) compared with reoperation, an effect markedly attenuated by risk adjustment.

The effect of drug-eluting stents, higher success in percutaneous recanalization of chronic total occlusions and improvements in surgical techniques and overall medical care needs to be evaluated prospectively, particularly in high-risk subsets defined by advanced age and systolic dysfunction, before a definitive recommendation can be made for this important segment of the coronary artery disease population (Brener et al., 2006).

4. Balloon angioplasty for the treatment of saphenous vein graft disease

Percutaneous treatment of saphenous vein grafts was attempted in the early days of balloon angioplasty.

4.1 Initial results of balloon angioplasty of saphenous vein bypass grafts

In carefully selected patients the initial success rate of balloon angioplasty for saphenous vein grafts varied from 75% to 94%, with a combined overall success rate of 88%. The initial success rate was dependent on the site of dilatation. The overall combined initial result of dilatation of the proximal site was 87%, of the graft body 94% and of the distal site 90%.

The procedure related death rate was <1%, the myocardial infarction rate was approximately 4% and the need for coronary bypass surgery was <2%. These results reflected the careful selection of patients and probably the exclusion of complex lesions (de Feyter et al., 1993).

4.2 Restenosis after successful balloon angioplasty of saphenous vein bypass grafts

The restenosis rate was also dependent on the site of dilatation within the graft. Ostial or very proximal graft lesions had very high restenosis rate (58% on average), the restenosis rate of the body of the graft was 52% and the restenosis rate in the distal anastomotic part of the graft was 28%. The overall combined restenosis rate was 42%(de Feyter et al., 1993).

It was suggested that the interval to restenosis after angioplasty of a saphenous vein graft was longer than the usual 6 months interval after angioplasty in native coronary arteries. In a series published by Douglas, the restenosis rate was 32% at six months, but it rose to 43%, 61% and 64% after 6-12 months, 1-5 years, and 5 years respectively. (Douglas, 1994). The reason for this late pattern according to some authors, could be the larger reference diameter, which means more time would be required to reach a minimum luminal diameter small enough to yield clinical findings. (Hong et al., 2000; Lozano et al., 2005)

4.3 Long term outcome after balloon angioplasty of saphenous vein bypass grafts

The 5-year follow-up was poor, and although 74% of the patients were still alive, only 26% were event free with no myocardial infarction or repeat revascularisation (de Feyter, 2003). The interval between balloon angioplasty and bypass surgery was a significant predictor for 5 year-event free survival.

4.4 Risk factors predictive of unfavourable outcome after balloon angioplasty of saphenous vein bypass grafts

Several variables predictive of unfavourable outcome after balloon angioplasty of saphenous vein graft were identified.

Factors that predicted a poor initial result included 1) diffuseness of saphenous vein graft disease; 2) attempted angioplasty of stenoses in grafts more than 4 to 6 years old; 3) chronic totally occluded grafts; and 4) the presence of intravein graft thrombus. The presence of one or more of those variables was associated with a high frequency of major complications, often due to embolization of friable material into the coronary circulation or the occurrence of abrupt occlusion with thrombosis formation.

Variables predictive of late restenosis after balloon angioplasty of saphenous vein grafts included 1) lesions in old (more than 36 months) grafts; 2) multiple lesions, diffuse graft disease and total occlusion; 3) small diameter (<2.2 mm) of the grafted coronary artery; 4)

length of stenosis grater than 10mm; and 5) dilation of lesion at the proximal site and body of the graft (de Feyter et al., 1993).

Some authors advocated the use of aggressive adjunctive pharmacotherapy with intravenous and intracoronary heparin, urokinase, nitroglycerin, oral aspirin, calcium channel blocking agents and Coumadin for patients undergoing balloon angioplasty of saphenous vein grafts (Morrison et al., 1994).

Balloon angioplasty of saphenous vein grafts is a palliative procedure, not a long-term solution in patients with previous coronary bypass graft surgery. The high restenosis rate is a serious limitation of balloon angioplasty (de Feyter et al., 1993).

5. Bare metal stents in the treatment of saphenous vein grafts

Given the limitations of balloon angioplasty for the treatment of saphenous vein graft disease stent implantation was suggested as an alternative therapeutic approach.

Initial observational studies with balloon-expandable stent implantation in saphenous vein graft lesions had claimed a high procedural success rate, low early complication rate, and more favourable long-term outcome than previously reported for balloon angioplasty alone (Hanekamp et al., 2003).

The SAVED (Saphenous Vein De Novo) trial was the first multicentre, prospective, randomized trial of saphenous vein graft stenting. This study compared the placement of Palmaz-Schatz stents (Johnson & Johnson Interventional Systems, Warren, N.J.) with standard balloon angioplasty in 220 patients with relatively focal de-novo lesions in aortocoronary-venous bypass grafts. The primary angiographic end point of this trial was restenosis, defined as stenosis of 50% or more of the luminal diameter at follow-up.

Patients assigned to stenting had a higher rate of procedural efficacy, defined as a reduction in stenosis to less than 50% of the vessel diameter without a major cardiac complication (92% versus 69%, $P<0.001$). Bleeding and vascular complications were significantly more common in the stent group (17 % versus 5%, $P<0.01$) probably related to the intense anticoagulation protocol used in this trial. Patients in the stent group had a larger mean increase in luminal diameter immediately after the procedure (1.92 ± 0.3 mm versus 1.21 ± 0.37 mm) and a greater mean net gain in luminal diameter at six months (0.85 ± 0.96 mm versus 0.54 ± 0.91 mm). The rate of event free survival (freedom from death, myocardial infarction, repeated bypass surgery and revascularisation of the target lesion) at 240 days was significantly greater for patients assigned to stenting than for patients assigned to balloon angioplasty (73% versus 58%, $P=0.03$). When the results were analysed according to intention-to-treat principles, restenosis was found in 37% of the patients in the stent group and in 46% of the patients in the angioplasty group, $p=0.24$ (Savage et al., 1997).

These authors concluded that as compared with conventional angioplasty, stent placement in new vein-graft lesions was associated with better initial angiographic results and higher rates of procedural success. Although the luminal diameter at six months was larger in the stent group, there was no significant difference in the rate of restenosis. However, major cardiac events occurred less frequently in the stent group (Savage et al., 1997).

The SAVED trial used aspirin in combination with dypiridamole and warfarin therapy post stent implantation, instead of thienopiridines.

The Venestent study was a prospective, randomised, multicenter study that compared balloon angioplasty versus elective Wiktor I stent (Medtronic, Minneapolis, MN) implantation using thienopyridines in 150 patients with de novo lesions in the body of a saphenous vein graft. Diffusely diseased grafts, ostial and restenotic lesions, total occlusions and grafts with angiographic evidence of thrombus were excluded. The primary end point of this study was the binary angiographic restenosis rate at 6-month follow-up. Restenosis was defined as diameter stenosis of more than 50%.

Seventy-three patients were randomised to balloon angioplasty and 77 patients to stent implantation. In 17 patients randomised to balloon angioplasty, a bailout stent was implanted, corresponding with a crossover rate of 23.3%.

The angiographic and the procedural success rates were comparable for the balloon and the stent group (97.3% versus 98.7% and 89.0% versus 89.6%, respectively). No difference was present between the balloon group and the stent group with respect to in-hospital major adverse cardiac events (9.6% versus 10.4%). The angiographic restenosis rate at 6-month follow-up was 32.8% in the balloon group and 19.1% in the stent group, p= 0.069. At one year follow-up, target vessel revascularisation rate was 31.4% versus 14.5%, $P < 0.05$; and event-free survival was 60.0% versus 76.3%, $P < 0.05$, for the balloon and the stent group, respectively.

The authors of this study concluded that elective stent implantation in de novo saphenous vein graft lesions was associated with a significantly lower target vessel revascularisation rate and a significant higher event-free survival at 1year follow-up as compared to balloon angioplasty (Hanekamp et al., 2003). Although the difference in restenosis rate between both groups was not statistically significant; a strong trend in favour of stenting was suggested.

As compared with balloon angioplasty elective stent implantation in selected de novo saphenous vein graft stenosis is associated with better initial angiographic results, higher rates of procedural success, lower target vessel revascularisation rate and significant higher event-free survival. It is important to note however, that the results of bare metal stents in saphenous vein grafts are less favourable than those in native vessels, with restenosis rates exceeding 30% (Savage et al., 1997; Silber et al., 2005).

6. Direct stenting in saphenous vein grafts

Lesions located in saphenous vein grafts have different characteristics to those located in native vessels with greater cellular and less fibrotic components, more necrotic debris, cholesterol, thrombi and foamy cells. Thus, one of the greatest restrictions to stent implantation with predilatation is the risk of distal embolisation, with a high incidence of peri-procedural myocardial infarction (Lozano et al., 2005).

Direct stenting is defined as stent deployment without predilation with balloon or preparation via atherectomy. Direct stenting was introduced as a strategy of percutaneous coronary revascularisation in native vessels and was equivalent or was associated with better results when compared with balloon angioplasty followed by stenting (Leborgne et

al., 2003). Direct stenting was also proposed as a strategy to reduce complications during the treatment of acute myocardial infarction, by reducing the distal embolization rate and the no-reflow phenomenon (Leborgne et al., 2003). Because saphenous vein graft lesions are more friable, the beneficial impact of direct stenting might be amplified in saphenous vein grafts compared to native arteries (Leborgne et al., 2003).

Distal embolization and CK elevation remain a common complication after percutaneous treatment of saphenous vein grafts. The postulated mechanisms by which direct stenting minimizes distal embolisation in saphenous vein graft intervention is that by direct stenting the stent acts as scaffold to trap the friable tissue of the plaque before inflation of a balloon and reduce its fragmentation (Leborgne et al., 2003).

In a retrospective assessment of 527 consecutive patients treated with stent implantation for saphenous vein graft stenosis, 170 patients with 229 lesions were treated with direct stenting and 357 patients with 443 lesions were treated with conventional stenting (stent deployment preceded by balloon predilation). Procedural success was high and results were similar between the 2 groups with the same rate of combined major in-hospital complications (death, Q-wave myocardial infarction, and emergent coronary artery bypass surgery). However, the maximum CK-MB elevation postprocedure (9.5 ± 18.1 versus 19.6 ± 47.8 mg/dl, $P < 0.001$), CK-MB elevation > 4 times the upper normal value (13.6% versus 23.0 %, $P = 0.012$), and non-Q wave myocardial infarction (10.7% versus 18.4%, $P = 0.024$) were much lower in the direct stenting group. At one year, the composite end point of death, Q wave myocardial infarction, and target lesion revascularisation was significantly lower in the direct stenting group (21.5%) versus the conventional stent group (34.3%), $p = 0.021$ (Leborgne et al., 2003).

In another retrospective study involving 117 consecutive patients who underwent stenting for at least 1 lesion located in saphenous vein grafts, 71 patients with 83 lesions had been treated with direct stenting and 46 patients with 54 lesions with stenting preceded by balloon predilatation. No differences were found between both groups regarding the success of the procedure. The distal embolisation rate was significantly higher in the predilatation group with a trend toward a greater frequency of periprocedural myocardial infarction. Median follow-up time was 36.1 months. No differences were found in long-term mortality between the two groups (Lozano et al., 2005).

Direct stenting seems to be actually the best approach for treating saphenous vein graft stenosis when it is technically feasible. This strategy may be especially useful when a distal protection device cannot be used (Leborgne et al., 2003).

7. Covered stents for the treatment of saphenous vein grafts

Despite the fact that stents have improved the outcome of percutaneous intervention of obstructed vein grafts, prognosis of patients undergoing this procedure is still poor. Targets to improve intervention in saphenous vein grafts are to inhibit distal embolisation of atherosclerotic debris and to reduce the restenosis rate, which is elevated, compared with native vessels (Stone et al., 2011). These targets provided the rationale to propose the use of a membrane-covered stent as a new option for the treatment of saphenous vein grafts.

Initial experiences using the JOSTENT coronary stent graft (Jomed GmbH, Rangendingen, Germany) were promising when used in saphenous vein grafts (Elsner et al., 1999).

The JOSTENT stent-graft consists of a distensible polytetrafluoroethylene (PTFE) membrane sandwiched between two 316L stainless steel slotted tube, balloon-expandable stents. This device is currently available as the GraftMaster (Abbott Vascular, Santa Clara, California) for treatment of life-threatening coronary perforations (Figure 1).

Hypothetical benefits of elective use of the JOSTENT PTFE stent-graft in saphenous vein grafts included reduced periprocedural myocardial infarction (by trapping potentially embolic degenerated atherosclerotic debris behind the PTFE membrane) and decreased restenosis (by serving as a barrier isolating the lumen from smooth muscle cell proliferation, migration, and extracellular matrix production arising from the media) (Stone et al., 2011).

Results of a German multicenter registry suggested that the PTFE-membrane-covered stent appeared to be a safe and efficient treatment strategy for obstructed vein grafts with restenosis rates of about 17% (Baldus et al., 2000). Several prospective, randomised, multicenter trials were then conducted to compare the JOSTENT stent-graft with different conventional stents in patients undergoing percutaneous coronary intervention of obstructed saphenous vein grafts.

Fig. 1. Image of the GraftMaster polytetrafluoroethylene membrane covered stent. Courtesy of Abbott Vascular.

The STING (STents IN Grafts) trial was a prospective, multicenter study that included a total of 211 patients who were randomly assigned to receive either a Jostent Flex coronary stent or a JOSTENT stent-graft for the treatment of de novo lesions in saphenous vein grafts with a lesion length between 5 and 45 mm and a reference diameter between 3.0 and 5.0 mm. Patients were pretreated with aspirin (100 mg per day). Ticlopidine (500 mg per day) or clopidogrel (75 mg per day) were started after loading doses at the day of the procedure and continued for three months.

The primary end point was binary restenosis rate at six months by core lab quantitative coronary angiography.

Postprocedural minimal luminal diameter was comparable between the two groups. Periprocedural events during the intervention were similar between groups.

At follow-up, there were no statistically significant differences in minimal luminal diameter or percent stenosis between the groups. With respect to the primary end point restenosis rate at six months, there was also no significant difference between the Flex (20%) and the Stentgraft groups (29%), p=0.15. The restenosis rate in both groups was lower in this study than in other contemporary studies involving vein graft stenting, probably related to patient selection. There was a nonsignificant trend toward a higher late occlusion rate in the Stentgraft group (7% versus 16%, p= 0.069) at follow-up. After a mean observation period of 14 months, cumulative event rates (death, myocardial infarction, or target lesion revascularisation were comparable in the two groups (31% versus 31%, p = 0.93) (Schächinger et al., 2003). The outcome of the stent graft group in this study was worse than the expectations.

The RECOVERS (Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts) trial was a prospective, multicenter trial that randomized 301 patients with saphenous vein graft lesions to either the polytetrafluoroethylene-covered JOSTENT stent-graft or the JoFlex stent. Angiographic and procedural success rates were similar between the 2 groups (97.4% versus 97.9% and 87.3% versus 93.8%, respectively). The incidence of 30-day of major adverse cardiac events was higher in the JOSTENT stent-graft group (10.9% versus 4.1%, p = 0.047) and was mainly attributed to myocardial infarction (10.3% versus 3.4%, p = 0.037). The primary end point, the restenosis rate at 6-month follow-up, was similar between the two groups (24.2% versus 24.8%, p =0.237). Although the 6-month non Q-wave myocardial infarction rate was higher in the stent-graft group (12.8% versus 4.1%, p =0.013), the cumulative major adverse cardiac event rate was not different (23.1% versus 15.9%, p=0.153). This study also failed to demonstrate a beneficial effect of the JOSTENT stent-graft for saphenous vein graft treatment (Stankovic et al., 2003).

The prior Trials of the JOSTENT stent-graft did not mandate high-pressure implantation or prolonged dual antiplatelet therapy, measures that might be necessary to mechanically optimize the implant and facilitate endothelialisation without thrombosis. Moreover, they were limited by short-term follow-up.

The BARRICADE (Barrier Approach to restenosis: Restrict Intima to Curtail Adverse Events) trial was a prospective, multicenter study that included 243 patients that were randomised to the JOSTENT versus any bare-metal stent.

JOSTENT post-dilation to ≥ 18 atmospheres was mandated to overcome limitations of prior studies, as was the use of dual antiplatelet therapy for ≥ 8 months, and all patients were followed for a total duration of 5 years.

The primary end point of in-lesion binary restenosis at 8 months was not statistically different between the groups and occurred in 31.8% of lesions treated with the JOSTENT versus 28.4% of lesions treated with bare-metal stents (relative risk: 1.12, 95% confidence interval: 0.72 to 1.75, p = 0.63).

At 9 months, the major secondary end point of target vessel failure (death, myocardial infarction, or clinically driven target vessel revascularisation) occurred in 32.2% of patients

treated with the JOSTENT versus 22.1% of patients treated with bare metal stents (hazard ratio: 1.54, 95% CI: 0.94 to 2.53, p = 0.08). During long-term follow-up, significantly more events accrued in the JOSTENT arm such that by 5 years target vessel failure had occurred in 68.3% of JOSTENT patients versus 51.8% of bare metal stent patients (hazard ratio: 1.59, 95% CI: 1.13 to 2.23, p =0.007). Although there were no statistically significant differences between the 2 stent types in the rates of myocardial infarction or stent thrombosis, target vessel occlusion was noted more frequently in the JOSTENT arm during long-term follow-up. This study was designed to overcome several potentially important limitations from prior randomised trials of the JOSTENT stent-graft in diseased saphenous vein grafts, despite this stent-grafts had a grater failure rate when used for this application than bare metal stents (Stone et al., 2011).

Covered stents showed a tendency toward a higher rate of total occlusions at follow-up. It has been speculated that a postponed re-endothelialisation or enhanced thrombogenicity of the PTFE membrane might predispose for late thrombotic occlusions. However, the clinical course of most documented late occlusions was surprisingly benign, with only a few cases associated with a myocardial infarction. The fact that late occlusions >150 days were not associated with myocardial infarction might indicate that progressively proliferating restenosis, rather than acute thrombosis, might be the mechanism of late occlusion in these patients (Schächinger et al., 2003)

The Symbiot self expanding polytetrafluoroethylene covered stent (Boston Scientific Corporation, Natick, MA) was developed to reduce the potential for acute and long term complications associated with percutaneous intervention in degenerated saphenous vein conduits. The Symbiot™ covered stent system consists of a self-expanding, nitinol, multi-segmented stent encased within a thin (13μm), porous, polytetrafluoroethylene polymer membrane designed to maintain cellular viability of the adjacent tissue.

Two nonrandomized registries were conducted with the Symbiot stent. Symbiot I enrolled 25 patients. Of the 16 patients with angiographic follow-up at 6 months, the mean percent diameter stenosis was 18.8 ± 28.6%, and 19% had in-stent binary restenosis (unpublished data, Boston Scientific corporation).

Symbiot II, which enrolled 77 patients (58 with angiographic follow-up), demonstrated excellent outcome for the Symbiot stent with a mean percent diameter stenosis of 26.1 ± 20.9%, an in-stent binary restenosis rate of 7.0%, and an overall major adverse cardiac event rate of 14.3% at 6 months. These two studies demonstrated promising results but were limited by the absence of an active control group for comparison and small sample size.

The Symbiot III trial was designed to evaluate the clinical and angiographic outcomes of the Symbiot covered stent versus bare metal stents for the treatment of saphenous vein graft disease. The Symbiot III trial was a prospective randomized trial of 400 patients, with 201 patients in the Symbiot covered stent group and 199 in the bare metal stent group. Randomization was stratified based on the intended use of embolic protection devices and glycoprotein IIb/IIIa inhibitors. The primary endpoint of the study was percent diameter stenosis at 8 months, as measured by quantitative coronary angiography. Secondary endpoints included major adverse cardiac events, consisting of cardiac death, myocardial infarction, and target vessel revascularization. In-hospital and 30-day overall major adverse

event rates were comparable between groups. At 8 months, percent diameter stenosis was comparable between groups (30.9% Symbiot, 31.9% bare metal stent, p=0.80). Although the rates of binary restenosis in the stented segment were similar (29.1% Symbiot, 21.9% bare metal stent, p=0.17), more patients in the Symbiot group had binary restenosis at the proximal edge (9.0% Symbiot, 1.8% bare metal stent, p=0.0211). Overall major adverse cardiac event rates at 8 months were comparable for both groups, with 30.6% of Symbiot patients and 26.6% of bare metal stents patients experiencing major adverse cardiac events (p=0.43).

This study failed to show an advantage for the Symbiot stent in the treatment of degenerated saphenous vein grafts. These authors concluded that the polytetrafluoroethylene covering does not appear to act as a barrier to reduce neointimal hyperplasia (Turco et al., 2006).

The hypothesis that covered stents for the treatment of saphenous vein grafts may reduce periprocedural myocardial infarction and decrease restenosis seems to have been invalidated. Covered stents should be reserved for life-threatening perforations of the coronary vasculature (Lansky et al., 2006; Stone et al., 2011).

8. Drug eluting stents in the treatment of saphenous vein graft disease

In recent times, drug-eluting stents have become the leading device for the treatment of native coronary artery disease, because of the reduction in the incidence of restenosis, target lesion revascularisation, and target vessel revascularisation compared with bare metal stents (Michishita, 2011). Drug-eluting stents were developed to remove the incidence of restenosis and target lesion revascularisation only, but it has been hypothesised that drug eluting stents can improve the mortality and myocardial infarction rates, compared with bare metal stents, because their effect on reducing restenosis is remarkable and because restenosis after bare metal stent implantation could manifest as acute coronary syndrome in some patients. In real-world nonrandomised observational studies with large numbers of patients, but with a potential for selection bias and residual confounding, use of drug-eluting stents in native coronary arteries has been associated with reduced mortality and myocardial infarction rates (Michishita, 2011). In randomized controlled trials, no significant differences have been observed in the long-term mortality or myocardial infarction rate after the use of drug-eluting stents or bare metal stents in native coronary arteries for either off-label or on-label indications (Michishita, 2011).

Although drug-eluting stents have been a major advance in interventional cardiology, evidence for using these devices does not exist for all types of lesions or for all subsets of patients. One area where data have been lacking is the indication of diseased aortocoronary saphenous vein grafts (Bittl, 2009). Lesions in saphenous vein grafts have been poorly represented if not totally excluded in pivotal drug-eluting stent trials. However, this lesion subset represents a consistent proportion of lesions in which percutaneous procedures are performed, up to 10% to 15%in most centres (Baim, 2003 & Vermeersch et al., 2007).

The current limited evidence of drug eluting stent use in saphenous vein graft intervention comes mainly from a few small but well performed mechanistic randomised trials, multiple larger observational studies and more recently from several meta-analysis that have included evidence from these randomised trials and observational studies.

8.1 Randomized trials

The RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent) trial was a randomised, double blind, non-industry sponsored trial performed in a single centre. Patients with one or more "de novo" target lesions localized in ore or more diseased saphenous vein grafts with a reference vessel diameter > 2.5 and < 4.0 mm were allocated randomly to treatment with Cypher Sirolimus-eluting stent or BX-Velocity bare metal stent (both from Cordis, Johnson & Johnson, Warren, New Jersey). Direct stenting was promoted. Clopidogrel was administered for 2 months in all patients. All were scheduled to undergo six-month coronary angiography.

A total of 75 patients with 96 lesions localized in 80 diseased saphenous vein grafts were included: 38 patients received 60 Sirolimus-eluting stents for 47 lesions, whereas 37 patients received 54 bare metal stents for 49 lesions. Distal protection devices were used in more than 80% of the lesions treated.

The six-month in-stent late lumen loss (primary end point of the study) was significantly reduced in Sirolimus-eluting stents (0.38 ± 0.51 mm versus 0.79 ± 0.66 mm in bare metal stents, p = 0.001). Binary in-stent and in-segment restenosis were reduced in the Sirolimus-eluting stents, 11.3% versus 30.6% (relative risk 0.37; 95% confidence interval 0.15 to 0.97, p = 0.024) and 13.6% versus 32.6% (relative risk 0.42: 95% confidence interval 0.18 to 0.97, p = 0.031), respectively. The pattern of restenosis was different between both groups. After Sirolimus-eluting stent implantation, most restenosis were focal (83.3%) whereas after bare metal stent implantation most restenosis (62.5%) had a non-focal pattern.

Target lesion and vessel revascularisation rates (all ischaemia-driven percutaneous interventions) were significantly reduced in the Sirolimus-eluting stent group, 5.3% versus 21.6% (relative risk 0.24; 95% confidence interval 0.05 to 1.0, p = 0.047) and 5.3% versus 27% (relative risk 0.19; 95% confidence interval 0.05 to 0.83, p = 0.012) respectively. Death and myocardial infarction rates were not different between groups.

The RRISC Trial suggested a benefit for Sirolimus-eluting stents over bare metal stents in diseased saphenous vein grafts mainly for a reduced revascularisation procedure rate at a follow-up of 6 months. The small sample size of this study made it underpowered for major clinical outcomes (Vermeersch et al., 2006).

Great focus has recently been put on the evaluation of long-term follow-up of drug-eluting stents in native coronary arteries, mainly after publication of original and meta-analytical studies showing a possible increase in "hard" adverse events, specifically very late stent thrombosis, after drug-eluting stent deployment with respect to bare metal stents (Vermeersch et al., 2007).

Due to the lack in long-term data in patients with saphenous vein graft lesions and to offer additional information to the debate on safety of Sirolimus-eluting stents, the investigators of the RRISC trial performed a clinical follow-up evaluation of the 75 patients enrolled in the RRISC trial up to 3 years, focusing specifically on all-cause mortality and was published as the DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) trial. The new post-hoc main end point of this secondary long-term follow-up analysis was all-cause mortality.

Death occurred in 11 patients (7 cardiac, of which one was caused by a very late stent thrombosis and 3 were sudden) after Sirolimus-eluting stent (29% [95% confidence limits 17% to 45%]) versus 0 after bare metal stents (0% [0% to 9%]) with an absolute difference of 29% (95% confidence interval 14% to 45%, $p < 0.001$). The overall rate of definite angiographically documented stent thrombosis was 5% in the Sirolimus-eluting stent group (2 of 38, both very late) versus 0% in the bare metal stent group (p=0.49), whereas the rate of any possible stent thrombosis was 13% (5 of 38, 2 late and 3 very late) after Sirolimus-eluting stents versus 0% after bare metal stents (Fischer exact test 2-sided p value = 0.054; log rank test = 0.022). The rates of myocardial infarction and target vessel revascularisation were not different; 18% and 34% after Sirolimus-eluting stents, respectively, versus 5% and 38% after bare metal stents, respectively (p = 0.15 and p = 0.74, respectively).

In this extended post hoc analysis of the RRISC trial, patients treated with Sirolimus-eluting stents showed a significant increase in total mortality and the benefits of Sirolimus-eluting stents in terms of reduced revascularisation procedures shown at 6 months (Vermeersch et al., 2006) was no longer evident up to 3 years, suggesting that in saphenous vein grafts there can be a potential late catch-up phenomenon leading to a lack of benefit of Sirolimus-eluting stents over bare metal stents in reduction of clinical restenosis (Vermeersch et al., 2007).

This study had several major limitations. First, the sample size of patients was small, thus the results could be underpowered to appropriately address specific questions and can be prone to type I and type II statistical error. Second, the recommended duration of double antiplatelet therapy was only mandatory for at least 2 months in this study. Recent evidence has shown that double antiplatelet therapy should be recommended in all patients receiving drug-eluting stents for at least 12 months (Grines et al., 2007). Therefore, it cannot be excluded that some of the events described in the DELAYED RRISC study could be explained by "premature" discontinuation of dual antiplatelet therapy. Third, this study presented a secondary post-hoc analysis; thus, the main end point (death) was not prespecified at the moment of the beginning of the trial (which was powered for a 6-month difference in angiographic late loss analysis). The authors of this study concluded that given that the observations seen in this secondary post hoc analysis may have arisen from the play of chance or other clinical factors unrelated to stent type, further studies were required before conclusions could be made about the safety or harm of using Sirolimus-eluting stents for saphenous vein graft lesions (Vermeersch et al., 2007).

The SOS (Stenting Of Saphenous Vein Grafts) Trial was a randomised, controlled multicenter, prospective trial. Patients with one or more de novo or restenotic lesions in a saphenous vein graft that were between 2.5 and 4.0 mm in diameter were randomised to a polymer-based paclitaxel-eluting stent (Taxus, Boston Scientific, Natick, Massachusetts) or a bare metal stent with similar design (Express2, Boston Scientific).

Eighty patients with 112 lesions in 88 saphenous vein grafts were randomised to receive a paclitaxel-eluting stent (41 patients, 45 grafts, 57 lesions) or to receive a bare metal stent (39 patients, 43 grafts, 55 lesions).

The primary end point of the study was binary angiographic restenosis/lesion, defined as a stenosis of ≥ 50% of the minimal luminal diameter in the target saphenous vein graft segment at 12-month angiographic follow-up. The use of embolic protection devices and intravascular ultrasound were strongly encouraged. Aspirin was administered indefinitely

after stenting. Clopidogrel was initially recommended for 6 months after paclitaxel-eluting stent placement and for at least one month after bare metal stent placement. Since December 2006 (patients were enrolled between 2005 and 2007), a minimum of one year of clopidogrel was recommended after paclitaxel-eluting stent placement. Primary stenting was used in most lesions. Procedural success was achieved in 96% of the patients.

Binary angiographic restenosis occurred in 51% of the bare metal stent-treated lesions versus 9% of the paclitaxel-eluting stent-treated lesions (relative risk: 0.18; 95% confidence interval: 0.07 to 0.48, $p < 0.0001$). During a median follow-up of 1.5 years the paclitaxel-eluting stent patients had less target lesion revascularisation (28% versus 5%, hazard ratio: 0.38; 95% confidence interval: 0.15 to 0.74, $p = 0.003$) and less target vessel failure defined as the composite end point of cardiac death, myocardial infarction and target vessel revascularisation (46% versus 22%, hazard ratio 0.65; 95% confidence interval: 0.42 to 0.96, $p = 0.03$). There were trends toward fewer myocardial infarctions (31% versus 15%, hazard ratio: 0.67; 95% confidence interval: 0.40 to 1.08, $p = 0.10$) and less target vessel revascularisation (31% versus 15%, hazard ratio: 0.66; 95% confidence interval: 0.39 to 1.05, $p = 0.08$) in paclitaxel eluting stent patients (Brilakis et al., 2009). An important finding of this 80-patient study was that all-cause mortality was similar between the 2 groups at a median follow-up of 1.5 years (Bittl, 2009; Brilakis et al., 2009). This study was limited by the relatively small number of patients and was underpowered to detect differences in clinical outcome (Brilakis et al., 2009).

In summary, the use of paclitaxel-eluting stents in saphenous vein graft lesions in the SOS trial was associated with lower rates of angiographic restenosis and target vessel failure than bare metal stents. The median follow-up of patients in this trial was 1.5 years; it is unknown whether the outcomes would change with longer-term follow-up.

The ISAR-CABG (Is Drug-Eluting Stenting Associated with Improved Results in Coronary Artery Bypass Grafts) trial randomized 610 patients with de novo lesions in saphenous vein grafts to receive either a drug-eluting stent (n=303) or a bare metal stent (n=307). Patients in the drug-eluting sent group received a paclitaxel-eluting, sirolimus-eluting, or bio-absorbable polymer sirolimus-eluting stent. The average age of the saphenous vein grafts was 13 years. The primary endpoint was a composite of major adverse cardiac events (death, myocardial infarction, or target lesion revascularization at 1-year follow-up).

At one-year post intervention the incidence of major adverse cardiac events was reduced by 35% in the drug-eluting stent cohort compared to the bare metal stent group (15.4% versus 22.1%, $p = 0.03$). The difference was almost entirely driven by a nearly 50% relative reduction in the risk of target lesion revascularization (7.2% versus 13.1%, $p= 0.02$). There were no statistically significant differences in the individual rates of death or myocardial infarction (Mehilli et al., 2011).

Two ongoing trials are comparing drug-eluting stents with bare metal stents in saphenous vein grafts; the BASKETSAVAGE (Basel Stent Kosten Effektivitäts Trial-Saphenous Venous Graft Angioplasty Using Glycoprotein IIb/IIIa Receptor Inhibitors and Drug-Eluting Stents) (NCT00595647); and the Veterans Affairs Cooperative Study # 571, DIVA (Drug-Eluting Stents Versus Bare Metal Stents in Saphenous Vein Graft Angioplasty) trials (NCT01121224) (Lee et al., 2011).

The results of randomised trials of drug-eluting stents in saphenous vein grafts can not be extrapolated to large saphenous vein grafts (with a reference vessel diameter > 4.0 mm) or to totally occluded vein grafts because they were excluded from randomisation in those studies.

8.2 Meta-analysis

Several meta-analysis including evidence from randomised trials and observational studies that compared the use of drug-eluting stents versus bare metal stents in the percutaneous treatment of saphenous vein graft disease have been published.

A meta-analysis by Lupi et al included 23 studies comparing drug-eluting stents versus bare metal stents enrolling a total of 7,090 patients with saphenous vein graft disease. Three of the 23 studies included in this meta-analysis were randomised controlled trials and the remaining 20 were non-randomised studies. These authors included in their meta-analysis randomised and/or non-randomised studies, studies reporting clinical outcomes as overall death and/or acute myocardial infarction and/or target vessel revascularisation and studies with follow-up period longer than 6 months.

Patients treated by drug-eluting stents showed lower overall mortality rates with marginal statistical significance compared with those treated by bare metal stents (odds ratio, 0.63; confidence interval, 0.40-0.99; p =0.05; 7.0% versus 15.3% respectively). Subgroup analysis revealed a difference in the outcome between randomised and non-randomised studies. In particular, a survival benefit following drug eluting stent implantation was observed in non-randomised studies (odds ratio, 0.57; confidence interval, 0.36-0.90; p=0.02), but not in randomised controlled trials (odds ratio, 2.23; confidence interval, 0.15-32.35; p=0.56).

Patients treated by drug-eluting stents showed no benefit in myocardial infarction rates compared with bare metal stent treated patients (odds ratio, 0.92; confidence interval, 0.64-1.33; p = 0.7; 6.7% versus 6.8% respectively). Prespecified separate analysis for randomised and non-randomised studies yielded similar results.

In patients treated by drug-eluting stents a strong significant reduction of target vessel revascularisation compared with bare metal stent-treated patients was observed (odds ratio, 0.53; confidence interval, 0.39-0.72; p < 0.0001; 12.3% versus 18.8%). Drug-eluting stent advantage was comparable and statistically significant for both randomised and non-randomised studies. The prespecified meta-regression analysis showed an advantage for drug-eluting stents in diabetic patients (p =0.03) and in percutaneous graft intervention performed with embolic protection devices (p = 0.04); reduction of target vessel revascularisation with dug-eluting stent use was directly proportional to saphenous vein graft age (p = 0.005).

This meta-analysis supports the use of drug-eluting stents to reduce target vessel revascularisation in patients with saphenous vein graft disease. However, in this patient population, clear benefits from the use of drug-eluting stents in the reduction of death and myocardial infarction were not observed (Lupi et al., 2011).

Another recent and large meta-analysis by Hakeem et al included 2 randomised trials, one subgroup analysis from a randomised trial and 26 observational studies comparing drug-eluting stents with bare metal stents for saphenous vein graft lesions comprising a total of

7,994 patients (4,187 patients in the drug-eluting stent arm and 3,807 patients in the bare metal stent group). This meta-analysis reaffirmed the benefit of drug-eluting stents over bare metal stents in major adverse cardiac event reduction, which was primarily driven by lower revascularisation rates in the drug-eluting stent group. The observed drug-eluting stent benefit was largely based on the outcome of observational studies. Pooled analysis of all studies in this meta-analysis showed a mortality benefit associated with the use of drug-eluting stents. However, for studies with 12 and 24 months of follow-up, there was no difference with respect to mortality between drug-eluting stents and bare metal stents. Hence, long-term use of drug-eluting stents was not associated with an increased risk of death. Target vessel revascularisation was 12% in drug-eluting stents compared with 17% in bare metal stents, with risk ratio of 0.71 (0.59, 0.85), p = 0.0002. This effect was sustained in studies with > 12 and > 24 months follow-up. This study observed a significant reduction in the risk of myocardial infarction with the use of drug-eluting stents compared with bare metal stents. Although there was no statistically significant difference in the incidence of stent thrombosis, there was a trend towards increased stent thrombosis in the bare metal stent group (1% in drug-eluting stents and 1.7% in bare metal stents with a risk ratio of 0.63 [0.36 - 1.11] p= 0.11). According to this authors, the use of drug-eluting stents in saphenous vein grafts appears to be safe both in the short term and long term as demonstrated primarily in observational nonrandomised studies.

Target vessel revascularization is the only outcome with consistent benefit from drug-eluting stent versus bare metal stents in saphenous vein grafts in both randomised and observational data. While patients undergoing saphenous vein graft percutaneous intervention are at higher baseline risk, this "negative result" on myocardial infarction and death is consistent with the overall experience. Meta-analysis of all drug-eluting stent versus bare metal stent randomized controlled trials (n = 22 studies with 9740 patients) yields no significant reduction in death [OR = 0.97 (0.81 – 1.15)] or myocardial infarction [OR = 0.94 (0.78 – 1.13)] in those randomly assigned to drug eluting stents (Hillegass, 2011). There is clear-cut target vessel revascularisation benefit of drug-eluting stents in largely native vessels [OR = 0.45 (0.37 – 0.54), p <0.001]. Interestingly, the point estimate for reduction in target vessel revascularisation with drug-eluting stents in saphenous vein grafts is similar to native vessels. Over the longer term of 2 years, however, we remain with limited proof of a prolonged saphenous vein graft patency advantage with drug-eluting stents versus bare metal stents in well-controlled trials (Hillegass, 2011).

9. No-reflow phenomenon a major complication during percutaneous intervention of saphenous vein grafts

Distal embolisation of atheroemboli is a well-known consequence of saphenous vein grafts intervention and may result in diminished blood flow to the distal vascular bed resulting in peri-procedural ischaemia and infarction. This appropriately named "no-reflow" phenomenon occurs as a result of distal embolisation of atheroembolic debris (Carter et al., 2007). No-reflow is defined as the failure to restore normal coronary antegrade flow despite appropriate treatment of a coronary obstruction in the absence of dissection, thrombus formation or vessel closure.

The cause of no-reflow is complex and multifactorial. Various mechanisms like alpha-adrenergic vascular constriction, local increase in angiotensin II receptor density,

neutrophils activation and interaction with endothelium, distal embolisation of plaque and/or thrombus, local release of vasoconstrictor substances have been thought to be among many causes of no-reflow (Habibzadeh et al., 2011).

As expected, no-reflow is associated with worse clinical outcomes including post-procedural myocardial infarction (17.7% versus 3.5%in patients with and without no-reflow, respectively) and death (7.4% versus 2%).

Various techniques, both interventional and pharmacological, have been used in the treatment of no-reflow. Covered stents, as already discussed, were thought to inhibit distal embolisation by sequestering friable atheroemboli; however, this hypothesis seems to have been invalidated. Clinical trials of the routine use of glycoprotein IIb/IIIa receptor blockers during percutaneous intervention of saphenous vein grafts have shown no benefit for the reduction of major adverse cardiac events (Carter et al., 2007). A pooled analysis of 5 randomised intravenous glycoprotein IIb/IIIa inhibitor trials assessed the outcomes of graft interventions at 30 days and 6 months. The study population consisted of 13,158 patients undergoing percutaneous treatment of native coronary arteries and 627 patients treated for by pass graft disease. Treatment assignment and complete follow-up data were available for 605 patients with graft intervention (96.5%). Among them 389 patients were randomised to IIb/IIIa integrin blockade (abciximab in 51% of cases and eptifibatide in 49% of cases) and 216 patients were allocated to placebo. The incidence of death myocardial infarction or urgent revascularization at 30 days was 16.5% among patients allocated to glycoprotein IIb/IIIa inhibitors and 12.6% among those receiving placebo (odds ratio 1.38; 96% confidence interval, 0.85 to 2.24; p = 0.18). At six months, the combined event rate of death, myocardial infarction or revascularisation was 39.4% and 32.7% (hazards ratio 1.29; 95% confidence interval, 0.97 to 1.72; p = 0.07), respectively. The incidence of major bleeding was 6.8% among graft percutaneous intervention patients randomised to platelet glycoprotein IIb/IIIa inhibitors and 1.4% among those allocated to placebo (p = 0.004). The corresponding incidences of minor bleeding were 14.9% versus 8.1% (p = 0.016) respectively. Accordingly, no benefit from IIb/IIIa integrin blockade was detected in terms of individual or combined end points either at 30 days or at 6 months in patients undergoing saphenous vein graft interventions. From a safety perspective, adjunctive glycoprotein IIb/IIIa receptor inhibition was associated with an increased incidence of major and minor bleedings (Roffi et al., 2002). The authors of this analysis stated that additional studies were needed to define whether the use of platelet glycoprotein IIb/IIIa receptor inhibitors in conjunction with embolic protection devices might improve outcomes. According to them profound platelet inhibition may have complementary beneficial effect in particular when associated with filter devices. In this regard, whereas the filter offers mechanical protection from larger particles, glycoprotein IIb/IIIa inhibitors could exert their beneficial effect on the microvasculature jeopardized from microparticles that escape the filters. In addition, the use of potent platelet inhibition may allow for reduced filter pore size by preventing filter thrombosis, thereby increasing filter efficiency (Roffi et al., 2002).

The SAFER and FIRE trials established the safety an efficacy of balloon occlusion/aspiration (GuardWire) and filter-based (FilterWire) protection devices as useful adjuncts during saphenous vein grafts intervention. In both trials the use of glycoprotein IIb/IIIa inhibitors was at the discretion of the investigator, with randomisation stratified by intention to use glycoprotein IIb/IIIa blockade so that roughly equal numbers of patients in each arm would

be treated with glycoprotein IIb/IIIa inhibitors. In the SAFER trial patients pre-selected for IIb/IIIa treatment in both the GuardWire assigned and control (unprotected) arms had higher rates of major adverse cardiac events than those not treated with glycoprotein IIb/IIIa inhibitors; this observation is most likely due to selection of a higher-risk cohort to receive IIb/IIIa antagonists.

Jonas et al., studied the FIRE trial database to examine whether glycoprotein IIb/IIIa blockers would interact differently with the FilterWire EX and the GuardWire embolic protection devices. The principal findings of their report were that patients pre-selected for glycoprotein IIb/IIIa inhibitor therapy manifested higher risk baseline characteristics, greater procedural complexity and correspondingly higher overall 30-day major adverse cardiac event rates. They also had higher bleeding risk and required more transfusions. Among patients randomised to distal embolic protection with the GuardWire, major adverse cardiac events were higher with glycoprotein IIb/IIIa inhibitors than without. In contrast among patients randomised to the FilterWire, major adverse cardiac events were not higher with glycoprotein IIb/IIIa inhibitors than without. Glycoprotein IIb/IIIa inhibitor therapy was associated with superior FilterWire (but not GuardWire) performance, including better preservation of flow through the filter, reduced procedural ischaemia and reduced occurrence of abrupt closure, no reflow, or distal embolization (Jonas et al., 2005).

Intracoronary calcium channel blockers and the vasodilators adenosine and nitroprusside are commonly used in the treatment of no-reflow. Unfortunately this therapy is usually employed once the phenomenon has occurred (Carter et al., 2007).

Nitroprusside is a direct donor of nitric oxide that is a potent vasodilator in the resistance arteriolar circulation and plays a significant role in the control of coronary blood flow through the microcirculation. In a retrospective analysis of 20 percutaneous coronary interventions including 9 (45%) in saphenous vein grafts, intracoronary nitroprusside administered for no-reflow (median injection dose 200 μg) led to a rapid improvement in both angiographic flow ($p<0.01$ compared with pretreatment angiogram) and blood flow velocity ($p<0.01$ compared with pretreatment angiogram). No significant hypotension or other adverse clinical events were associated with nitroprusside administration (Hillegass, 2001).

Adenosine inhibits platelet activation, impedes platelet aggregation, and is a potent arteriolar dilator that has been shown to reduce the incidence of no-reflow following percutaneous coronary intervention in native vessels, and reverse but not prevent no-reflow in degenerated saphenous vein grafts. Intracoronary adenosine has an extremely short half-life and duration of action, and thus requires repetitive dosing during percutaneous coronary intervention (Fischell, 2008). In a small study, 8 patients who experienced 9 no-reflow and 2 slow flow events complicating saphenous vein graft interventions were treated with the rapid and repeated injection of adenosine (average of 12.1 ± 3.4 boluses of adenosine per event, with 3-4 saline 3-ml flushes following each adenosine syringe bolus). All 11 no-reflow/slow-flow events were substantially improved within 7 minutes of treatment. Angiographically normal flow (TIMI 3) was achieved in 10 of 11 events (91%). These authors hypothesized that the combination of microvascular (arteriolar) vasodilatation by adenosine combined with forceful mechanical flushing of embolic debris

out of the target vascular bed may act synergistically to reverse the no-reflow process (Fischell, 1998).

Intracoronary nicardipine has been shown to be the most potent vasodilator used for no-reflow prevention. Intragraft administration of nicardipine can cause longer vasodilation with a lower risk of serious systemic side effects compared to intracoronary diltiazem or verapamil infusion.

In 2007, Fischell et al reported some promising results with the use of intracoronary nicardipine to prevent no-reflow without distal mechanical protection in saphenous vein graft intervention. They evaluated 83 saphenous vein grafts interventions involving 68 consecutive patients. All saphenous vein grafts lesions underwent successful stent placement. All patients received 200-300 μg of intragraft nicardipine (10-15 μg/ ml of normal saline) injected via the guiding catheter immediately prior to stenting (Habibzadeh et al., 2011). These authors showed favourable results with reduction in major adverse cardiac events comparable to that of the early distal protection trials (Carter et al., 2007).

Despite the increasing use of pharmacologic means to prevent no-reflow, distal embolic protection remains a vital component of therapy (Carter et al, 2007). It is of note; however, that despite the use of protection devices, significant no-reflow can occur during saphenous vein graft intervention. The no-reflow phenomenon might be predominantly caused by microvascular spasm and not directly by mechanical obstruction from distal embolisation (Habibzadeh et al., 2011). A combination of intragraft administration of nicardipine together with the use of protection devices has not been studied but appears to be logical, with significant potential to reduce the occurrence of no-reflow compared to each preventive measure alone (Habibzadeh et al., 2011).

10. Embolic protection devices during saphenous vein graft interventions

There are two types of embolic protection devices: balloon occlusion-aspiration (proximal or distal) and filter devices. These systems have different characteristics and to date none has demonstrated enough advantages over the other mechanism to be ideally recommended universally (Morís et al., 2009).

10.1 Distal balloon occlusion devices

The Guard-Wire (Medtronic, Minneapolis, MN) temporary occlusion-aspiration system, consist of a wire with a central lumen that inflates an elastomeric balloon at the distal tip of the wire. The lesion is crossed with the Guard-Wire. Once the balloon is inflated (2.5 to 5.0 mm or 3.0 to 6.0 mm in diameter) with diluted contrast using an adaptor device, it occludes flow distal to the target lesion. The procedure (angioplasty and stenting) is then performed over the Guard-Wire shaft instead of using a standard angioplasty guidewire. Liberated plaque and thrombotic debris trapped proximal to the balloon are then aspirated through a 5 French monorail Export aspiration catheter. The balloon is then deflated with restoration of antegrade flow (Figure 2).

The SAFER (Saphenous vein graft Angioplasty Free of Emboli Randomized) trial enrolled 801 patients with signs of myocardial ischemia resulting from a target lesion > 50% diameter stenosis located in the mid-portion of a saphenous vein graft, with a reference vessel

diameter between 3 and 6 mm. Four hundred and six patients were randomized to stent placement over the shaft of the distal protection device and 395 were assigned to stent placement over a conventional angioplasty guidewire (control group). There was a 6.9% absolute (42% relative) reduction in the 30-day primary end point - a composite of death, myocardial infarction, emergency bypass, or target lesion revascularisation – 9.6% for GuardWire patients versus 16.5% for control patients; p = 0.004. The reduction in major adverse cardiac events was driven by a reduction in myocardial infarction of all magnitudes (8.6% versus 14.7%, p= 0.008). In addition, rates of TIMI grade 3 flow were higher for the GuardWire arm (98%) compared with the control arm (95%; p = 0.04) and the incidence of clinically evident no-reflow was reduced (3% versus 9%; p = 0.001). A per-protocol analysis on the patients with technically successful use of the GuardWire (90.1%) showed an even lower incidence of myocardial infarction (7.9%) and no-reflow phenomenon (2.4%). The rates of the primary end point and no-reflow in patients with technical failure of Guard-wire arm were similar to the control arm (Baim et al., 2002).

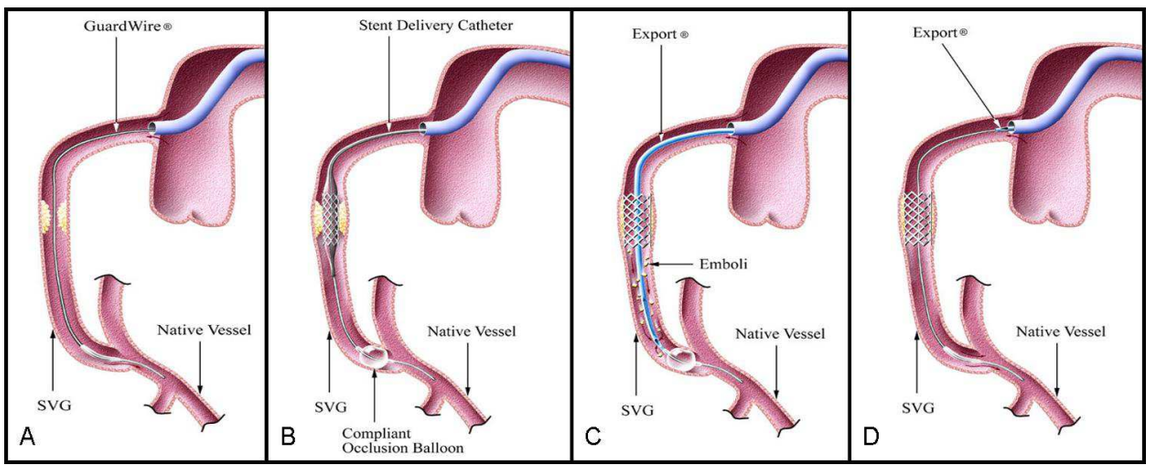


Fig. 2. Diagram of the GuardWire temporary occlusion and aspiration system. A) The lesion is crossed with the GuardWire. The distal occlusion balloon is positioned proximal to anastomosis. The stent/balloon is advanced to the tip of the guide catheter. B) The compliant occlusion balloon at the GuardWire tip is inflated to occlude flow before the stent is deployed. C) After stent deployment, an Export catheter is advanced over the GuardWire and aspiration is performed to remove the stagnant column of blood with suspended embolic debris. D) The GuardWire balloon is deflated to restore antegrade blood flow. Courtesy of Medtronic.

A morphometric and histological analysis of aspirated debris in the SAFE (Saphenous Vein Graft Angioplasty Free of Emboli) trial, using the GuardWire, showed grossly visible red and/or yellow debris extracted from 91% of the patients (Figure 3). Scanning electron microscopy documented particles ranging from 17 to 807 μm in diameter, with 81% of the aspirated particle size smaller than 96 microns (Grube et al., 2020). This is of particular consideration when one considers that the FilterWire (Boston Scientific, Natic, MA) has an 80 μm diameter pore size (Carter et al., 2007).

Despite these results there are some disadvantages with the use of these devices. The resulting absence of antegrade flow during balloon inflation may result in distal ischaemia,

which is poorly tolerated by some patients. Sixty one percent of patients in the SAFE trial developed angina during balloon inflation; however, in no patient was ischaemia so severe as to prompt premature deflation of the occlusion balloon. Additionally, balloon-induced injury may occur if they are not used carefully and it is difficult to get adequate imaging during the procedure while the distal vessel is occluded (Morís et al., 2009).

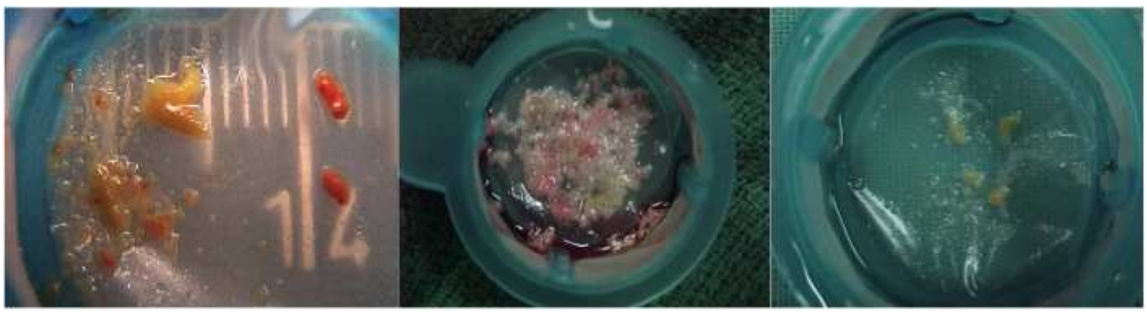


Fig. 3. Aspirated debris from a saphenous vein graft. Courtesy of Medtronic.

A second-generation distal balloon occlusion device, TriActiv (Kensey Nash Corp., Exton, PA), has 4 principal components: a balloon guidewire consisting of a 0.014" hypotube with a carbon dioxide–inflated compliant occlusion balloon on the wire (balloon diameter 3-5 mm), a modified syringe filled with sterile carbon dioxide used to inflate the occlusion balloon, a 4F side-attachable flush catheter, and a drive console with mechanical pumps for infusion and extraction. The lesion is crossed with the balloon guidewire and the occlusion balloon is positioned at least 20 mm beyond the distal edge of the target lesion. The occlusion balloon is inflated with carbon dioxide. A stent is delivered over the Balloon Guidewire and deployed at the lesion. The flush catheter is advanced over the balloon guidewire and saline is infused via holes in the distal end. Extraction of fluid and debris is performed through the guiding catheter. The occlusion balloon is deflated and flow is restored (Carrozza et al., 2005a).

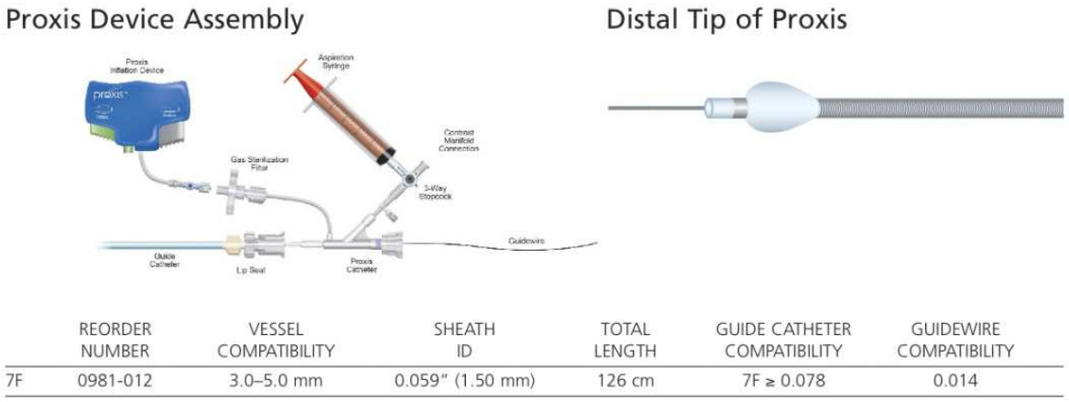
The PRIDE (Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization) study was a prospective randomized trial, which enrolled patients with coronary ischemia and lesions in saphenous vein grafts in two cohorts. Cohort I randomized patients to protection with the TriActiv System versus percutaneous coronary intervention without embolic protection, to demonstrate superiority of the TriActiv System compared with an "unprotected" group. Given the small number of patients in Cohort I, meaningful conclusions regarding the superiority of TriActiv to saphenous vein graft intervention without embolic protection could not be made.

Cohort II randomized 631 patients to embolic protection with the TriActiv System or control group (Guardwire System [Medtronic] or Filterwire EX [Boston Scientific]) to establish non-inferiority to other distal protection devices. The incidence of major adverse cardiac events at 30 days was 11.2% for the TriActiv group and 10.1% for the control group (relative risk = 1.1%; 95% confidence interval 0.67 to 1.76; p = 0.65; p = 0.02 for non-inferiority). Safety and efficacy end points were similar between groups except that patients randomized to the TriActiv System had more hemorrhagic complications (10.9% vs. 5.4%; p = 0.01). Patients in the TriActiv group were more likely to require blood transfusion. Sub-group analysis indicated that the higher rate of transfusion in the TriActiv cohort was associated with an early design of the haemostatic valve in combination with 8-F guiding catheters. The

TriActiv System was shown to be not inferior to approved embolic protection devices for the treatment of diseased saphenous vein grafts (Carrozza et al., 2005b).

10.2 Proximal balloon occlusion devices

The Proxis Embolic Protection System (St. Jude Medical, Maple Grove, Minnesota) is a unique single-operator catheter that is deployed proximal to the target lesion before crossing. Inflation of the sealing balloon interrupts antegrade flow during the period of lesion intervention. Stagnated blood and emboli liberated during intervention is then retrieved by gentle aspiration or via ancillary flushing of the vessel (Figure 4).



	REORDER NUMBER	VESSEL COMPATIBILITY	SHEATH ID	TOTAL LENGTH	GUIDE CATHETER COMPATIBILITY	GUIDEWIRE COMPATIBILITY
7F	0981-012	3.0–5.0 mm	0.059" (1.50 mm)	126 cm	7F ≥ 0.078	0.014

Fig. 4. Image of the Proxis embolic protection system. Courtesy of St. Jude Medical.

The PROXIMAL (Proximal Protection During Saphenous Vein Graft Intervention) trial was a multicenter prospective randomized trial, which compared 2 treatment strategies in a noninferiority format. Patients with saphenous vein graft stenosis were randomized to 1 of 2 treatment strategies: a current-care control arm (distal embolic protection device with FilterWire or GuardWire whenever possible, and no embolic protection when not) or a test arm (proximal protection with the Proxis system whenever possible and distal embolic protection when anatomy precluded proximal protection).

A total of 594 patients undergoing stenting of 639 saphenous vein grafts were prospectively randomized. The primary composite end point of death, myocardial infarction, or target vessel revascularization at 30 days by intention to treat analysis occurred in 10.0% of control and 9.2% of test patients; difference = -0.8% (95% confidence interval [CI] -5.5% to 4.0%); p for noninferiority= 0.0061. In device specific analysis, this composite end point occurred in 11.7% of distal protection patients and 7.1% of proximal protection patients (difference = -4.6% [95% CI -9.6% to 0.3%]; p for superiority = 0.10, p for noninferiority = 0.001). Finally, in the subset of patients with lesions amenable to treatment with either proximal or distal protection devices (n = 410), the primary composite end point occurred in 12.2% of distal protection patients and 7.4% of proximal protection patients; p for superiority = 0.14, p for noninferiority = 0.001.

This study concluded that using proximal embolic protection whenever possible during treatment of diseased saphenous vein grafts produced outcomes similar to those with distal embolic protection (Mauri et al., 2007).

Unfortunately, this device also has limitations: there is no antegrade flow with the subsequent possibility of myocardial ischaemia during the procedure, its utilization is more complex than the distal filters and they can not be used in ostial disease (Morís et al., 2009).

10.3 Filter devices

Distal embolic filter devices maintain distal perfusion and allow injection of contrast medium during PCI while trapping most particulate debris. The advantages are that they preserve antegrade flow, contrast imaging is possible throughout the procedure and they are very simple to use. However, they are associated with limitations such as the fact that may not be able to capture all the debris, it may also be difficult to evaluate retrieval of the debris during the procedure, delivery catheters may cause embolization before filter deployment and the possibility of snagging of the retrieval sheath on the stent (Morís et al., 2009).

The FilterWire EZ (Boston Scientific) consists of a distal polyurethane filter with a 110 μm pore size mounted on a 0.014-inch guidewire. The latest version has a 100 μm pore size. The system consists of a protection wire, a delivery sheath, a retrieval sheath and accessories (Figures 5 and 6). When deployed, the protection wire's filter bag is designed to capture and recover emboli that may be released during the procedure. The protection wire is used as the primary guidewire during the procedure. The floppy tip of the protection wire and the filter loop are radiopaque to enable visual guidance during placement. At the completion of the procedure, the filter is captured using the retrieval sheath and then removed from the patient (Figure 7). The loop of the device is designed to appose vessels ranging from 3.5 to 5.5 mm.

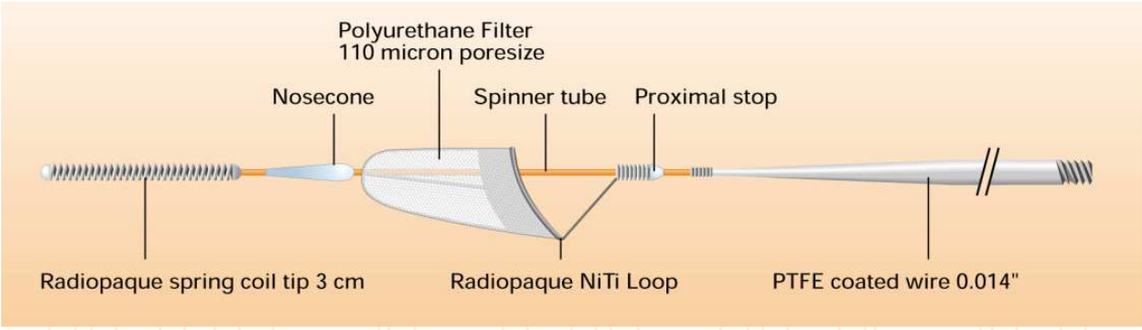


Fig. 5. Image of the FilterWire EZ. Courtesy of Boston Scientific.

The FIRE (FilterWire EX Randomized Evaluation) trial was a multicenter randomized trial designed to evaluate the safety and efficacy of distal microcirculatory protection with the FilterWire EX compared with the GuardWire balloon occlusion and aspiration device during percutaneous intervention of diseased saphenous vein grafts. Six hundred and fifty one patients undergoing stent implantation in 682 de novo lesions in saphenous vein grafts with a reference diameter between 3.5 to 5.5 mm were randomized. Device success (defined as the ability to deliver, deploy and retract a device at and from the target location for FilterWire and the ability to deliver a device to the target, obtain distal occlusion and perform aspiration without loss of occlusion attributable to leak or rupture for GuardWire) was 95.5% and 97.2% with the FilterWire EX and GuardWire, respectively (p= 0.25).

Postprocedural measures of epicardial flow, angiographic complications and the extent of myonecrosis were similar between the 2 groups. The primary end point of the study, the composite occurrence of major adverse cardiac events, including death, myocardial infarction or target vessel revascularization at 30-days occurred in 9.9% of FilterWire EX patients and 11.6% of GuardWire patients (difference [95% confidence interval] = -1.7% [-6.4%, 3.1%]; p for superiority = 0.53, p for noninferiority = 0.0008). This was driven primarily by non-Q wave myocardial infarction. Although exploratory subgroup analyses demonstrated a possible benefit of the FilterWire EX compared with the GuardWire in smaller vessels and eccentric lesions, the mechanistic explanation for these observations is uncertain, and these findings may be attributable to chance. It is important to note that, event rates were very low in both groups when only one stent was implanted or the total length of stents was limited. Conversely, the longer the lesion and the greater the number and length of stents implanted, the higher the event rate with both protection devices. Periprocedural adverse event rates were also increased in thrombotic lesions and degenerated vein grafts (Stone et al., 2003). By 6 months, the outcomes of the FIRE trial showed similar major adverse cardiac event increases to 19.3% in the FilterWire EX and to 21.9% in the GuardWire groups (p= 0.44) (Halkin et al., 2006).

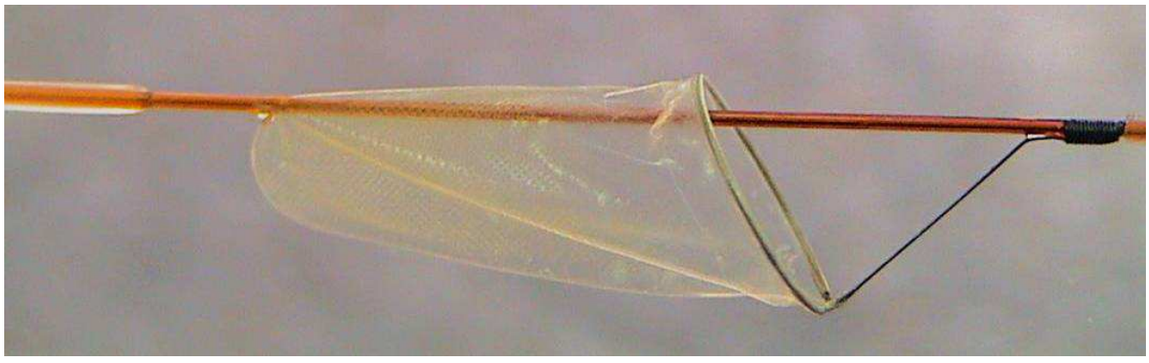


Fig. 6. Image of the FilterWire EZ. Courtesy of Boston Scientific.

The SpiderRX embolic protection device (eV3, Plymouth, MN) is a nitinol mesh filter system. One major innovation of this filter is the ability to cross the lesion with a conventional 0.014-inch guidewire, then deploying the filter via monorail delivery catheter (Carter et al., 2007). This device was assessed in the Spider trial, which randomized 732 patients to saphenous vein intervention using either the Spider device or a control arm of distal protection with the GuardWire or the FilterWire. Major adverse cardiac event rates were statistically similar between both groups after 30 days. Compared with controls, the SpiderRX showed non-inferiority in terms of all secondary end points, including device success, in-hospital major adverse cardiac events, clinical success and procedural success (Carter et al., 2007 & White, 2006).

One concern regarding the use of filter based systems versus balloon occlusion systems has been the functional limitations of the pore size and retrieved particulate debris. This concern however, has not been substantiated by the outcomes of the clinical trials. In fact, one analysis of retrieved particles using a filter device and the GuardWire showed retrieval of particles well less than 100 μm. It is possible that deposition of platelets and debris reduces the functional pore size (Carter et al., 2007).

Although, as has been mentioned above, none of these devices has demonstrated more efficacy than others in a randomized trial, some recommendations can be made based on anatomical considerations and tolerance of absence of antegrade flow: distal occlusion may be the preferred choice in cases of proximal disease with high plaque or thrombus burden; filters may be proposed in cases of poor tolerance for ischaemia or single remaining grafts without distal disease and proximal occlusion devices would be indicated in grafts with distal disease, especially in relatively straight vessels (Morís et al., 2009).

Distal protection devices have been shown to enhance procedural success rates, reduce the occurrence of no reflow, and prevent large as well as small periprocedural infarctions; the former of which is clearly prognostically relevant. These results thus support the general recommendation for routine use of distal protection devices during saphenous vein graft intervention when possible. However, it should be recognised that the long-term course after intervention in diseased saphenous vein grafts is not benign even when distal protection is used. Periprocedural major adverse events still occur in approximately 10% of patients, and the rates of death, myocardial infarction and repeat revascularisation procedures are relatively high compared with percutaneous coronary interventions in native coronary arteries, due not only to restenosis at the target site but also to disease progression in sites remote from that of the index intervention. These observations underscore the need for intensive post-discharge surveillance and secondary prevention measures in this population (Halkin et al., 2006).

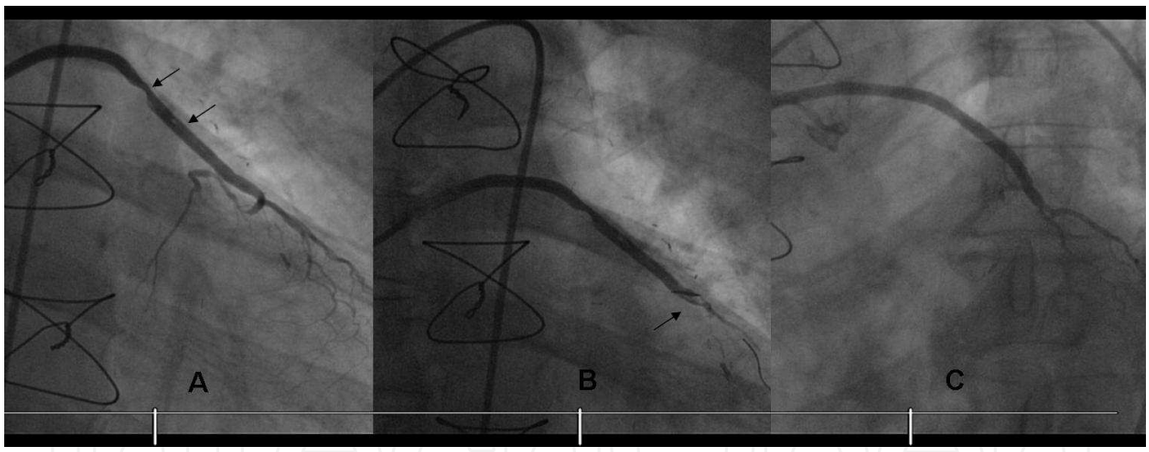


Fig. 7. Percutaneous intervention in a saphenous vein graft using a FilterWire embolic protection device. A) Saphenous vein graft stenosis with superimposed thrombus (arrows). B) Particulate debris trapped within the FilterWire embolic protection device (arrow). C) End result after removing the FilterWire.

11. Conclusions

Saphenous vein graft disease represents the "Achilles heel" of coronary artery bypass surgery interventions, due to the high failure rate of saphenous vein grafts (Lupi et al., 2011).

Stenosed saphenous vein grafts can be treated by percutaneous intervention or a second coronary artery bypass surgery; however, a repeated bypass surgery is burdened by a higher risk of death and provides less symptomatic improvement (Lupi et al., 2011).

Attempts at percutaneous revascularisation in saphenous vein graft lesions with balloon angioplasty were limited by a relatively low procedural success rate and a high incidence of angiographic recurrence.

Stent implantation in patients with focal saphenous vein graft lesions improved procedural success and clinical outcome compared with balloon angioplasty. However, even with the use of stents treatment of saphenous vein graft lesions is associated with a high incidence of acute complications, principally distal embolisation and periprocedural myocardial infarction, because of the more friable atherosclerotic or thrombotic components of the saphenous vein graft lesions (Stankovic et al., 2003). Besides, the results of bare metal stents in saphenous vein grafts are less favourable than those in native vessels, with restenosis rates exceeding 30% (Savage et al., 1997; Silber et al., 2005). In fact some authors recommend carrying out percutaneous coronary intervention in native vessels whenever possible even when there is complete obstruction or to consider the possibility of new revascularisation surgery rather than percutaneous saphenous vein graft intervention (Lozano et al., 2005).

In an attempt to improve the outcome of intervention in stenotic vein grafts, several approaches and adjunctive pharmacological regimens have been studied, but with the exception of distal protection devices, none showed a clear benefit in reducing the incidence of distal embolisation, especially in complex lesions (Stankovic et al., 2003). However, despite the existence of successful proximal and distal filters and balloons, 30-day major adverse cardiac event rates still hover between 8% and 10%. A logical approach to assess a potential reduction in the incidence of no-reflow phenomenon and its deleterious consequences would be to conduct prospective, randomised, controlled trials assessing the combination of distal filter protection devices, glycoprotein IIb/IIIa inhibitors and pre-treatment with intra-graft administration of vasodilators, particularly nicardipine.

Drug-eluting stents have been shown to reduce restenosis in many lesion types and clinical syndromes. However, there is a paucity of prospective data on drug-eluting stents in saphenous vein graft intervention (Brilakis et al., 2009). Most meta-analysis of randomised trials and observational studies comparing drug-eluting stents and bare metal stents in saphenous vein graft percutaneous intervention suggest that drug-eluting stent use in saphenous vein graft is safe and reduces target vessel revascularisation.

Patients with previous coronary artery bypass graft surgery suffer from diffuse atherosclerosis of native coronary arteries as well as rapid saphenous vein graft degeneration, thus the benefit from drug-eluting stents could be largely diluted by acute coronary syndromes arising from other previously untreated coronary lesions (Lupi et al., 2011).

In addition, it is well established that the long-term prognosis of patients with diseased saphenous vein grafts is mainly impacted by progression of disease in the nonintervened saphenous vein grafts segments (Ellis et al., 1997 & Keeley et al., 2001).

Large, prospective, multicenter, randomised-controlled clinical trials that use a clinical rather than angiographic end point are needed to confirm the beneficial role of drug-eluting stents in saphenous vein graft lesions (Brilakis & Berger, 2008). Additionally, longer-term follow-up of at least 3 to 5 years is essential for randomised trials involving the use of drug-eluting stents in saphenous vein grafts to address two potentially harmful events. First, the

possibility of late restenosis catch-up with drug-eluting stents in saphenous vein graft disease, considering their higher restenosis rate and more delayed restenosis process than in native vessels. Second, the possible risk of late stent thrombosis, which has been already shown for native coronary arteries (Mc Fadden et al., 2004; & Ong et al., 2005), in a potentially favourable milieu such as that in saphenous vein graft disease.

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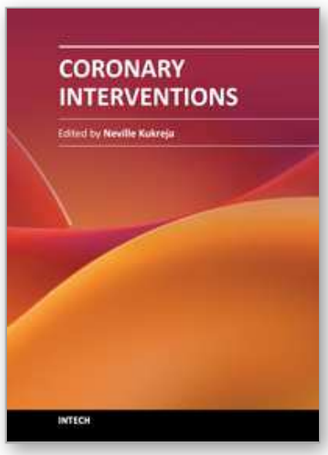

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