Embolic Protection Devices in Aortocoronary Saphenous Vein Graft Intervention

Reduced MACE rates after intervention support continued use, although device development and innovation are imperative.

BY JASON H. ROGERS, MD, AND REGINALD I. LOW, MD

Embolic protection devices (EPDs) were first developed to provide cerebral protection during carotid artery stenting and have led to marked reductions in the combined endpoints of stroke or death.[1,2] Therefore, it was natural that these devices should be applied to native coronary and aortocoronary saphenous vein graft (SVG) interventions to reduce clinically significant athero- and thromboembolism. Despite multiple clinical trials, few data currently exist to support the routine use of any EPD in patients with acute coronary syndromes undergoing percutaneous native coronary intervention.[3] Reasons for this are likely multiple, including a markedly prothrombotic milieu, liberation of small thrombi or vasoactive substances that may pass through an EPD, or in situ thrombus formation distal to the site of protection.

Based on current clinical data, SVGs have emerged as the primary target for EPDs. SVG interventions are known to result in a high risk (~20%) of major adverse cardiac events (MACE) and a significant risk of slow- or no-reflow, resulting in periprocedural myocardial infarction.[4] The reason for the differential benefit of EPDs in SVGs over native coronaries reflects the disparate composition of plaque between these two vessel types. SVG athero-occlusive disease tends to be rich in cholesterol, with less calcium and intimal proliferation than in native coronary arteries.[5] Slow- or no-reflow in SVG intervention is more often related to distal embolization of friable, lipid-rich plaque than thrombus.[6] This concept has been demonstrated in aspirate analyses after SVG intervention during distal balloon occlusion in which copious plaque constituents (cholesterol crystals, foam cells, fibrous plaque, and necrotic core) were recovered.[7,8] The preponderance of nonthrombotic, plaque-rich emboli explains why glycoprotein (GP) IIb/IIIa inhibitors have not been as efficacious in SVG intervention as they are in native coronaries.[9,10]

> ". . . MACE rates are significant, highlighting the need for improved device development and further understanding of diseased vein graft pathophysiology."

TYPES OF EPDs

There are three main types of EPDs employed in SVG intervention: distal filtration, distal balloon occlusion, and proximal occlusion devices. Thrombus extraction catheters and covered stents have not been found to be useful in reducing MACE in routine SVG intervention.[11,12] The EPDs for which there exist strong clinical data to support use in SVG intervention include (1) distal filtration: FilterWire EX/EZ (Boston Scientific Corporation, Natick, MA), Spider/SpideRX (ev3 Inc., Plymouth, MN), Rubicon filter (Rubicon Medical Corporation, Salt Lake City, UT), and Interceptor wire (Medtronic AVE, Inc., Santa Rosa, CA); (2) distal balloon occlusion: GuardWire (Medtronic, Inc., Minneapolis, MN), and TriActiv FX system (Kensey Nash, Exton, PA); and (3) proximal occlusion: Proxis (St. Jude Medical, Inc., St. Paul, MN), and F.A.S.T.

TABLE 1. EMBOLIC PROTECTION DEVICES IN SFG INTERVENTION: MAJOR CLINICAL TRIALS

Trial Name	Device	No. of Patients	Trial Design	Follow-Up and Endpoints	Results (EPD vs Control)
SAFE	GuardWire	105	Registry	(1°) In-hospital MACE	5%
				(2°) Final TIMI-3 flow	99%
				(2°) No reflow	0%
SAFER	GuardWire	801	Randomized: GuardWire vs no EPD	(1°) 30-day MACE	9.6% vs 16.5%, *P*=.004
				(2°) No reflow	3% vs 9%, *P*=.02
FIRE	FilterWire EX	651	Randomized: FilterWire EX vs GuardWire	(1°) 30-day MACE	9.9% vs 11.6%, *P*=NS
				(1°) 6-month MACE	19.3% vs 21.9%, *P*=NS
BLAZE I, BLAZE II	FilterWire EZ	221	Combined registry	(1°) 30-day MACE	5% (vs 9.9% in FIRE, *P*=.03)
SPIDER	Spider/SpideRX	747	Randomized: SpideRX vs FilterWire EX/EZ or GuardWire	(1°) 30-day MACE	9.2% vs 8.7%, *P*=NS
PRIDE	TriActiv System	631	Randomized: TriActiv System vs FilterWire EX or GuardWire	(1°) 30-day MACE	11.2% vs 10.1%, *P*=NS
				(2°) Vascular complications	10.9% vs 5.4%, *P*=.01
CAPTIVE	CardioShield	652	Randomized: CardioShield vs GuardWire	(1°) 30-day MACE	10% vs 12%, *P*=NS
TRAP	Trap Vascular Filtration System (VFS)	358 (incomplete enrollment)	Randomized: Trap VFS vs no EPD	(1°) 30-day MACE	12.7% vs 17.3%, *P*=.24
PROXIMAL	Proxis	594	Randomized: Proxis vs FilterWire or GuardWire	(1°) 30-day MACE	9.2% vs 10%, *P*=NS

Funnel Catheter (Genesis Medical Interventional, Inc., Redwood City, CA).

The number, size, and volume of particulate debris liberated by SVG stenting have been studied comparing the GuardWire with a distal vascular filter having an average distal pore size of 100 µm. During SVG intervention, the amount and character of retrieved matter were similar. For both filter and GuardWire populations, most particles were <100 µm in longest dimension (87% and 90% of particles, respectively). The distribution of particle sizes and embolic load captured was equivalent.[13] These data and others are important in establishing the principle that despite a nominal pore size of ~100 µm, the functional orifice size of a filter is smaller, likely due to deposition of aggregate debris, platelets, or fibrin on the filter surface.[14]

CLINICAL TRIALS

Numerous clinical trials to date have demonstrated the clinical efficacy of EPDs in reducing MACE during routine percutaneous intervention on aortocoronary SVGs (Table 1). It should be noted, however, that despite the use of current-generation EPDs, MACE rates are still significant, highlighting the need for improved device development and further understanding of diseased vein graft pathophysiology.

DISTAL EPDs

SAFE

The first published study to demonstrate the clinical efficacy and safety of an EPD utilized the AngioGuard Emboli Collection Guidewire in 11 patients undergoing SVG intervention. Outcomes were promising with 0% in-hospital MACE.[15] The SAFE registry (Saphenous vein graft Angioplasty Free of Emboli) was a larger series of 105 patients that utilized the GuardWire and provided additional evidence that EPDs could improve procedural outcomes.[8] In this registry, thrombus burden was relatively low, and GuardWire balloon occlusion was well tolerated. In-hospital MACE was low (5%), which was superior to historical controls that reported significant in-hospital complication rates as high as 31%.[16] These results gave rise to the first randomized trial (SAFER, Saphenous vein graft Angioplasty Free of Emboli Randomized) to confirm improved SVG intervention clinical outcomes when compared to a control group in which distal protection was not used.[17] An absolute 6% reduction in 30-day MACE was achieved, with improvement in secondary angiographic and myonecrotic endpoints.

FIRE and BLAZE I and II

The use of the FilterWire was originally reported in a registry that identified failure of complete device apposition in phase 1 results, subsequently corrected in phase 2.[18] This experience highlighted some of the technical considerations for distal EPD use, which must be carefully observed: proper device sizing and full apposition to prevent distal embolization. The pivotal FIRE trial (FilterWire EX Randomized Evaluation) compared the FilterWire and GuardWire in a randomized manner in patients undergoing elective SVG intervention with low thrombus burden and brisk preprocedural flow.[19] Thirty-day and 6-month MACE rates were favorable and noninferior to the GuardWire arm of the trial.[20] Subgroup analyses demonstrated improved procedural outcomes with GP IIb/IIIa inhibitor use in conjunction with the FilterWire, as well as improved outcomes with the FilterWire in smaller vessels.[21,22] The latest FilterWire EZ device (improved primarily with a more central suspension arm and lubricious coating) was studied in the BLAZE I and II registries.[23] In these combined registries, 221 patients underwent stenting of 229 SVG lesions using the FilterWire EZ system. Inclusion criteria were identical to the FIRE trial except that curved segments and smaller 2.25-mm to 3.5-mm reference diameter vessels were allowed. Overall 30-day MACE rates were 5.0%, an improvement compared to 9.9% MACE in FIRE (P=.03).

SPIDER

The SpideRX distal embolic protection device has been studied in the SPIDER (Saphenous vein graft Protection In a Distal Embolic protection Randomized) trial. This trial randomized 747 patients undergoing SVG intervention to receive either the Spider or SpideRX EPD versus control devices (GuardWire or FilterWire EX/EZ).[24] Baseline characteristics were similar in both groups, and in-hospital and 30-day MACE were similar in both groups (30-day MACE, 9.2% for the study group and 8.7% for the control, P=NS). A potential advantage of the SpideRX system is that it is available in 1-mm incremental sizing from 3 mm to 7 mm.

PRIDE and ASPIRE

The PRIDE (PRotection during saphenous vein graft Intervention to prevent Distal Embolization) study was a prospective trial randomizing 631 patients with SVG lesions to distal embolic protection with the TriActiv System versus a control group that used either the GuardWire or FilterWire EX. Thirty-day MACE was 11.2% for the TriActiv group and 10.1% for the control group (P=NS), proving noninferiority. However, the TriActiv System resulted in more hemorrhagic complications (10.9% vs 5.4%, P=.01), best explained by the use of larger 8-F guiding catheters, which resulted in a higher aspiration and vascular complication rate.[25] A follow-up registry, ASPIRE (Angioplasty in SVGs with Post Intervention Removal of Embolic debris), using the second-generation TriActiv FX system, enrolled 113 patients with SVG lesions, and compared outcomes to the active control arm of the PRIDE trial. In-hospital (2.2%) and 30-day MACE (3.2%) were remarkably low (vs 10.1% historical control, P=.013), with no excess hemorrhagic complications using the modified device.[26]

CAPTIVE

The CAPTIVE (CardioShield Application Protects during Transluminal Intervention of Vein grafts by reducing Emboli) trial was a multicenter trial comparing the CardioShield embolic protection device with the GuardWire. It was first designed as a superiority trial (CardioShield compared to no distal protection; n=197), but changed into a noninferiority trial (CardioShield vs GuardWire; n=652) as market conditions changed. The CardioShield was not found to be noninferior by a very narrow margin.[27]

TRAP

The Trap Vascular Filtration System (VFS) (Microvena, White Bear Lake, MN) was evaluated in a prospective randomized trial designed to enroll 752 patients. Patients with SVG lesions were randomized to undergo stenting with or

without the Trap device. Unfortunately, this study was terminated early by the sponsor because of poor recruitment once the GuardWire was approved by the FDA for clinical use. Although use of the Trap VFS was shown to be safe, the study lacked sufficient power to detect a significant benefit with this device.[28]

RULE and RULE SVG

Other distal EPDs include the low-profile Rubicon filter that was studied in a feasibility trial in Europe (RULE, RUbicon fiLtEr in saphenous vein grafts and native coronaries). The device was used in 42 patients (45% SVGs) with 4.5% 30-day MACE. A larger, randomized US pivotal trial, RULE SVG, is currently evaluating the Rubicon filter against the FilterWire in SVGs treated with a Taxus Liberte stent (Boston Scientific Corporation, Natick, MA).[29] The Interceptor wire is another distal EPD that was studied in 26 patients undergoing SVG intervention with low (7.7%) MACE.[30] Larger randomized trials are pending.

PROXIMAL EPDs

FASTER and PROXIMAL

The Proxis system was the first to demonstrate that retrograde blood flow could be achieved during proximal occlusion during SVG intervention and that embolic material could be captured. The FASTER trial (Feasibility And Safety Trial for its embolic protection device during transluminal intervention in coronary vessels: a European Registry) was a prospective, nonrandomized, multicenter clinical feasibility and safety study that enrolled 40 patients who underwent treatment of stenotic lesions (58% SVGs) with the Proxis system. Proxis was successfully used 95% of the time, and embolic debris was qualitatively identified in all cases. MACE occurred in only two patients (5.0%).[31] This preliminary work led to the PROXIMAL trial (PROXimal Protection During Saphenous Vein Graft Intervention Using the Proxis Embolic Protection System: A Randomized, Prospective, Multicenter TriAL). PROXIMAL was a randomized, prospective, multicenter trial. The test arm (n=294) involved use of the Proxis system whenever possible and a FilterWire or GuardWire when use of Proxis was not possible. The control arm (n=300) involved use of a FilterWire or GuardWire whenever possible and no protection when use of either wire was not possible. In an intention-to-treat analysis of 30-day MACE, patients in the Proxis and control arms had statistically similar incidence rates of 9.2% vs 10% (*P*=NS).[32]

Other proximal protection systems aimed primarily at proximal protection during carotid artery stenting include the Gore Neuro Protection (formerly the ArteriA/Parodi device, Gore & Associates, Flagstaff, AZ) and Mo.Ma systems (Invatec, Brescia, Italy). A recent novel device is the F.A.S.T. Funnel Catheter. Results of a multicenter feasibility trial, which demonstrate a low MACE rate, will be announced publicly at TCT 2006. Larger trials are planned.[33]

TECHNICAL CONSIDERATIONS

The interventionist's choice of EPD during SVG stenting will depend on a variety of factors, including feasibility, device familiarity, ease of use, cost, and perceived efficacy. Despite strong clinical data, a recent survey found that interventionists are currently using EPDs in only half of all eligible SVG cases.[34] In a recent consecutive series of 147 SVG interventions, 57% of grafts had angiographic exclusion criteria for a distal balloon occlusion system, and 42% had exclusions for a distal filter.[35] Exclusions in this series were based on the device instructions and included total occlusions, true ostial lesions, lesions <5 mm from the ostium or <20 mm from the distal anastomosis (inadequate landing zone), and a landing zone vessel diameter <3 mm or >6 mm. In addition, the decision to use a distal EPD mandates the ability to cross the lesion prior to device deployment, which may prematurely embolize debris. Because of these limitations, attention continues to be focused on lower-profile, improved distal protection systems as well as proximal protection devices. Techniques that can aid in crossing severely stenotic or tortuous vessels include the use of guiding catheters with adequate backup, the "buddy wire" technique, or predilation with a 2-mm balloon. Proximal protection systems should expand the utilization of EPDs in SVG intervention, and preliminary data are encouraging.

CONCLUSION

Despite the numerous advances that have been made in the arena of percutaneous coronary intervention, SVG revascularization remains a relatively high-risk procedure. Clinical trials have clearly demonstrated the efficacy of EPDs in reducing in-hospital, early, and intermediate MACE after routine SVG intervention. Based on current clinical trials, EPDs should, when feasible, be the standard of care in all SVGs. However, since MACE rates remain substantive despite current EPD technology, continued device development and innovation in this area should remain a high priority. ■

Jason H. Rogers, MD, is with the Division of Cardiovascular Medicine, University of California, Davis Medical Center, Sacramento, California. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Rogers may be reached at

(916) 734-3764; jason.rogers@ucdmc.ucdavis.edu.

Reginald I. Low, MD, is with the Division of Cardiovascular Medicine, University of California, Davis Medical Center, Sacramento, California. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Low may be reached at (916) 734-3764; pciwithdes@aol.com.

1. Theron J, Courtheoux P, Alachkar F, et al. New triple coaxial catheter system for carotid angioplasty with cerebral protection. Am J Neuroradiol. 1990;11:869-74; discussion 875-877.
2. Wholey MH, Al-Mubarek N. Updated review of the global carotid artery stent registry. Cath Cardiovasc Interv. 2003;60:259-266.
3. Gorog DA, Foale RA, Malik I. Distal myocardial protection during percutaneous coronary intervention: when and where? J Am Coll Cardiol. 2005;46:1434-1445.
4. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of "no-reflow" after percutaneous coronary intervention. Circulation. 1994;89:2514-2518.
5. Garratt KN, Edwards WD, Kaufmann UP, et al. Differential histopathology of primary atherosclerotic and restenotic lesions in coronary arteries and saphenous vein bypass grafts: analysis of tissue obtained from 73 patients by directional atherectomy. J Am Coll Cardiol. 1991;17:442-448.
6. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. Circulation. 2000;101:570-580.
7. Webb JG, Carere RG, Virmani R, et al. Retrieval and analysis of particulate debris after saphenous vein graft intervention. J Am Coll Cardiol. 1999;34:468-475.
8. Grube E, Schofer JJ, Webb J, et al. Evaluation of a balloon occlusion and aspiration system for protection from distal embolization during stenting in saphenous vein grafts. Am J Cardiol. 2002;89:941-945.
9. Ellis SG, Lincoff AM, Miller D, et al. Reduction in complications of angioplasty with abciximab occurs largely independently of baseline lesion morphology. EPIC and EPILOG investigators. Evaluation of 7E3 for the prevention of ischemic complications. Evaluation of PTCA to improve long-term outcome with abciximab GPIIb/IIIa receptor blockade. J Am Coll Cardiol. 1998;32:1619-1623.
10. Mathew V, Grill DE, Scott CG, et al. The influence of abciximab use on clinical outcome after aortocoronary vein graft interventions. J Am Coll Cardiol. 1999;34:1163-1169.
11. Stankovic G, Colombo A, Presbitero P, et al. Randomized evaluation of polytetrafluoroethylene-covered stent in saphenous vein grafts: the Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts (RECOVERS) Trial. Circulation. 2003;108:37-42.
12. Turco MA, Buchbinder M, Popma JJ, et al. Pivotal, randomized U.S. study of the Symbiottrade mark covered stent system in patients with saphenous vein graft disease: Eight-month angiographic and clinical results from the Symbiot III trial. Cath Cardiovasc Interv. 2006;68:379-88.
13. Rogers C, Huynh R, Seifert PA, et al. Embolic protection with filtering or occlusion balloons during saphenous vein graft stenting retrieves identical volumes and sizes of particulate debris. Circulation. 2004;109:1735-1740.
14. Quan VH, Huynh R, Seifert PA, et al. Morphometric analysis of particulate debris extracted by four different embolic protection devices from coronary arteries, aortocoronary saphenous vein conduits, and carotid arteries. Am J Cardiol. 2005;95:1415-1419.
15. Grube E, Gerckens U, Yeung AC, et al. Prevention of distal embolization during coronary angioplasty in saphenous vein grafts and native vessels using porous filter protection. Circulation. 2001;104:2436-2441.
16. Hong MK, Mehran R, Dangas G, et al. Creatine kinase-MB enzyme elevation following successful saphenous vein graft intervention is associated with late mortality. Circulation. 1999;100:2400-2405.
17. Baim DS, Wahr D, George B, et al. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. Circulation. 2002;105:1285-1290.
18. Stone GW, Rogers C, Ramee S, et al. Distal filter protection during saphenous vein graft stenting: technical and clinical correlates of efficacy. J Am Coll Cardiol. 2002;40:1882-1888.
19. Stone GW, Rogers C, Hermiller J, et al. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. Circulation. 2003;108:548-553.
20. Halkin A, Masud AZ, Rogers C, et al. Six-month outcomes after percutaneous intervention for lesions in aortocoronary saphenous vein grafts using distal protection devices: results from the FIRE trial. Am Heart J. 2006;151:915 e1-7.
21. Jonas M, Stone GW, Mehran R, et al. Platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment during saphenous vein graft stenting: differential effects after randomization to occlusion or filter-based embolic protection. Eur Heart J. 2006;27:920-928.
22. Swaminathan A, Stone GW, Rogers C, et al. Influence of vessel diameter on the efficacy of distal protection devices during saphenous vein graft intervention. Am J Cardiol. 2005;95:651-654.
23. Cox D, Lui H, Caputo R, et al. The combined BLAZE I and BLAZE II registries. Am J Cardiol. 2005;96(suppl 7A):5H.
24. SPIDER SVG Clinical Report Nov-2005, ev3 Inc.
25. Carrozza JP Jr, Caussin C, Braden G, et al. Embolic protection during saphenous vein graft intervention using a second-generation balloon protection device: results from the combined US and European pilot study of the TriActiv Balloon Protected Flush Extraction System. Am Heart J. 2005;149:1136.
26. Metzger C. ASPIRE Investigators, Oral presentation, Angioplasty in SVGs with post intervention removal of embolic debris. ACC 2006; Atlanta, GA.
27. Holmes DR, Jr. CAPTIVE Study, Oral presentation, CardioShield application protects during transluminal intervention of vein grafts by reducing emboli. TCT 2004; Washington, DC.
28. Dixon SR, Mann JT, Lauer MA, et al. A randomized, controlled trial of saphenous vein graft intervention with a filter-based distal embolic protection device: TRAP trial. J Interv Cardiol. 2005;18:233-241.
29. Leon MB. Oral Presentation, Clinical experiences with the rubicon filter and the RULE-SVG trial. TCT 2005, Washington, DC.
30. Young JJ, Kereiakes DJ, Rabinowitz AC, et al. A novel, low-profile filter-wire (Interceptor) embolic protection device during saphenous vein graft stenting. Am J Cardiol. 2005;95:511-514.
31. Sievert H, Wahr DW, Schuler G, et al. Effectiveness and safety of the Proxis system in demonstrating retrograde coronary blood flow during proximal occlusion and in capturing embolic material. Am J Cardiol. 2004;94:1134-1139.
32. Late Breaking Clinical Trials, Proximal protection during saphenous vein graft intervention using the proxis embolic protection system: a randomized, prospective, multicenter trial. TCT 2005; Washington, DC.
33. Genesis Medical Interventional, Clinical Report, to be presented at TCT 2006, Washington, DC.
34. Lim MJ, Young JJ, Senter SR, et al. Determinants of embolic protection device use: case study in the acceptance of a new medical technology. Cath Cardiovasc Interv. 2005;65:597-599.
35. Mathew V, Lennon RJ, Rihal CS, et al. Applicability of distal protection for aortocoronary vein graft interventions in clinical practice. Cath Cardiovasc Interv. 2004;63:148-151.