Devices for Distal Protection During Percutaneous Coronary Revascularization

Laura Mauri, MD; Campbell Rogers, MD; Donald S. Baim, MD

Despite early perceptions that distal embolization of atherosclerotic plaque contents was a rare event during balloon angioplasty, it has now become clear that manipulation of atherosclerotic lesions with wires, balloons, atherectomy catheters, or stents does liberate plaque debris. The tendency of this liberated debris to cause clinical manifestations depends on the amount of debris, the size of particles, and the sensitivity of the perfused organ. Additionally, clinical experience with various embolic protection devices (EPDs) has shown that the capture and retrieval of potentially embolic debris reduce adverse events in situations where the amount of debris is largest (eg, saphenous vein grafts [SVGs]) and where the end organ is most sensitive (myocardium, with no reflow and creatine kinase [CK]-MB release; brain with new lesions on magnetic resonance imaging or clinical stroke). In contrast, other adjunctive medical therapies such as glycoprotein IIb/IIIa receptor antagonists, which have been shown to reduce overall rates of CK-MB release during other coronary interventional procedures, have failed to mitigate the impact of distal embolization in SVG intervention.1–3 Embolic protection is thus now firmly established as a routine component of SVG and carotid stenting, although randomized trials have not been performed for the latter indication.4,5

Although it is almost certain that atherosclerotic or atherothrombotic debris is released during other interventions on peripheral, renal, and native coronary arteries, the link between such embolization and clinical events (and hence the rationale for embolic protection) has been more difficult to demonstrate. This may be due to smaller amounts of embolic debris, less sensitive metrics of end-organ damage, or less complete capture of debris by devices tested to date in those locales. For example, initial trials of distal embolic protection in native coronaries during primary angioplasty for acute myocardial infarction have shown retrieval of smaller amounts of debris than seen during SVG intervention,6 in a clinical setting where the background elevation of CK and size of infarction may make it more difficult to discern any incremental reduction provided by embolic protection. Moreover, early generations of EPDs were themselves burdened by large-sized delivery systems and incomplete retrieval of liberated debris (due to poor wall apposition, stagnant pools of debris liberated after device retrieval, shunting of debris-laden blood into proximal side branches, etc). The purpose of the present review is to examine the classes of EPDs, consider specific examples therein, and summarize clinical evidence with regard to their use.

Embolic Protection: Mechanism of Action of Current and Novel Devices

There are 4 basic classes of EPDs, categorized according to their mechanism of operation: (1) distal occlusion, (2) distal filter, (3) proximal occlusion, and (4) local plaque trapping (Figures 1 and 2). Available clinical trial data on their use in SVGs are summarized in Table 1, with approval status listed in Table 2 and experience in native coronary arteries summarized in Table 3.

Distal Occlusion Devices

The concept of distal occlusion is to block the vessel being treated several centimeters beyond the target lesion so that plaque liberated from the lesion during angioplasty or stent placement remains suspended in the resulting stagnant column of blood. If that column of blood (and the suspended debris it contains) can be aspirated completely before the distal occlusion is relieved and antegrade flow is restored, distal embolization of debris will be prevented. Embodiments of this concept include the PercuSurge GuardWire (Medtronic, Minneapolis, Minn), and the TriActiv system (Kensey Nash, Exton, Pa). Each consists of a 0.014-inch-diameter hypotube on which an inflatable occlusion balloon is mounted. The balloon tip is passed across the lesion in its deflated state before any sort of angioplasty or stenting takes place, and the hypotube shaft is used as the interventional guidewire throughout the procedure. The distal balloon is inflated before intervention and remains inflated until a distal aspiration catheter (PercuSurge Export, Medtronic) or a distal saline infusion catheter used in conjunction with guiding catheter aspiration (Kensey Nash) has been used to aspirate or lavage the stagnant blood column and its suspended debris. At that point, the occlusion balloon is deflated, flow is restored, and the protection device is removed.
The strengths of this concept include the low crossing profile (typically 0.026 to 0.033 inches), which may lessen dislodgement of particles during positioning of the protection device before protective occlusion is established. Furthermore, distal occlusion theoretically traps both small and large particles as well as soluble mediators, as opposed to filters that may allow some smaller particles and soluble mediators to pass through. Limitations of this approach, however,
include the need for several minutes of end-organ ischemia caused by occlusion throughout the intervention, limited contrast opacification of the target lesion during occlusion, shunting of debris into proximal side branches (except in conduits like SVGs or the internal carotid artery, which lack proximal branches), potential failure of simple laminar aspiration to recover debris in stagnant pools near the fonnices of the occlusion balloon or in the loosely adherent boundary layer near the stent surface, and the inability of the interventionalist to tailor his or her guidewire choice to other procedural requirements.

US Food and Drug Administration (FDA) approval of the first such device (the distal occlusion GuardWire, Medtronic Vascular) was predicated on a 42% reduction in 30-day major adverse coronary event (MACE) rates in a large randomized trial of saphenous vein coronary bypass graft percutaneous coronary intervention (PCI), as compared with stenting over a conventional guidewire without embolic protection.5 This study showed consistent benefit, independent of glycoprotein IIb/IIIa antagonist use, across lesion subgroups at varying risk for MACE based on angiographic quantification of graft degeneration and estimated lesion plaque volume.7 It established embolic protection as the standard of care for SVG stenting, with favorable cost-benefit profile.8 Subsequently the TriActiv device (Kensey Nash) distal balloon occlusion device was approved by the FDA on the basis of the Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization (PRIDE) trial, which demonstrated noninferiority of this device as compared with the GuardWire or FilterWire devices in the prevention of MACE during SVG PCI.9

Whereas the benefits of the GuardWire shown in the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial changed the standard of care for SVG PCI, several similar randomized, controlled trials in the native coronary arteries during PCI for ST-elevation myocardial infarction have shown no reduction of infarct size (measured by single-photon emission computed tomography) and no improvement in ST-segment resolution.10–12 These negative results may be the consequence of the particular devices tested, the timing of intervention (after much of the injury had taken place), the difficulty of measuring benefit against the background of a large infarction and other mechanisms for cell death such as reperfusion injury and tissue edema, or the challenge of measuring the impact of a smaller embolic load than seen in SVG.6,13 On the basis of these results, there is no FDA-approved or guideline-based indication for use of distal protection in the native coronary arteries. The possibility does remain, however, that alternative embolic protection approaches may yet demonstrate benefit in certain native coronary settings in future randomized trials.

**Distal Embolic Filters**

The concept of distal filters for embolic protection depends on the concept that the deployed filter can allow ongoing perfusion and yet trap some, if not all, particulate debris. Although filters might be expected to retrieve only larger particles, careful analysis shows nearly identical particle size distribution and aggregate volume of debris retrieved after SVG PCI either with a distal filter (100-μm pore size) or a distal occlusion/aspiration system.6,14 The ability of filters to trap particles far smaller than their nominal pore size may include the need for several minutes of end-organ ischemia caused by occlusion throughout the intervention, limited contrast opacification of the target lesion during occlusion, shunting of debris into proximal side branches (except in conduits like SVGs or the internal carotid artery, which lack proximal branches), potential failure of simple laminar aspiration to recover debris in stagnant pools near the fonnices of the occlusion balloon or in the loosely adherent boundary layer near the stent surface, and the inability of the interventionalist to tailor his or her guidewire choice to other procedural requirements.

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stem from the tendency of particles to clump or strand across filter pores, reducing the functional pore size. Even if distal filters did allow smaller debris particles to pass through, experimental data by Hori et al\textsuperscript{15} suggest that embolic particles <100 μm are tolerated in far larger number before interfering with microcirculatory function than are larger particles, and smaller particles are thus less likely to cause end-organ damage. Moreover, the clinical confirmation of equivalency of some distal filters and distal occlusion devices in SVG PCI has been demonstrated in several trials comparing distal filter devices to the GuardWire distal occlusion device, confirming the limited clinical impact of either smaller embolic particles and humoral substances (eg, thromboxane) that may pass through a distal filter’s pores.\textsuperscript{9,16} Of note, however, some filters have failed to meet equivalency margins in clinical testing during SVG stenting,\textsuperscript{17} suggesting shortcomings in their lesion crossing or debris capture efficiency.

The strengths of distal filters include their ease of use, maintenance of distal perfusion, and the possibility of contrast imaging during operation. Weaknesses include the larger-diameter sheath (≈0.040 to 0.050 inches) generally required to maintain most filters in their collapsed state during advancement across the lesion (with potential dislodgement of debris or the need for unprotected predilation), reduced maneuverability of integrated-filter guidewire systems as compared with stand-alone guidewires, the potential for distal emboli to pass through filter pores (or between an incompletely opposed filter support ring and the vessel wall), inability to tailor guidewire characteristics to specific lesions, and occasional difficulties in advancing the requisite retrieval catheter across a tortuous stented segment to recover the filter at the end of the procedure. Some of these limitations are being addressed in later-generation filters capable of being delivered in their sheaths over conventional bare guidewires (Spider, eV3; MedNova, Abbott, Abbott Park, Ill) or by the use of a sheathless constraint system that matches the very low delivery profiles of distal occlusion devices (Rubicon, Boston Scientific, Natick, Mass; Interceptor, Medtronic).

The FilterWire (Boston Scientific) is the only current distal filter with SVG FDA approval, but several other distal filters including MedNova (Abbott), Accunet (Guidant, Indianapolis, Ind), and Spider (eV3) have FDA approval for use in carotid arteries, and others have had promising clinical trial results (AngioGuard Cordis, Miami Lakes, Fla). The spectrum also includes some devices, such as the Interceptor (Medtronic) and Trap (eV3, Plymouth, Minn), that use a nitinol mesh rather than a perforated polymer sheet filter.

### Proximal Occlusion Devices

The principle of this family of devices is the use of inflow occlusion proximal to a target lesion (rather than beyond the target lesion, as with the GuardWire) to suspend antegrade flow during target vessel intervention. Proximal occlusion can be created by a guiding catheter or super-selective sheath with an inflatable balloon tip. As with distal occlusion devices, stagnant blood containing suspended debris particles must then be evacuated before restoring flow. The most studied coronary proximal occlusion system is the Proxis system (St. Jude Medical, Minneapolis, Minn), which has a distal balloon that seals the end of the inner sheath to the vessel wall upstream of the lesion, while a proximal balloon seals the inner sheath to the inside of the guiding catheter. This allows blood and suspended debris to be aspirated from the treated vessel via the guiding catheter. Similar devices (Parodi, Arteria, San Francisco, Calif; MOMA, Invatec, Roncadelle, Italy) have been used during carotid stenting.

Strengths of these devices include potentially complete recovery of particles of all sizes and humoral substances, the establishment of protection before any device is passed across the target lesion, the ability to protect vessels with multiple side branches or distal lesions prohibitive for distal protection devices, and compatibility with any conventional guidewire. Weaknesses include the dependence on adequate collaterals for perfusion during occlusion and aspiration of suspended debris (although a distal infusion catheter can be used if spontaneous aspiration is inadequate) and the smaller-sized internal working diameter of the short sheath, which may limit applicability in some complex lesions. The Proximal Protection During Saphenous Vein Graft Interventions Using the Proxis Embolic Protection System (PROXIMAL) trial compared the Proxis device in SVG PCI to distal protection devices and demonstrated noninferiority in preventing 30-day
MACE,\textsuperscript{18} but the device is currently cleared only for “flow control” during intervention.

**Local Plaque-Trapping Devices**

The concept of an interventional device that traps all potentially embolic debris against the vessel wall at the treatment site has been attractive. Conventional stents liberate large amounts of debris when deployed in SVGs (and may continue to shed some debris even after the PCI has been completed and the EPD no longer in place), but it was hoped that a stent covered with microporous polytetrafluoroethylene (as used to treat of life-threatening coronary perforations) could also serve as a form of “local filter” during SVG interventions. Early trials, however, showed no reduction in acute MACE and an increase in late occlusion with covered as opposed to bare metal stents.\textsuperscript{19,20} Currently, FDA-approved covered stents include Jostent (Abbot Vascular), Graftmaster (Abbott Vascular), iCast (Atrium Medical, Hudson, NH), and Sym-biot (Boston Scientific) stents, but neither clinical evidence nor FDA approval status currently favors their use in SVG interventions. In contrast to their approved use in the treatment of life-threatening coronary or graft perforations, novel local plaque-trapping approaches under study include a nitinol stent in which the structural nitinol elements are covered by an integral nitinol mesh (Palmaz-Schatz-Bailey, Cordis), which has shown promise in pilot human testing.

**Clinical Role of Embolic Protection**

The past 4 years have clearly established that athereoembolization is a common or even ubiquitous consequence of atherosclerotic lesion manipulation. Those emboli may cause end-organ compromise by simple plugging of medium or microcirculatory channels, promotion of local platelet adhesion/thrombosis (plaque constituent contains abundant macrophages and tissue factor), and promotion of microvascular spasm (through thromboxane release). This manifests as the “no-reflow” phenomenon or end-organ infarction. Although distal administration of microcirculatory vasodilators (calcium channel blockers, nitroprusside, epinephrine, adenosine) can improve the no-reflow manifestations, there is no evidence that they can protect against infarction.\textsuperscript{21}

Similarly, platelet glycoprotein IIb/IIIa receptor blockers may reduce secondary platelet clumping around embolic particles, but several studies have failed to demonstrate a protective effect during SVG intervention.\textsuperscript{1,3} However, some operators prefer to use the combination of a distal filter and a glycoprotein IIb/IIIa inhibitor on the basis of a secondary analysis of the FilterWire EX During Transluminal Intervention of Saphenous Vein Grafts (FIRE) trial, which indicated that glycoprotein IIb/IIIa receptor blocker use was associated with better outcomes in high-risk patients treated with FilterWire,\textsuperscript{22} despite a potential increase in hemorrhagic complications with their use.

EPDs thus stand alone as devices for enhancing PCI safety, in their ability to satisfy Koch’s first 2 postulates: They capture embolic material, and they reduce the secondary phenomena of no-reflow and end-organ infarction. (The third postulate, the ability to reproduce infarction by infusion of embolic debris, has not been confirmed for obvious ethical reasons!)

**Clinical Evaluation of Newer EPD Technology**

In general, data suggest that the first 3 classes of embolic protection have similar efficacy in SVG settings, although specific devices may offer advantages or disadvantages in certain clinical anatomic situations (eg, proximal or distal lesion locations). The initial trials by necessity were superiority trials that compared distal occlusion to intervention using no protection. Once the benefit of distal protection was demonstrated and the first device commercially available, however, such randomization was neither ethical nor practical. Subsequent trials were thus designed as noninferiority trials demonstrating that each new device was equivalent to or better than an approved index device (ie, the PercuSurge GuardWire or the EPI FilterWire), within a statistical margin (delta) specified by the FDA during trial design. After nearly 4000 patients enrolled in such trials (Table 1), however, one could ask: “Why do we need to keep randomizing patients to the index devices?” In other fields, such as surgical heart valves, once the behavior of “good” devices has been established, this behavior becomes the basis for a set of objective performance criteria against which other devices can be judged. In the case of EPDs, however, it is clear that the observed rate of MACE is also influenced strongly by patient factors such as the extent of the graft that is diseased and the estimated volume of plaque in the lesion being stented.\textsuperscript{7} A risk model based on those variables was developed from the SAFER trial to predict MACE\textsuperscript{7} and has now been refined and validated in more than 2500 SVG patients (Coolong et al, unpublished data, 2006). This now resembles the situation that existed with bare metal stents once their basic performance was understood and the patient-specific predictors of restenosis were identified.\textsuperscript{23} In the case of bare metal stents, this large body of clinical trial data was used to establish methods for nonrandomized, Bayesian evaluation of new bare metal stents without further randomization.\textsuperscript{24} A similar approach (based on the available embolic protection data and MACE model) thus could be used for future evaluations of efficacy of a new device by comparing the outcomes with the new EPD to those that would have been expected (ie, predicted by the model) in that patient mix, had a currently FDA-approved EPD been used.

The other important area for future progress will be the development of even more effective EPD that could further reduce the “floor” MACE rate in usual-risk SVG below its current 6% to 10%. If such devices were available in smaller sizes (2.0 to 3.5 mm, rather than the 3.5- to 5.5-mm sizes used for SVGs), they could also be used to probe further the benefits of embolic protection in native coronary arteries (perhaps studying the benefit during stenting of lipid-rich plaques in patients with unstable angina or non–ST-elevation myocardial infarction, rather than the acute myocardial infarction indication, where low signal-to-noise ratio remains a problem). It is likely that similar testing may confirm the benefit of embolic protection in other areas such as renal stenting, where preliminary reports suggest that use of such devices reduces the incidence of poststent deterioration in
renal function.25 Even before this broadening of indications, however, it is clear that these devices have already changed the interventional paradigm by establishing the importance of distal embol by causing complications of catheter-based intervention and the value of embolic protection in making such interventions safer.

**Disclosures**

Dr Rogers is on speakers’ bureaus for Boston Scientific, Guidant, Medtronic, and St. Jude. Dr Baim is a consultant to EPI/Boston Scientific. Dr Mauri reports no conflicts.

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