Percutaneous coronary intervention (PCI) of saphenous vein graft (SVG) lesions is associated with a uniquely high risk of peri-procedural myocardial infarction (MI) and mortality—much greater than routine native coronary PCI. This is related to distal embolization which manifests as slow-flow and no-reflow phenomenon (SFNR) in 10% to 15% of SVG PCIs. Histopathology of SVG disease predisposes to its occurrence—the SVG plaques are large, soft, friable lipid-rich, containing large necrotic debris, cholesterol crystals and foam cells, lack calcification and fibrous caps, and are often associated with overlying thrombus. Fragmentation of the lipid-rich thrombotic plaque during PCI leads to distal embolization, platelet and leukocyte activation, release of vasoactive mediators (serotonin, endothelin), and activation of chemotactic mediators (tissue factor, thrombin/anti-thrombin III complex, and prothrombin fragments). The final result of plaque embolization is a triad of microvascular embolization, microvascular spasm, and microvascular thrombosis manifesting as SFNR.  

Embolic protection devices (EPD) have been advocated in the AHA/ACC/SCAI PCI guidelines, when technically feasible, to reduce the risk of distal embolization during SVG PCI (Class I recommendation). This recommendation was based on the results of a single randomized controlled trial, the SAFER study, which showed significant reduction in major adverse cardiac events (MACE) with the use of a distal balloon occlusion device. 

In this issue of Circulation: Cardiovascular Interventions, Paul et al1 have attempted to evaluate the benefit of routine use of EPDs in SVG PCI. They performed a meta-analysis of 52,893 patients from 8 studies (6 registry/observational studies and 2 small randomized controlled trials) comparing all-cause mortality, MACE, MI (peri-procedural and late MI) and target vessel revascularization with and without use of EPDs. Because the National Cardiovascular Data Registry (NCDR) CathPCI Registry data included the largest number of patients among all the studies, a separate analysis was performed after excluding this study to prevent skewing of results. So the analysis was performed in a stratified fashion by including all the studies, only NCDR CathPCI Registry study, 7 pooled studies excluding the NCDR CathPCI Registry, observational studies, and observational studies excluding the NCDR CathPCI Registry. The authors analyzed these data using a fixed effect model and a random effect model and reported the results on these stratified subsets. When data from all patients from all studies were analyzed, there was no difference in overall mortality, MACE, target vessel revascularization, and late MI with or without use of EPDs, but EPD use was associated with higher risk of peri-procedural MI in a fixed model analysis. Excluding the NCDR CathPCI Registry, data from the 7 pooled studies showed that EPDs use had a beneficial effect on all-cause mortality and MACE. When data from only observational studies were included, there was no difference on all end points with and without EPD use, at least in the random effect model. The analysis by inclusion of these data from different studies using different models yielding different results certainly adds to some confusion. Obviously, there is only one truth, so where lies the truth?

Several limitations of this meta-analysis exist. A significant heterogeneity between these studies in terms of study design (there were 2 randomized controlled trials, rest being registry of prospective and retrospective observational studies), sample size, inclusion criteria (incidence of acute coronary syndromes and MI varied or was not provided in some studies), outcome end points, definition of MACE, length of follow-up is obvious. The type of EPD used varied among studies (Filterwire/Spider/TRAP distal embolic filters, Guardwire distal occlusion/aspiration device, and Proxis proximal occlusion/aspiration device), and in some studies these data were not provided. Data on plaque morphology, lesion length, thrombus burden, or vein graft degeneration score, procedural techniques used (like prophylactic vasodilators, direct stenting, and stent type and undersizing) were not provided. Selection bias likely played a role as EPDs were used in <25% of all cases—possibly more often in complex cases. These limitations compromise the strength of the data and thereby recommendations from this meta-analysis.

How does one reconcile the data from this meta-analysis that suggest that a proportion of patients can undergo SVG PCI without the use of EPDs? There are 6 determinants factoring the degree of benefit of EPDs—efficacy of EPDs, the sensitivity of the vascular bed, morphology of the lesions,
patient characteristics, technical issues, and the type of clinical outcomes measured.

First, the efficacy of EPDs in protecting against distal embolization of plaque debris is well established. Embolized debris includes necrotic atheromatous core, lipid-rich foam cells, cholesterol clefts, and fibrin, and 80% of debris particles are <100 μm in diameter. Larger particulate debris causes more plugging and compromise of myocardial perfusion than smaller particles. Distal EPD filters have pore sizes between 100 to 110 μm and capture particles >110 μm thereby protecting against macroembolization. However, protection provided by EPDs is never absolute or uniformly efficacious. Causes of incomplete embolic protection include large device crossing profile causing plaque disruption, device-mediated intimal trauma, incomplete conduit occlusion or filter apposition, filter movement, incomplete aspiration, filter pore size discrepancy (either too large or too small), filter embolic overload, side branch backwash, delayed platelet-white cell embolization from the target site, and release of soluble mediators. Hence, even when used correctly, EPDs may not completely abolish distal embolization.

Second, the relative sensitivity of a vascular bed determines the clinical significance of the outcomes resulting from distal embolization. Even a miniscule embolus would clinically manifest in a very sensitive vascular bed of the central retinal artery arising from the internal carotid. Intracranial embolism is rarely clinically silent, hence, EPDs are the standard of care in carotid stent interventions. However, distal embolization to a skeletal muscle artery during peripheral vascular intervention may escape clinical recognition. The coronary bed is an intermediate-sensitivity vascular bed, the myocardium can withstand ischemia from distal embolization unless it reaches an intense proportion or occurs to an extensive segment of viable myocardium or to an already jeopardized myocardium with left ventricular dysfunction. Distal embolization of fine particulate matter is routine in rotational and orbital atherectomy, but becomes clinically significant when it occurs to the sensitive atrioventricular node in dominant right coronary or left circumflex interventions. Normally, functioning left ventricular myocardium can withstand small to moderate intensity transient ischemic insult without clinically manifest outcomes in the absence of a large territory extensive ischemia. However, even smaller territory transient ischemia could be clinically significant in the setting of left ventricular dysfunction.

Third, the morphology of the SVG lesion and coronary anatomy often provides estimation of risk of embolism and SFNR. Degenerated grafts with large lipid-rich plaques, thrombotic lesions with filling defects, patients presenting with acute coronary syndromes, distal runoff into small caliper postanastomotic coronaries all predispose to high risk of SFNR. SVG Degeneration Score and the Estimated Plaque Volume Formula estimate embolization risk and show some correlation with MACE outcomes. Focal fibrotic lesions, aorto-ostial lesions, distal anastomotic lesions, and instant restenosis lesions have low embolization risk and may be treated without EPD.

Fourth, the patient characteristics often determine the risk of morbidity and mortality with an SFNR episode. A sole surviving graft, large area of viable myocardium supplied by the SVG, left ventricular dysfunction, atrioventricular nodal artery supply through the SVG in the absence of an artificial pacemaker—increase the clinical risk after a SFNR episode—and should be treated with EPD if feasible.

Fifth, EPD use is often limited by technical and anatomic challenges (graft size, inadequate landing zone, distal lesion, and vessel tortuosity). Experience with the use of EPDs prevents device related complications like native coronary or graft dissection and perforation, embolization from device misuse, and device entrapment. EPD use generally increases the technical complexity, time, radiation exposure, and costs of the procedure.

Sixth, the outcomes measured have variability in their relationship (proportionality) to distal embolization. Some outcomes (like peri-procedural MI, cardiac marker elevation) are strongly related to the occurrence and degree of distal embolization (highly proportional to distal embolization). On the other hand, outcomes like target vessel revascularization and late MI may have little or no relationship (low proportionality) to distal embolization. When these outcomes with high and low proportionality to distal embolization are clumped together in MACE, the effect of distal embolization on MACE outcomes often becomes diluted. The diluted benefit of EPD on these clumped outcomes does not imply a lack of benefit to the use of EPDs. Also, distal embolization may have a threshold relationship with certain outcomes like mortality; death in SVG PCI often follows a clinically significant embolization in a high-risk anatomic or patient morbidity subset. On the other hand, peri-procedural myocardial infarction would manifest with even small degree of distal embolization and has no threshold effect (highly sensitive to distal embolization). Any study to assess the efficacy of EPDs should include only outcomes which have a defined biologically plausible proportional relationship to distal embolization.

The keep-it-simple mantra has led many operators toward exploring alternative strategies to reduce risk of SFNR during SVG PCI, notwithstanding scant data on their efficacy. These include direct stenting, stent undersizing, use of covered stent grafts, and aspiration thrombectomy. Adjunctive administration of intragraft anti-thrombotic agents (abciximab and thrombolytics in setting of thrombus) and prophylactic use of vasodilators (verapamil, nicardipine, adenosine, and nitroprusside) have yielded positive outcomes in anecdotal reports and small studies, but efficacy has not been confirmed in large randomized trials.

There is no question that EPDs are useful in SVG PCI. Filter-based EPDs prevent macroembolization during SVG PCI, but a finite residual risk of SFNR remains, possibly related to incomplete embolic protection and or escape of soluble mediators. Because a clinically significant episode of severe SFNR can never be predicted and given limited efficacy of available treatments after its occurrence, it is best to practice prevention of SFNR with use of multiple strategies. Perhaps the optimal strategy in treating grafts with high embolic potential would be a combined pharmacomechanical approach, using besides EPDs and direct stenting, prophylactic intragraft vasodilators (to prevent/reverse microvascular
spasm), and possibly intragraft abciximab (to prevent/treat macro- and microvascular thrombosis). A randomized controlled trial using a multifactorial design and measuring clinically relevant and proportional outcomes may be best way to answer the question about relative utility of each of these strategies, but it may never occur. Until then, it may not be ethical exposing some patients to the risk of a catastrophic SFNR episode unless the lesions involve low risk of embolization, that is, aorto-ostial lesions, distal anastomotic lesions, instent restenosis lesions, and focal fibrotic lesions. In all others, it may be too early yet to suggest taking off the routine use of EPDs in SVG interventions.

**Disclosures**

None.

**References**


**Key Words:** Editorials, coronary bypass graft, embolic protection devices, percutaneous coronary intervention, thrombosis
Embolic Protection Devices in Saphenous Vein Graft Intervention: A Stitch in Time Saves Nine
Sanjiv Sharma and Joel A. Lardizabal

Circ Cardiovasc Interv. 2017;10:
doi: 10.1161/CIRCINTERVENTIONS.117.006124
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/10/12/e006124

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/