Secondary Prevention, the Interventional Way
Prophylactic Drug-Eluting Stents for Nonobstructive Saphenous Vein Graft Disease

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The pathophysiology of accelerated atherosclerosis in saphenous vein grafts (SVG) relates to progressive atheroma burden, neointimal hyperplasia, and vascular remodeling. Unfortunately, the therapeutic and clinical consequences of SVG disease are not trivial, and interventional cardiologists are wary of performing percutaneous coronary interventions (PCI) on degenerated SVG. Intervening on flow-limiting stenoses in SVG has long been associated with high complication rates; what was not well known to this date was the risk of stenting non–flow-limiting disease in SVG. Although techniques to mitigate distal embolization during SVG intervention have proliferated in the past decade, even optimal intervention with embolic protection devices, including proximal protection devices, filters, aspiration tools, and covered stents, have attendant higher complication rates than does native vessel PCI. Drug-eluting stents (DES) are of benefit in reducing restenosis compared with bare metal stents in SVG, but clinical adverse events are only marginally reduced, if at all.

In this context, one may be perplexed by the report of Rodes-Cabau et al in this issue of Circulation, which proposes stenting non–flow-limiting stenoses in SVG with paclitaxel-eluting stents. Their study was founded on reasonable scientific grounds. Emboldened by the findings in native coronary stenoses that DES deployment in nonobstructive lesions resulted in relatively low rates of major adverse cardiac events and restenosis and the rapid progression of disease in degenerated SVG, these investigators hypothesized that in patients referred for symptom-driven coronary angiography, prophylactic stenting of nonculprit mild to moderate angiographic stenoses (30% to 60% diameter stenosis) in SVG would not be deleterious and would result in superior intravascular ultrasound (IVUS) end points such as minimum luminal area compared with medical therapy alone. Without dispute, the study end points were met, inasmuch as those patients receiving medical therapy experienced progression of their moderate stenoses and the stent group experienced no significant restenosis. However, this seemingly ordinary research exercise carries with it profound implications to the current paradigm of cardiovascular diagnosis and therapeutic. The interventionalist has long been uneasy with the perception that PCI offers only improvements in quality-of-life measures rather than mortality benefit, except in the case of acute coronary syndromes. As a result, many interventionists have embraced the idea of treating or “passivating” non–flow-limiting disease, given our current understanding that angiographically mild to moderate disease is implicated in coronary thrombosis. In considering the concept of secondary prevention via PCI, one wonders whether it is our ultimate goal to prevent cardiovascular events—namely, death or myocardial infarction—or to prevent silent disease from progressing into symptomatic syndromes. This study exemplifies this point, for the authors can only infer a trend toward anatomic benefit. It is a good start, but achieving convincing prospective data for secondary prevention using vascular devices will take time and much larger study populations.

Unfortunately, the solutions to prevent heart attack using localized device implants are not risk free, and the search for them has been hampered by our inability to precisely identify appropriate targets. The term “vulnerable plaque” (VP) has been used primarily to denote arterial disease with imminent risk of causing a cardiovascular event, but its precise definition remains unclear. In this study, the authors used “lumenographic” methods to define their target, not taking into account plaque burden and other plaque characteristics that could have been extracted from the baseline IVUS. The first large prospective study investigating the natural history of nonobstructive coronary atherosclerosis, the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial, was presented recently (Gregg W. Stone, MD, 2009). The investigators used IVUS as their primary tool to identify nonculprit vessel disease that may be at risk of causing cardiovascular events in patients presenting with acute coronary syndrome. Interestingly, the anticipated high frequency of cardiovascular events did not occur, with only a 1% rate of myocardial infarction and no deaths directly attributable to nonculprit vessels during 3 years of follow-up. By contrast, the results suggest that nonculprit coronary plaques are most likely to be associated with increasing symptoms, with 8.5% of patients presenting with worsening angina and 3.3% with unstable angina. Whether or not rapid plaque progression is a hallmark of VP is debatable, but these recent data suggest that a proper...
medical history, physical examination, and clinical surveillance may be equally effective in identifying and predicting progression of plaques from “vulnerable” into “obstructive” disease.

This brings us back to the concept of prophylactic treatment of rapidly progressive non–flow-limiting disease in SVG and to the current study. Whereas PROSPECT attempted to identify VP in the native circulation without proposing a therapeutic strategy, the present study leaps further forward by deploying first-generation DES to passivate lesions in diseased SVG, with the rationale that DES would diminish the risk of restenosis. This proposition seems to be bit ahead of its time, for many believe that all SVG plaques are somewhat vulnerable; yet, >50% of SVG occlude without causing any appreciable symptoms. A similar glimpse into the future was recently highlighted by the interventional cardiology group at the Thoraxcenter in Rotterdam. That group used IVUS and optical coherence tomography to target therapy with a novel, self-expanding, lower–radial force device expressly designed to seal VPs in native coronary arteries. Although pathology data are not yet available, in vivo imaging at 6 months with IVUS and optical coherence tomography revealed minimal neointimal hyperplasia within these stents. This is likely the direction in which the field will migrate: with specifically engineered, vascular-health–promoting devices that may or may not require permanent implantation. Were we to speculate about the optimal device or therapy for the purpose of “plaque sealing,” it would have these characteristics:

- Deployed at a device-to-artery ratio of 1:1, given that plaque stabilization rather than lumen gain is the main goal of treating VP.
- Composed of a material that helps restore normal vascular physiology, is conformable to the vessel anatomy, and imposes minimal injury to deeper vessel wall structures.
- Nonpermanent: retrievable, biodegradable or non–stent-based material.
- Delivery systems for a “prohealing” compound or compounds targeting inflammatory and thrombotic mediators such as monocoye chemoattractant protein-1 and the prothrombotic phenotype seen in SVG rather than potent cell cycle inhibitors such as paclitaxel.
- Delivered and monitored with contemporary imaging, preferably radiation-free modalities such as magnetic resonance imaging and/or high-resolution intravascular imaging modalities such as optical coherence tomography.

Significant advances in the field of percutaneous SVG intervention have been made in the past decade, and it is likely that DES will remain important in this regard while the clinical data evolve. However, the idea of prophylactic SVG intervention of nonobstructive lesions, adapting coronary devices designed to block smooth muscle cell proliferation—a critical component of arterial wall and plaque stability—might not be “ready for prime time.” We are certainly encouraged by these recent developments and hopeful that future investigations, when coupled with specifically engineered devices, contemporary imaging technologies, and appropriate patient selection, can extend our ability as interventional cardiologists to not only improve but prolong patients’ lives.

Disclosures
Dr Costa has received honoraria and consulting fees from LightLab, Boston Scientific, Abbott Vascular, Sanofi, Medtronic, Scitech and Cordis/Johnson and Johnson. Dr Parikh reports no conflicts.

References


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