Percutaneous Treatment of Saphenous Vein Graft Disease

The Ongoing Challenge*

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Although virtually all of the 400,000 coronary bypass surgeries performed in the U.S. each year use at least one arterial graft conduit (internal mammary or free radial), most still involve the placement of one or more saphenous vein grafts. These grafts immediately begin to develop intimal hyperplasia in response to surgical trauma, a loss of intrinsic vascular supply, and exposure of the thin-walled structure to an abrupt increase in wall stress as it is moved from the low-pressure venous to the high-pressure arterial environment. This sets the stage for subsequent atherosclerotic degeneration and superimposed thrombus, causing more than 50% of these grafts to fail by seven years after surgery and accounting (along with progressive native coronary disease) for late recurrent angina in this patient population. Given the risk of injuring other patent grafts and the generally higher risk of re-operation in an older and sicker patient population, percutaneous treatment of failing saphenous vein grafts is generally preferred (1) and accounts for some 10% to 15% of coronary intervention in most centers. But these interventions present several unique challenges based on the soft and friable nature of the degenerated vein graft lesion, the tendency for distal atheroemobilization to produce peri-procedural no-reflow and myocardial infarction (MI), the frequent association or large thrombi superimposed on critical graft stenosis or recent occlusion, and the high long-term recurrence rate (due to both restenosis at the target site and progression of disease at other sites to cause target vessel failure). Given these multiple challenges, it is natural that catheter management of the diseased saphenous vein graft has been the subject of multiple device development strategies. Although some progress has been made (2), short- and long-term results remain far worse than those of native vessel intervention (3).

The core interventional technology is, as in other vascular territories, stent placement. The predictable ability of bare metal stent placement to provide a large and smooth vascular lumen has made stenting the default interventional modality in the diseased saphenous vein graft. Despite the limited nature of the original randomized trials in this area (with rapid adoption of stenting in the mid-1990s and the subsequent reluctance of operators to randomize patients to conventional balloon angioplasty), balloon expandable and, to a lesser extent, self-expanding stents are used in virtually every graft intervention. Stent placement may be performed after balloon pre-dilation or directly when the graft and lesion anatomy are favorable. If large associated luminal thrombi are present, thrombectomy with the Possis AngioJet rheolytic thrombectomy catheter (Possis Medical Inc., Minneapolis, Minnesota) has been shown to be superior to overnight infusion of a thrombolytic agent (4). The EndiCOR X-Sizer catheter (ev3, Plymouth, Minnesota) has recently shown benefit in reducing large MIs in thrombotic saphenous vein grafts despite its failure in reducing the overall prespecified 30-day composite death, MI, urgent revascularization end point (5). Newer ultrasonic thrombectomy devices also are just entering clinical testing.

Whether or not thrombus is present, a large part of the acute complications of saphenous vein graft intervention stems from the compromise of the distal (arteriolar) myocardial microcirculation, evident as peri-procedural MI (17% to 20% of procedures) (6), or the no-reflow phenomenon (8% of procedures) (7). For most of the 1990s, these complications were felt to result from spasm of these vessels induced by serotonin or other vasoconstrictors and treated accordingly with small vessel vasodilators (calcium channel blockers, nitroprusside, or adenosine), with encouraging but imperfect results. The other causative candidate was platelet aggregation, but clinical trials have shown no benefit of platelet glycoprotein IIb/IIIa receptor blockers in this lesion type (8). The problem has been clarified significantly by the introduction of distal embolic protection devices, such as the PercuSurge distal occlusion GuardWire (Medtronic AVE, Santa Rosa, California), whose 801-patient Saphenous Vein Graft Angioplasty Free of Emboli Randomized trial (9) demonstrated a significant reduction in both 30-day adverse events (from 17% to 9.6%) and the no-reflow phenomenon (from 8.3% to 3.3%), compared with stenting performed over a conventional guidewire. More recently, the distal Boston Scientific/EPI FilterWire (Natick, Massachusetts) has shown equivalence (noninferiority) to the GuardWire in the 651-patient FIRE trial (10). Several other distal filter devices and two devices for proximal occlusion (which allow emboli to be collected into the guiding catheter) are now under study for this indication. To date, however, none of the embolic protection devices have been able to totally eliminate the distal embolic risk in this challenging patient subset and bring the adverse clinical even rate below 9% in a high-risk cohort.

Aside from acute procedure safety, percutaneous vein graft treatment is frustrated by the fact that a larger proportion (35% to 40% vs. 20% to 25%) of treated saphenous vein grafts fail over the next 12 to 18 months.
compared with treated native vessels. About one-half of those failures represent restenosis of the stented site and the other half represent failure of the treated vessel because of progression of subclinical disease elsewhere that the original stented lesion (11,12). With current stents, operators are understandably reluctant to minimize this latter failure mode by “relining” the entire graft because of the penalty of increasing restenosis risk with increasing stent length. Because the mechanism of in-stent restenosis in vein grafts is also neointimal hyperplasia and the response of in-stent restenosis to brachytherapy is similar (13), one may hope for a similar benefit from antiproliferative drug-eluting stents to that seen in native vessels, but studies of such drug-eluting stents in vein grafts are not yet available.

Developing in parallel with distal protection devices, thrombectomy, and drug-eluting stents, another approach to both distal embolization and restenosis in saphenous vein grafts are membrane-covered stents that hopefully would trap friable plaque against the wall and reduce the degree of subsequent neointimal proliferation inside the stent. Despite some early registry data to that effect (14), the larger randomized trials are beginning to show a consistent lack of benefit in either regard. That is certainly the case for larger randomized trials are beginning to show a consistent lack of benefit in either regard. That is certainly the case for restenosis to brachytherapy is similar (13), one may hope for a similar benefit from antiproliferative drug-eluting stents to that seen in native vessels, but studies of such drug-eluting stents in vein grafts are not yet available.

A low event rate in the control arm could also reflect treatment of “low-risk” graft lesions because we have yet to develop a robust model that predicts unprotected event rates in vein graft stent patients as a function of lesion length and extent of overall graft degeneration. But the lack of evident embolic protection by the covered stent in STING is consistent with the preliminary data from RECOVERS (16). That 301-patient Italian trial was similar in design except for lower use of IIb/IIIa blockers (~15%) but showed significantly more periprocedural MIs and six-month cumulative major adverse clinical events with the covered as opposed to bare metal stent. This likely reflects dislodgement of emboli during advancement of the relatively rigid device, or a “toothpaste” effect by which material is squeezed from the center to the ends of the lesion, allowing it to escape from the covered area. Final confirmation will come from the large U.S. BARRICADE trial, which is still in active enrollment, but even increased embolization would not be lethal to this strategy if the covered stents were deployed over an embolic protection device.

However, the primary end point of STING was the ability of the StentGraft to reduce six-month angiographic restenosis. The performance of the bare FlexStent was better than expected, with late loss of 0.95 mm and a 20% angiographic restenosis, nearly one-third (7%) of which represented total occlusion. The low restenosis rate may indicate favorable baseline clinical factors in the trial as a whole or simply the play of chance, but could also reflect the use of an earlier angiographic restudy time-point than the 8 to 12 months used in some other graft trials. However, if anything, the performance of the covered StentGraft was worse than a bare metal stent, with a late loss of 1.17 mm and a restenosis rate of 29%, one-half (16%) of which represented late occlusion. This is even more disappointing than the RECOVERS data, where the StentGraft group had an unchanged 24% restenosis, half of which (11% to 12%) represented late occlusion.

It is not clear how many of these late occlusions in STING were just the result of intense in-stent proliferation rather than subacute thrombosis, but the antithrombotic regimen (heparin and abciximab intraprocedure and a thienopyridine for three months after stent placement) was standard. Acute thrombosis is the presumed culprit in one early (2 day) and one late (125 day) occlusion of a StentGraft accompanied by abrupt chest pain and CK elevation but is not excluded by absence of these markers in the 11 remaining StentGraft occlusions. Nor do we know whether the period required for complete endothelialization of this composite device is as short as the two- to four-week period reported for bare metal stents, or more like the eight–plus month period seen when a new metallic stent is placed in conjunction with brachytherapy. Certainly clinical users of this device, which is marketed in Europe and the U.S. (under a Humanitarian Device Exemption for the treatment of coronary perforation) might well consider prolonging the
duration of clopidogrel treatment to eight months to minimize this risk.

The STING trial also raises issues relating to the pre-specified 12-month clinical end points, which include death, MI (using the CK >3 times the normal cutoff), and target lesion revascularization (TLR). Death (8.8% vs. 5.8%) and MI (9.8% vs. 7.7%) were nonsignificantly higher with the StentGraft, but repeat TLR revascularization was nonsignificantly lower (17% vs. 21% for the target lesion and 20% vs. 24% for the target vessel). That difference in TLR was thus an important contributor to achieving a similar composite clinical event rate (31% vs. 31%) at 12 months. However, in the face of higher angiographic restenosis and total occlusion, this lower TLR rate reflects more a reluctance of operators to proceed to reintervention in an occluded graft (only four of the StentGraft occlusion underwent such reintervention) rather than a measure of long-term clinical benefit. Had a broader end point of target vessel failure been used, the performance of the StentGraft might have been demonstrated to be significantly worse than the bare FlexStent.

WHERE DO WE STAND?

At this point, the best treatment for a degenerated stenotic saphenous vein graft is probably bare metal stenting of the stenotic segment performed in association with distal embolic protection. If a large associated thrombus is present, this should be preceded by mechanical thrombectomy (positional protection). If a large associated thrombus is present, they will resist proliferation or encourage functional endothelial coverage. Even if trials show significant benefit against bare metal stents, however, they will also have to demonstrate benefit over drug-eluting stents. Although we are clearly making progress, the ultimate solution to the percutaneous management of diseased saphenous vein graft is thus still under development!

REFERENCES