Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 42, No. 8, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)01039-8

## EDITORIAL COMMENT

# Percutaneous Treatment of Saphenous Vein Graft Disease

## The Ongoing Challenge*

Donald S. Baim, MD, FACC
*Boston, Massachusetts*

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

**See page 1360**

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 atheroembolization 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 Angio-Jet rheolytic thrombectomy catheter (Possis Medical Inc., Minneapolis, Minnesota) has been shown to be superior to overnight infusion of a thrombolytic agent (4). The Endi-COR 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

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Center for Integrating Medicine and Innovative Technology, Brigham and Women's Hospital, Boston, Massachusetts.

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 graft 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 the 211-patient multicenter STents IN Grafts (STING) trial, which was conducted in late 1999 and throughout 2000, and is reported in this issue of the *Journal* by Schächinger et al. (15). In STING, patients underwent treatment of lesions between 5 and 45 mm in length in 10-year-old grafts with an average reference diameter of 3.4 mm, randomized at 12 German and Austrian sites to undergo placement of either a conventional metal Jomed Flex Stent (Helsingborg Sweden) or the hand-mounted Jomed StentGraft, which consists of a layer of polytetrafluoroethylene sandwiched between an inner and an outer metallic stent. Both devices are available in multiple lengths (9, 16, and 26 mm). Although the additional material makes the StentGraft somewhat stiffer to deliver and harder to expand fully (note the maximum deployment pressure of 16.4 vs. 15.0 atms for the StentGrafts), it was delivered successfully in all but 3 of the 102 patients assigned to the StentGraft group. We were not told the lesion length, but the total stent length of 19 mm (representing 1.2 stents per lesion) and residual stenosis (4.5% vs. 6.6%) were comparable with those in patients assigned to the bare FlexStent. This study thus constitutes a fair test of the Jomed StentGraft in typical vein grafts.

Although the study details do not describe how this was ascertained, there was no evidence of reduced distal embolization. Of note, the 5.6% and 4.9% MI rates reported in the two arms of STING are far below the 15% or greater rates in the literature. This was not due to liberal use of distal embolic protection devices (<10% of both groups) and more likely reflects the use of a non-standard enzyme criterion for MI (creatine kinase [CK] >3 times normal), rather than the more standard (total CK >2 times normal or CK-MB fraction >3 times normal as used in SAFER). 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

JACC Vol. 42, No. 8, 2003
October 15, 2003:1370–2

duration of clopidogrel treatment to eight months to minimize this risk.

The STING trial also raises issues relating to the prespecified 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 (possibly over the shaft of the embolic protection device). Once large-diameter drug-eluting stents are available (and their benefit in saphenous vein grafts is established) they will likely be substituted for bare metal stents, with concomitant reduction in restenosis. This would also enable us to treat preemptively longer graft segments, in an effort to reduce late failures due to rapid progression of moderate disease. But based on the available data from STING and RECOVERS, the Jomed StentGraft provides no additional benefit against either distal embolization or restenosis. Therefore, barring distinctly different data from the pending BARRICADE trial using this device or positive data from trials of the Boston Scientific self-expanding Symbiot covered stent, the use of covered stents under the current Humanitarian Device Exemption should probably be reserved for the covered indications of vessel perforation and local aneurysms. We should not rule out the possibility that future composite stent grafts could be treated with compounds that would 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!

**Reprint requests and correspondence:** Dr. Donald S. Baim, Harvard Medical School, Center for Integrating Medicine and Innovative Technology, Brigham and Women's Hospital, Boston, Massachusetts 02115. E-mail: dbaim@partners.org.

## REFERENCES

1. Morrison DS, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience for post-CABG patients. J Am Coll Cardiol 2002;40:1951–4.
2. Hong MK, Mehran R, Mintz GS, et al. Are we making progress with percutaneous vein graft treatment? A comparison of 1990 to 1994 and 1995 to 1998 results. J Am Coll Cardiol 2001;38:150–4.
3. Keeley EC, Velez CA, O'Neill WW, Safian RD. Long-term clinical outcome and predictors of major adverse cardiac events after percutaneous interventions on saphenous vein grafts. J Am Coll Cardiol 2001;38:659–65.
4. Kuntz RE, Baim DS, Cohen DJ, et al., for the VeGAS 2 Investigators. A trial comparing rheolytic thrombectomy with intracoronary urokinase for coronary and vein graft thrombus (The Vein Graft AngioJet Study [VeGAS 2]). Am J Cardiol 2002;89:326–30.
5. Stone GW, Cox DA, Low R, et al. Safety and efficacy of a novel device for treatment of thrombotic and atherosclerotic lesion in native coronary arteries and saphenous vein grafts: results from the multicenter X-sizer for treatment of thrombus and atherosclerosis in coronary applications trial (X-TRACT) study. Cathet Cardiovasc Interv 2003;58:419–27.
6. 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;100:2400–5.
7. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of "no-reflow" after percutaneous coronary intervention. Circulation 1994;89:2514–8.
8. Ellis SG, Linkoff AM, Miller D, et al. Reduction in complications of angioplasty with abciximab occurs largely independently of baseline lesion morphology. J Am Coll Cardiol 1998;32:1619–23.
9. Baim DS, Wahr D, George B, et al., on behalf of the Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) Trial Investigators. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. Circulation 2002;105:1285–90.
10. 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;108:548–53.
11. Laham RJ, Carrozza JP, Berger C, Cohen DJ, Kuntz RE, Baim DS. Long-term (4–6 year) outcome after Palmaz-Schatz stenting—paucity of late stent-related problems. J Am Coll Cardiol 1996;28:820–6.
12. Ellis SG, Brener SJ, De Luca S, et al. Late myocardial ischemic events after saphenous vein graft intervention—importance of initially "nonsignificant" vein graft lesions. Am J Cardiol 1997;79:1460–4.
13. Waksman R, White RL, Chan RC, et al. Intravascular gamma radiation for in-stent restenosis in saphenous-vein bypass grafts. N Engl J Med 2002;346:1194–9.
14. Baldus S, Koster R, Reimers J, Meinertz T, Hamm CW. Membrane-covered stents: a new treatment strategy for saphenous vein graft lesions. Cathet Cardiovasc Interv 2001;53:1–4.
15. Schächinger V, Hamm CW, Münzel T, et al. A randomized trial of polytetrafluoroethylene-membrane covered stents compared with conventional stents in aortocoronary saphenous vein grafts. J Am Coll Cardiol 2003;42:1360–9.
16. 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.