Clinical Presentation and Angiographic Characteristics of Saphenous Vein Graft Failure After Stenting

Insights From the SOS (Stenting Of Saphenous Vein Grafts) Trial

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Objectives We sought to compare the clinical presentation and angiographic patterns of saphenous vein graft (SVG) failure after stenting with a paclitaxel-eluting stent (PES) versus a similar bare-metal stent (BMS).

Background The mode of SVG failure after stenting has been poorly characterized.

Methods The SOS (Stenting Of Saphenous Vein Grafts) trial enrolled 80 patients with 112 lesions in 88 SVGs who were randomized to a BMS or PES. Angiographic follow-up at 12 months was available in 83% of the patients.

Results Binary angiographic restenosis occurred in 51% (24 of 47) of BMS-treated lesions versus 9% (4 of 43) of PES-treated lesions (p < 0.0001). Graft occlusion occurred in 9 of the 21 SVGs (43%) that failed in the BMS group and in 2 of 4 SVGs (50%) that failed in the PES group. SVG failure after stenting presented as an acute coronary syndrome in 10 of the 24 patients (42%) (7 of those 10 patients presented with non–ST-segment elevation acute myocardial infarction), stable angina in 9 (37%) patients, and without symptoms in 5 (21%) patients. Of the 19 patients (with 20 grafts) who developed symptomatic graft failure, repeat SVG revascularization was successfully performed in all 13 (100%) subtotally obstructed SVGs but was attempted (and successful) in only 1 of 7 (14%) occluded SVGs. Revascularization of a native coronary artery was performed in an additional 4 of 7 (57%) symptomatic patients with an occluded SVG.

Conclusions SVG failure after stenting often presents as acute myocardial infarction and with SVG occlusion. Compared with BMS, PES reduce SVG failure. (J Am Coll Cardiol Intv 2009;2:855–60) © 2009 by the American College of Cardiology Foundation
Although saphenous vein graft (SVG) stenting is associated with high failure rates, there are limited data on the clinical presentation and angiographic patterns of SVG failure after stenting. Although traditionally considered a benign event, native coronary artery in-stent restenosis was recently reported to present with an acute coronary syndrome (ACS) in up to 50% of patients (1,2). We recently reported the results of a multicenter, randomized clinical trial (SOS [Stenting Of Saphenous Vein Grafts]) that compared a paclitaxel-eluting stent (PES) with a similar bare-metal stent (BMS) in SVGs (3). In this analysis, we sought to determine the angiographic patterns and clinical presentation of SVG stent failure, as observed in the SOS Trial.

Methods

The design and primary results of the SOS trial (registry identifier NCT00247208) have been published (3). Briefly, the SOS trial was a randomized, controlled, single-blinded, multicenter trial designed to test the hypothesis that implantation of a polymer-based PES (Taxus, Boston Scientific, Natick, Massachusetts) in SVG lesions would be associated with reduced angiographic restenosis (>50% of the minimum lumen diameter stenosis in the target SVG segment) at 12 months compared with a similar design BMS (Express2, Boston Scientific). Patients were asked to return for repeat coronary angiography 12 months after stent implantation and were contacted by phone until 24 months after enrollment to determine whether any late cardiovascular events had occurred. Angiographic follow-up was available in 80% of the treated lesions in 83% of the patients. The pattern of in-stent restenosis was reported according to the Mehran classification (4). Continuous variables were summarized as mean ± 1 SD and discrete variables were presented as frequencies and group percentages. The study was approved by the institutional review board of each participating site, and all patients provided written informed consent.

Acute coronary syndrome was defined as either myocardial infarction (MI) or unstable angina. Myocardial infarction during follow up was defined as typical rise and fall of troponin or creatinine kinase-myocardial band (CK-MB) above the upper limit of normal with either ischemic symptoms or electrocardiographic changes indicative of ischemia (ST-segment elevation or depression or development of pathologic Q waves) (3). Unstable angina was defined as typical anginal symptoms occurring in an increasing pattern or at rest requiring hospital stay without elevation of troponin or CK-MB.

Results

Angiographic findings. In the BMS group, 20 of 33 patients (61%) developed angiographic restenosis in 24 of 47 lesions (51%) in 21 of 37 SVGs (57%). In the PES group, 4 of 33 patients (12%) developed angiographic restenosis in 4 of 43 lesions (9%) in 4 of 35 SVGs (11%) (p < 0.0001 for all comparisons between BMS and PES).

Among patients in the BMS group with vein graft failure, occlusion of the SVG (Fig. 1) was seen in 8 of 20 patients (40%), 8 of 21 grafts (38%), and in 11 of 24 lesions (46%) (3 patients had 2 lesions treated in the same SVG). Subtotal obstruction (50% to 99%) was seen in 13 lesions, in 13 SVGs in 12 patients (1 patient developed restenosis in 2 lesions located in 2 SVGs). The pattern of restenosis was focal (type I) in 9 lesions (7 were focal body-type IC, and 2 were focal margin-type IB) (Fig. 2), diffuse intrastent (type II) in 2 lesions, and diffuse proliferative (type III) in 2 lesions.

In the PES group, 4 patients each had a lesion in an SVG. Two of the 4 SVGs were occluded, and the other 2 had focal body-in-stent restenosis (type IC).

Clinical presentation. Ten of 24 patients (42%) with SVG failure presented with an ACS (Table 1). Of the 10 patients who developed SVG occlusion, 3 met the Academic Research Consortium (ARC) definition for definite stent thrombosis (an occluded graft in the setting of an acute MI). The first patient presented with a non–ST-segment elevation acute myocardial infarction (NSTEMI) complicated by ventricular fibrillation 2 weeks after stenting of an SVG to the right posterior descending artery (PDA). His initial procedure was complicated by recurrent chest pain and Thrombolysis in Myocardial Infarction flow grade 2 SVG the following day requiring repeat balloon angioplasty and catheter thrombectomy (Angiojet, Possis Medical, Minneapolis, Minnesota). Two weeks later he represented with an NSTEMI. On repeat coronary angiography the SVG to PDA was found to be occluded with no other significant changes from his baseline angiogram. Repeat PCI

Abbreviations and Acronyms

ACS = acute coronary syndrome
ARC = Academic Research Consortium
BMS = bare-metal stent(s)
CABG = coronary artery bypass grafting
DES = drug-eluting stent(s)
MI = myocardial infarction
NSTEMI = non–ST-segment elevation acute myocardial infarction
PCI = percutaneous coronary intervention
PDA = posterior descending artery
PES = paclitaxel-eluting stent(s)
SVG = saphenous vein graft

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of the SVG to PDA was not attempted, but native coronary artery PCI was performed. The second patient presented with an NSTEMI complicated by ventricular fibrillation and was found to have an acute occlusion of an SVG to the right PDA 11 months after stent placement. The SVG flow was restored with primary PCI (Fig. 1). The third patient presented with an NSTEMI 22 months after stent placement and was found to have an occluded SVG to the first obtuse marginal branch. He was treated medically. The remaining 7 patients found to have an SVG occlusion presented with unstable angina (n = 1), stable angina (n = 3), or were asymptomatic (n = 3).

One additional patient presented initially with subtotal in-stent restenosis but subsequently developed definite stent thrombosis after repeat PCI. This patient presented with stable angina 12 months after randomization due to sub-total in-stent restenosis as well as a new severe stenosis more distally in an SVG supplying the right PDA. He underwent repeat PCI of both SVG lesions, and 5 days later he developed stent thrombosis.

All 4 cases of ARC definite stent thrombosis occurred in patients randomized to BMS. The patient who presented with late stent thrombosis at 22 months had stopped clopidogrel 9 months after randomization (13 months before the event). The other 3 patients with ARC definite stent thrombosis were taking dual antiplatelet therapy at the time of the stent thrombosis. There were 2 additional cases of probable stent thrombosis both occurring within 1 week of randomization. One patient had sudden death 6 days after receiving a PES without angiographic or autopsy evidence of stent thrombosis. Another patient presented with an NSTEMI in the myocardial distribution supplied by the original SVG (on the basis of electrocardiographic changes and new wall motion abnormalities) 6 days after receiving a BMS and was managed medically, without angiography. Both patients were taking dual antiplatelet therapy at the time of the event.

Of the remaining 7 patients with occluded vein grafts (without definite stent thrombosis) at follow-up, 4 were still taking dual antiplatelet therapy at the time of follow-up and 3 had stopped clopidogrel before the discovery of the occluded SVG.

Revascularization. The outcomes of repeat PCI procedures in the SOS patients who developed SVG failure are summarized in Table 2. None of the 5 asymptomatic patients with SVG failure at follow-up angiography underwent a repeat revascularization procedure. Seventeen of the 19 symptomatic patients underwent repeat revascularization of 20 failed SVGs. Twelve of the 19 patients had subtotal in-stent restenosis within 13 grafts and were all treated with repeat PCI (1 BMS patient developed SVG restenosis in 2 SVGs, both of which underwent repeat stenting with a PES). The remaining 7 symptomatic patients (3 of whom had initially undergone treatment of 2 lesions in the target SVG) had occluded grafts. Only 1 of these patients (who presented with stent thrombosis) (Fig. 1) underwent repeat SVG PCI. Four patients underwent PCI of a native artery supplying the territory originally supplied by the occluded SVG (3 at the time of follow-up angiography and 1 at 4 months after angiography when medical therapy failed to control his angina). The remaining 3 symptomatic patients with occluded SVGs received medical therapy alone.

Discussion

The most important findings of this study are that failure after SVG stenting: 1) frequently presents with an acute MI; and 2) is often due to SVG occlusion.

Although in-stent restenosis has traditionally been considered a low-risk event, recent studies have shown that this might not be true. Chen et al. (1) reported that, among 1,186 cases of BMS restenosis at the Cleveland Clinic, 36% presented with an ACS (26% unstable angina and 10% with MI). In that
study, prior coronary artery bypass grafting (CABG) was an independent predictor of development of an ACS, although whether that was due to restenosis within an SVG was not reported (11.3% of the target vessels were SVGs). Similarly, Steinberg et al. (2) reported that restenosis within a BMS presented with an acute MI in 6.7% and with unstable angina in 47% of 2,539 patients at the Washington Hospital Center. In the SOS trial, nearly one-third of the patients who developed SVG stent failure presented with an acute MI, which was partly due to the high frequency of ARC definite/probable stent thrombosis (6 of 80 patients, 7.5%, 5 of whom were taking dual antiplatelet therapy at the time of the event). This could explain the high mortality (5% to 7%/year) and risk of MI in patients with prior CABG undergoing diagnostic angiography (5) or PCI (6). Administration of dual antiplatelet therapy was similar in the 2 SOS study groups (3), likely because most patients initially presented with an ACS. Yet, in view of the high risk for developing an ACS after SVG stenting, prolonged dual antiplatelet therapy should be considered.

All patients developing acute MI during follow-up, including all 4 patients with definite stent thrombosis, presented with an NSTEMI. The lack of ST-segment elevation in these cases is likely secondary to partially preserved antegrade coronary

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**Table 1. Clinical Presentation of Stent Failure in the SOS Trial**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Total Patients</th>
<th>BMS Patients</th>
<th>PES Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>10 (42%)</td>
<td>7 (35%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>7 (29%)</td>
<td>6 (30%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>UA</td>
<td>3 (13%)</td>
<td>1 (5%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>9 (37%)</td>
<td>9 (45%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>5 (21%)</td>
<td>4 (20%)</td>
<td>1 (25%)</td>
</tr>
</tbody>
</table>

Values are n (%).

ACS = acute coronary syndrome; BMS = bare-metal stent(s); NSTEMI = non-ST-segment elevation acute myocardial infarction; PES = paclitaxel-eluting stent(s); UA = unstable angina.

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**Table 2. Coronary Revascularization in Asymptomatic and Symptomatic Patients Participating in the SOS Trial**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Number of Failed SVGs</th>
<th>SVG PCI</th>
<th>Native Coronary Artery PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% SVG occlusion</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal SVG occlusion</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100% SVG occlusion</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Subtotal SVG occlusion</td>
<td>13</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

PCI = percutaneous coronary intervention; SVG = saphenous vein graft.
flow and more developed collateral flow in patients with prior CABG, although it might also be associated with failure of SVGs to an obtuse marginal branch (in 2 of the 7 NSTEMI patients in our study).

In native coronary arteries, in-stent restenosis causes vessel occlusion in <1% of patients, whether a DES or a BMS is used (7,8). In contrast, occlusion after stent placement in an SVG is not rare. The 6-month occlusion rates of a BMS placed in an SVG was 13% in the SAVED (Saphenous Vein De Novo Trial Investigators) trial (9), 13% in the Venestent trial (10), 7% in the STING (STents IN Grafts) trial (11), 12.5% in the RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent) trial (12), 8% in a study by Hoffman et al. (13), and 11.5% in a study by Wohrle et al. (14). The rate of SVG occlusion in the BMS arm of the SOS trial (23% of treated lesions) is somewhat higher than the aforementioned studies, most likely because follow-up angiography was performed after 12 rather than 6 months, which illustrates that SVG failure risk might remain high even beyond 6 months. In the SOS trial, although restenosis occurred significantly less often in PES-treated than in BMS-treated patients, SVG occlusion occurred in one-half (2 of 4) of the PES restenotic lesions.

The high rates of SVG occlusion seen in the SOS trial could be related to a local prothrombotic state caused by slow antegrade flow in the setting of in-stent restenosis (15) or to atherosclerosis progression in nonstented SVG segments (16). Moderate SVG lesions might rapidly progress to severe (16,17). Ellis et al. (16) reported the rate of long-term (29 ± 13 months) ischemic events in untreated nonobstructive SVG lesions. Saphenous vein graft lesions with 41% to 50%, 31% to 40%, and <30% diameter stenosis at baseline were associated with a 45%, 18%, and 2% incidence, respectively, for ischemic events at follow-up (16). Rodés-Cabau et al. (17) evaluated predictors of SVG lesion progression in 86 patients with untreated nonobstructive SVG lesions at baseline who had clinically driven angiographic follow-up after 20 ± 15 months. On multivariate analysis, predictors of angiographic progression (>0.6 mm decrease in minimal luminal diameter or >10% increase in maximal diameter stenosis) were baseline high-density lipoprotein cholesterol and the SVG atherosclerotic burden score; the only predictor of clinical events related to SVG disease progression was maximal percent SVG diameter stenosis at baseline (17). The DES are unlikely to affect SVG atherosclerosis progression outside the stented SVG segment and might paradoxically be associated with higher rates of nontarget SVG lesion progression. If a stented SVG segment remains patent, lesions in nonstented segments might progress, whereas if the SVG occludes due to failure of the stented segment no further SVG failure is possible. This might explain why in the PES arm of the SOS trial target lesion revascularization was dramatically reduced, whereas there was only a trend for lower target vessel revascularization (3); indeed, target SVG revascularization was due to progression of SVG atherosclerosis outside the stented segment in 4 of 6 (66%) such patients in the PES arm versus in only 1 of 12 (8%) such patients in the BMS arm (3).

Treating SVG occlusions is challenging, whether the occlusion is acute or chronic, and angiographic success might not correlate with improved clinical outcomes (18). According to the 2005 American College of Cardiology/American Heart Association PCI guidelines, “PCI is not recommended in patients with prior CABG for chronic total vein graft occlusions” (Class III indication) (19). Acute SVG occlusions are usually associated with large thrombus burden, often necessitating stenting of a long length of the SVG to restore patency. Patients with chronic SVG occlusions and medically refractory symptoms might be best treated with PCI of the native coronary artery, when technically feasible (20,21); yet this might be challenging, due to the high prevalence of chronic occlusions in the native coronary arteries of prior CABG patients. In view of the poor short- and long-term outcome after PCI of occluded vein grafts (19), prevention of SVG occlusion is of paramount importance. On the basis of the SOS trial, PES implantation provides significant clinical benefit compared with BMS implantation not only at reducing overall SVG failure but also of reducing occlusion, although large studies are needed to determine the long-term clinical benefits of placing DES in SVGs (22,23).

This study is primarily limited by the relatively small number of patients enrolled and incomplete angiographic follow-up, although the SOS trial obtained 12-month angiographic follow-up data in contrast to 6-month follow-up data provided by most previous studies. The mandatory angiographic follow-up could have increased the rates of repeat revascularization, although none of the asymptomatic patients with SVG restenosis were revascularized (Table 2). In the SOS trial the interventional cardiologists and physicians treating the patients were not blinded to stent assignment, yet the patients and outcome assessors were blinded (3).

Conclusions

SVG stent failure often presents as acute MI and with SVG occlusion. Therapies that might prevent SVG in-stent restenosis, such as DES, markedly reduce the probability of SVG failure and occlusion and could significantly improve the clinical outcomes of patients undergoing SVG PCI.

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