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EDITORIAL COMMENT

Are Our Patients Better Off With Drug-Eluting Stents in Saphenous Vein Grafts?*

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In spite of their limited durability, saphenous vein grafts (SVGs) have for 40 years been the most frequently used conduit in coronary artery bypass graft surgery (CABG). The intermediate and late-term failure of SVGs due to atherosclerosis is the leading cause of recurrent myocardial ischemia in post-coronary artery bypass graft surgery patients who often present with high-risk acute coronary syndromes. In such patients, interventional cardiologists face vexing decisions regarding revascularization options given on one hand SVG-percutaneous coronary intervention (PCI) with increased procedural risk, complexity, and uncertain long-term outcome, and on the other the increased upfront morbidity and mortality of reoperative surgery without a clear long-term mortality benefit. In the very earliest experience with balloon angioplasty, Andreas Gruentzig perceptively recognized the poor outcomes achieved after treatment of SVGs. In the first 50 patients reported, he noted restenosis in 60% of the patients who underwent balloon angioplasty of SVGs causing him to write "the different kind of disease may explain the high incidence of recurrence in graft stenoses" (1). These disappointing results caused Gruentzig to question the place of balloon angioplasty in SVGs. Subsequent experience showed that excellent long-term results of SVG balloon angioplasty were largely confined to the treatment of early post-operative anastomotic stenosis (2). The advent of stents in the second decade of angioplasty modestly improved outcomes of SVG-PCI. In the randomized SAVED (Saphenous Vein De Novo) trial, event-free survival was significantly higher in stented patients, but the restenosis rate at 6 months was not significantly improved (37% with stent vs. 46% with balloon, $p = 0.24$), and the mortality rate of stented patients was 7% (3). Bare-metal stents (BMS) subsequently became the default strategy in spite of a high late event rate that was probably underappreciated. Embolic protection made the SVG-PCI procedure safer by reducing periprocedural myocardial infarction by about 50% and permitted complex SVG disease to be more safely treated with PCI. Other strategies such as direct stenting, stent undersizing to reduce the "cheese-grater" effect of stents, and pre-treatment with vasodilators appear reasonable for certain situations, but lack proof of benefit. Despite 30 years of innovation, the intermediate- and long-term results of SVG-PCI have remained poor compared with those achieved in native vessels leading some to question the wisdom of SVG-PCI except in the most narrowly defined indication (single lesion, nonleft anterior descending coronary artery SVG). It was hoped that drug-eluting stents (DES) would improve the durability of SVG-PCI, but reports have been conflicting.

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In this issue of *JACC: Cardiovascular Interventions*, an enterprising group of practitioners report their experience with over 1,000 patients who underwent SVG-PCI in 8 U.S. centers comparing outcomes after DES or BMS implantation (4). This analysis of an investigator-initiated registry used propensity scores to adjust for baseline differences in patients who were followed out to 2 years. It is, by far, the largest reported experience addressing this important issue. Seven-hundred eighty-five patients received DES and 343 patients received BMS implantation at the discretion of the operator over a 3-year period. Patients in these 2 groups were significantly different, with BMS-treated patients having more emergent procedures, approximately twice as many ST-segment elevation myocardial infarctions, larger vein graft diameter (3.7 mm vs. 3.3 mm, $p < 0.001$), and more no reflow (6.9% vs. 3.3%, $p = 0.003$). DES-treated patients, in addition to having smaller vessels, had longer lesions, more Thrombolysis In Myocardial Infarction flow grade 3 pre-procedure, more hyperlipidemia and bivalirudin use, and a longer stented segment. In-hospital death and myocardial infarction were not significantly different. At 9 months post-procedure, DES-treated patients experienced less major adverse cardiac events (14% vs. 21%, $p = 0.001$), a lower composite of death or myocardial infarction (8.7% vs. 14%, $p = 0.006$), and the target vessel revascularization (TVR) rate was lower after adjustment (hazard ratio: 0.36, $p < 0.001$) as was the stent thrombosis rate. At 2 years, DES-treated patients had less death and death or myocardial infarction. However, Kaplan-Meier analysis indicated that the differences in death or myocardial infarction were largely related to changes occurring in the first few weeks (a finding not attributable to DES), and that the benefit of reduced TVR and stent thrombosis at 9 months

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was no longer present at 2 years. Subgroup analysis indicated that the benefit of lower TVR at 9 months with DES was confined to patients with SVG diameter <3.5 mm.

This study has a number of limitations that the authors acknowledge. Paramount among them are its observational nature and the selection bias among operators, which resulted in very significant between-group differences and the inability to distinguish between repeat revascularization for stent restenosis or progression at nontarget sites. In addition, there is little angiographic data including lesion morphology, extent of SVG degeneration, and presence of thrombus and clinical data such as graft age and presence of factors influencing stent selection (bleeding risk, patient compliance, comorbidity). If a lower-risk cohort was selected for DES implantation, it would be difficult to determine this, in part due to the absence of these descriptors. If the DES-treated patients were a lower-risk group, the efficacy and safety of DES may be overestimated as adjustment techniques may not correct for these differences. Outcomes could also be affected by dual-antiplatelet and lipid-lowering therapy, which were not controlled or recorded. The "late catch up" in TVR in the second year of follow-up in the DES group is interesting and has been described previously (5–7). In a small randomized trial of sirolimus-eluting stents versus BMS reported by Vermeersch et al. (5), angiographic follow-up was performed at 6 months, and restenosis and TVR were less with DES (14% vs. 33%, $p = 0.03$ and 5% vs. 27%, $p = 0.01$, respectively). At a median follow-up of 32 months, "late catch up" had occurred, and TVR rates were comparable (34% vs. 38%, p = NS) (6). A substantial portion of this "late catch up" in the DES arm was due to progression outside the stented segment since late target lesion revascularization was only 19%. Applegate et al. (7) in a study of 74 consecutive patients who received DES in SVGs compared with 74 propensity score matched BMS-treated patients noted a "late catch up" in TVR at 2 years. Brilakis et al. (8) in a prospective, randomized trial of 80 patients with SVG lesions (39 treated with BMS and 41 with paclitaxel-eluting stents) reported significantly less target lesion revascularization with DES at a median follow-up of 1.5 years (5% vs. 28%, $p = 0.003$) and a trend toward less TVR (15% vs. 31%, $p = 0.08$) indicating a need for nontarget intervention in about 10% of patients. It has been recognized for many years that SVGs can deteriorate rapidly once stenoses begin to occur (2). Rodes-Cabau et al. (9) reported that about one-half of patients with mild to moderately diseased SVGs show significant progression after 15 months in spite of low-density lipoprotein levels <90 mg/dl. Ellis et al. (10) first reported the important prognostic implications of moderate SVG lesions (a 45% cardiac event rate compared with 2% in patients without them) and suggested a strategy of "sealing" moderate SVG lesions with stents. In the Late Breaking Trials at the 2009 American College of Cardiology annual meeting, Rodes-Cabau et al. (11) reported in a randomized angiographic and intravascular ultrasound trial that "sealing" moderate SVG lesions with paclitaxel-eluting stents significantly reduced SVG disease progression without adverse affects, and this resulted in a trend towards lower major adverse cardiac events at 1 year (3% in DES group vs. 19% with medical therapy, $p = 0.09$). It appears, therefore, that interventionalists in the future will increasingly be faced with decisions not only regarding severe SVG lesions, but moderate stenoses as well.

Does the work of Brodie et al. (4) further our understanding of the use of DES in SVGs? It suggests that the use of DES in SVGs is safe. Death or myocardial infarction was less, and there was no difference in stent thrombosis. A pooled analysis of available trials by Blankenship (12) also suggested that mortality was not higher and may even be lower with the use of DES. The Brodie et al. (4) study suggests that the benefit of DES in SVG may be less than in native vessels, and confined to SVGs <3.5 mm in diameter with loss of TVR benefit after 9 months. It focuses our attention on the cause of this "late catch up." Was this "catch up" due to late developing target site restenosis or disease progression at nontarget sites, and will more liberal stenting of moderate lesions be in our future? Clearly more study of this issue is needed.

In the absence of a large, multicenter, randomized trial of DES versus BMS in SVGs, how should we proceed? The interventionalist advising a patient considering repeat revascularization should keep in mind the substantial 5% to 10% annual mortality in patients after SVG-PCI as well as the need for TVR in about a one-quarter of patients within a year or two. Native vessel PCI including chronic total occlusions should be considered whenever possible as an alternative to SVG-PCI. In the presence of multiple SVG involvement, diffuse SVG disease, stenosis of the LAD graft or other critical conduits, and in middle-aged patients with acceptable reoperative risk, repeat surgery should be considered. When performing SVG-PCI, embolic protection should be utilized whenever possible. The choice of DES over BMS should hinge on the assurance of reliable, long-term dual-antiplatelet therapy and be favored in SVGs <3.5 mm in diameter and in the presence of longer lesions realizing the benefit of DES over BMS may be short term. The optimal type of DES for SVG disease is yet to be determined.

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Key Words: stents ■ saphenous vein grafts ■ coronary artery grafts.