Long-term Follow-up of Lesion-specific Outcomes Comparing Drug-eluting Stents and Bare Metal Stents in Diseased Saphenous Vein Grafts

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Saphenous vein grafts (SVGs) are a common choice for bypassing obstructed coronary arteries. Repeat coronary artery bypass grafting has been found to have substantial rates of morbidity and mortality; therefore, SVG percutaneous intervention has emerged as a positive alternative for revascularization. Stenting of SVGs has been shown to be more beneficial than medical management or balloon angioplasty alone. The literature is conflicting with regard to which type of stent—bare metal stent (BMS) or drug-eluting stent (DES)—is best suited for treating graft failure. The authors provide long-term follow-up data of lesion-specific outcomes when comparing DES versus BMS in SVGs.

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KEY WORDS

Saphenous vein graft • Percutaneous intervention • Drug-eluting stent • Bare metal stent • Restenosis

Saphenous vein grafts (SVGs) remain one of the most common conduits of choice for bypassing significantly obstructed native coronary arteries.[1,2] With an estimated graft failure rate of 12% to 20% at 1 year, and approaching 50% at 10 years,[3] reoperation is often required. Repeat coronary artery bypass grafting (CABG) has been found to have substantial rates of morbidity and mortality.[4] Therefore, SVG percutaneous intervention (PCI) has emerged as an advantageous alternative for revascularization.[5] Stenting of SVGs has been shown to be more beneficial than

medical management or balloon angioplasty alone.[6,7] In the early stages, the immediate postoperative complication secondary to the choice of stent—drug-eluting stent (DES) versus bare metal stent (BMS)—was of less concern when a 15% to 20% incidence of major adverse coronary events (MACE) complicated the post-PCI period.[8] The more pressing concern was the decision of whether or not to proceed with SVG PCI. Currently, with the widespread use of embolic protection devices to prevent plaque embolization, MACE rates have dropped significantly,[9-13] thus making SVG PCI a sound method of treatment. More recently, attention has shifted toward a new topic of debate: which stent—BMS or DES—is best suited for treating graft failure?

Literature continues to be conflicting regarding this topic. Therefore, the aim of our study is to provide long-term follow-up data of lesion-specific outcomes comparing DES and BMS in SVGs.

Methods

Study Population

After obtaining Institutional Review Board approval, we retrospectively reviewed records of all CABG patients who underwent PCI at St. John Providence Hospital (SJPH) between January 2003 and December 2005. Records included medical charts from both the hospital and the ambulatory clinics where patients received follow-up care. Patients with prior stent placement to native coronary vessels or left internal mammary artery bypass grafts and patients with original stent placement prior to 2003 were excluded.

During the 36-month period, 299 patients with a history of CABG underwent PCI at SJPH. Indication for heart catheterization leading to PCI was either symptom driven or secondary to a positive or indeterminate stress test result. Of the 299 patients, 147 were included in our study. All of the 147 patients must have had their first stent placed in an SVG during the aforementioned time frame and have had a minimum of 2-year follow-up.

The primary clinical endpoint was all-cause mortality directly related to MACE. MACE encompasses cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). If unexpected or unwitnessed deaths occurred, they were considered cardiac in origin. MIs were divided into two categories: periprocedural and nonperiprocedural. Periprocedural MI was diagnosed if creatine-kinase-MB levels reached three times the upper limit of normal (> 10.5 ng/mL). Nonperiprocedural MI was defined as a new ischemic event with positive troponin levels or electrocardiographic presence of new pathologic Q waves.

Coronary angiography results were reviewed to assess for the timing and extent of in-stent restenosis. We categorized occurrence of restenosis based on previously defined time frames.[14] Specifically, these were defined as early (l < 30 d), late (> 30 d but < 1 y), and very late (> 1 y).

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Data collection consisted of the number and type of stents placed in a SVG, patient comorbidities, and relevant medical therapy (Table 1). Patients were then categorized based on the type of stent they received: BMS or DES.

TABLE 1

Patient Demographics, Risk Factors, and Medical Therapy

Demographics	DES (n = 75)	BMS (n = 87)	*P* Value
Age	68 ± 2 y	68 ± 1 y	1
Male	76%	86%	.09
History of MI	86%	85%	.93
Tobacco abuse	71%	73%	.68
DM	73%	78%	.47
Hypercholesterolemia	91%	92%	.77
CAD family history	74%	72%	.85
Statin	85%	81%	.41
ACE-I/ARB	64%	59%	.48
β-Blocker	79%	78%	.93
Antiplatelet	95%	95%	.83

As shown here, there is not a statistically significantly difference between the two groups.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare metal stent; CAD, coronary artery disease; DES, drug-eluting stent, DM, diabetes mellitus; MI, myocardial infarction.

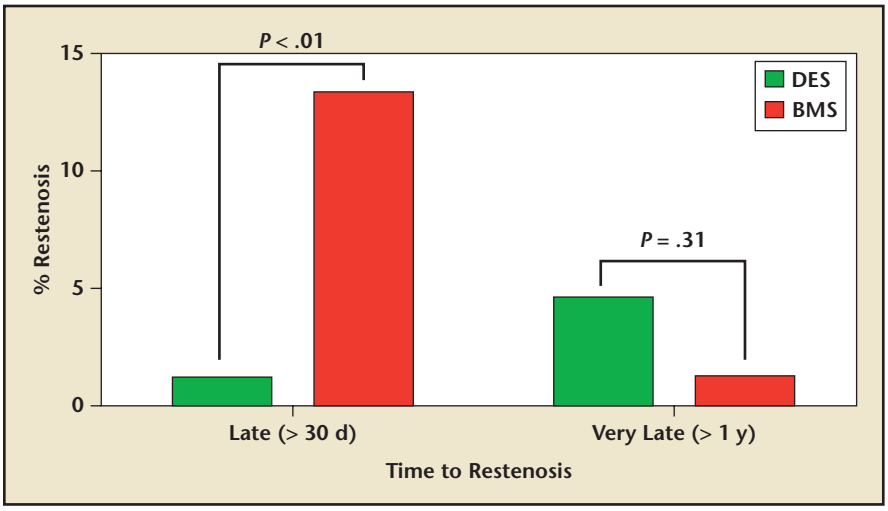


Figure 1. Comparison of in-stent restenosis rates in relation to time. BMS, bare metal stent; DES, drug-eluting stent.

Results

A total of 162 stents were placed in 151 lesions. Of the 147 patients in the study, 76 patients (51.7%) received DES and 71 patients (48.3%) received BMS. In the DES group, there were 78 lesions requiring 87 stents. In comparison, the BMS group had 73 lesions requiring 75 stents. Of the 15 patients who experienced in-stent restenosis, 11 (73.3%) had received BMS and 4 (26.7%) had received DES. Although early restenosis did not occur in any patient, there were 15 cases of late restenosis (Figure 1) with predominance in the BMS group (91% BMS vs 9% DES; $P < .01$). Very late restenosis occurred more frequently in the DES group; however, the difference was not statistically significant (25% BMS vs 75% DES; $P = .31$).

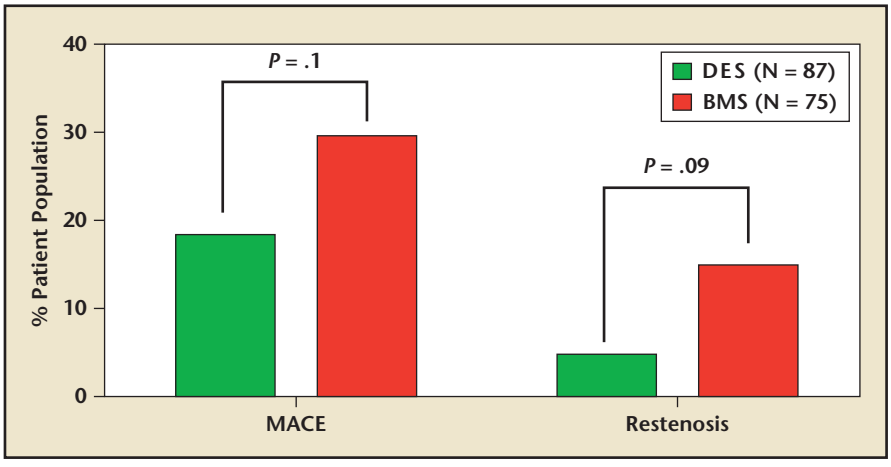
We uncovered 38 cases of all-cause mortality related to MACE (58% BMS vs 42% DES, P = NS). Despite that, just three patients experienced a MACE directly attributed to restenosis, with all three patients having received BMS. Even though the higher MACE rate related to BMS did not prove to be statistically significant (Figure 2), it is thought that these data are of clinical significance. Overall, patients who received BMS experienced an accelerated rate of restenosis (Figures 3 and 4), had nearly three times as many restenotic stents, and had a higher incidence of MACE directly and indirectly related to the stent itself. There was no statistically significant difference between the clinical make-up of either of the two patient populations (Table 1).

Discussion

The main catalyst prompting us to review our institution's data was the conflicting evidence reported in the medical literature. A prospective study by Vermeersch and colleagues[14] reported a higher long-term mortality rate associated with DES when compared with BMS in SVG disease. A retrospective review by Bansal and colleagues[15] that followed 1 year later reported findings similar to those reported by Vermeersch and coauthors.[14] They assessed 109 patients with SVG target vessel revascularization (TVR) and TLR and concluded that patients treated with DES incurred higher rates of MACE when compared with patients treated with BMS. In contrast, four retrospective studies comparing BMS and DES reported data that contradict the aforementioned studies. Three of the four articles demonstrated a lower incidence of overall MACE.[16-18] The fourth study reported a lower incidence of MI.[19]

We are reporting the longest follow-up in patients with PCI of SVGs. Our institution's data clearly display an advantage in decreased total incidence of MACE and MI. In addition, an important distinction that separates our data from those of other investigators is that, over a 2-year period, our data supporting DES are consistent. The four articles we reference show a clear benefit with the use of DES, but the data reported are limited to less than 1-year follow-up. This point was of utmost significance when the results of the Reduction of Restenosis In Saphenous Vein

Figure 2. MACE and overall restenosis. BMS, bare metal stent; DES, drug-eluting stent; MACE, major adverse coronary events.



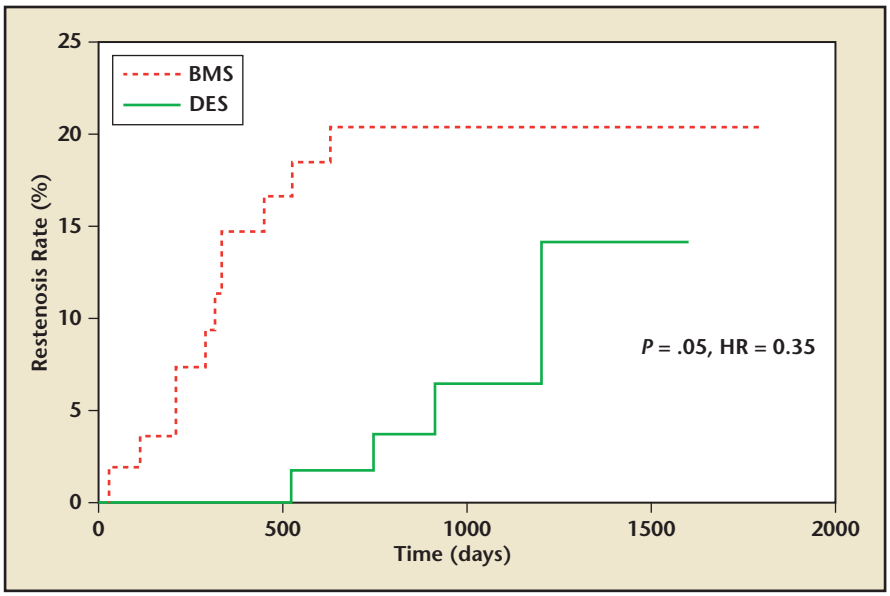


Figure 3. Kaplan-Meier curve demonstrating the earlier onset of in-stent restenosis of BMS. BMS, bare metal stent; DES, drug-eluting stent; HR, hazard ratio.

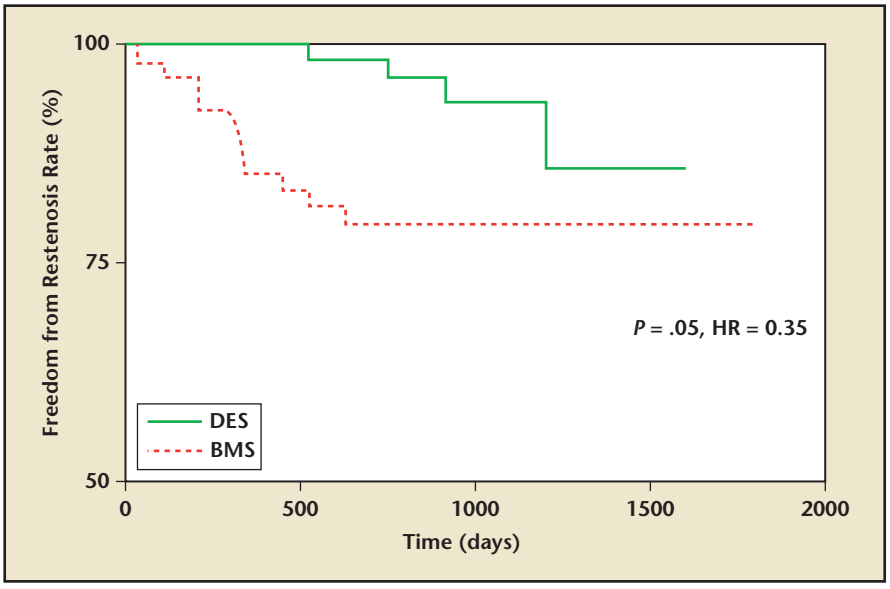


Figure 4. Kaplan-Meier curve illustrating the long-term benefit of DES with regard to restenosis. BMS, bare metal stent; DES, drug-eluting stent; HR, hazard ratio.

Grafts With Cypher Sirolimus-Eluting Stent (RRISC) trial became available.[14] RRISC was the first prospective, randomized, controlled clinical trial comparing BMS with DES. This trial showed clear evidence that DES were superior to BMS in areas of repeat TLR and MACE; however, initial trials were limited to the initial 6-month follow-up period. Late follow-up data of patients enrolled in the RRISC trial proved to be very concerning.[14] At a median 32-month follow-up, mortality rates were significantly higher for those patients who received DES versus those who received BMS (29% vs 0%; $P = .001$).

A more recent prospective, randomized, controlled clinical trial comparing BMS to DES, the Stenting of Saphenous Vein Grafts (SOS) trial, has shown more promising results for the use of DES.[14,20] SOS differs from RRISC in two significant aspects. The first is that SOS compares a paclitaxel-eluting stent with an equivalent BMS, whereas RRISC used a sirolimus-eluting stent with its BMS counterpart. The second is that SOS used a multicenter approach, whereas RRISC was a single-center study. The SOS trial demonstrated strong evidence supporting the use of DES with regard to angiographic restenosis; however, clinical endpoints (ie, MACE) were not measured. Despite not assessing for clinical endpoints, the SOS data did not show an increase in mortality rate in either arm of their study at 12 months and at 18 months. Regardless, the main drawback that cannot be ignored with both SOS and RRISC is the small number of patients enrolled. To this point, prospective studies on this subject have been underpowered and have provided us with conflicting evidence. There is hope that the Drug-Eluting Stents vs Bare Metal Stents In Saphenous Vein Graft Angioplasty (DIVA) trial will address these issues. DIVA is a multicenter, prospective, randomized, clinical trial that will compare DES with BMS in SVG angioplasty.[21] The primary outcome measure studied will be target vessel failure. This will be defined as the composite of cardiac death, target vessel MI, and TVR. Patients will be followed for a minimum of 12 months after being enrolled; there will be a host of secondary outcome measures including clinical and angiographic endpoints as well as cost analysis. The study will involve 21 Veterans Affairs Medical Centers across the United States and is expected to enroll 520 participants. Enrollment began in September 2010 with initial analysis of primary outcome measures anticipated by September 2013.

Our study, as with any retrospective analysis, is limited. In addition, our data are further hampered by

the fact that this is a single-center experience with a distinct patient population and select number of interventional cardiologists. Also, our data were collected at a time when DES was first introduced to the market. We do not have data analyzing newer DES technology. We acknowledge that the concept of no-reflow was not addressed in our study. This is secondary to the fact that this was not a phenomenon that was largely encountered in the cases we reviewed. The theory of insignificant no-reflow phenomena documented during this study is likely secondary to the technique of the interventionalist at the time of stent placement. It was found that the operators follow a similar technique during SVG PCI, which may explain the low rates of no-reflow at our facility. This technique entails the administration of intracoronary nitroglycerin pre- and postballoon dilation as well as pre- and poststent deployment, along with the use of intravenous glycoprotein IIb/IIIa receptor inhibitors.

Conclusions

After reviewing our data and the current literature, it appears that patients with SVG failure undergoing PCI are likely to experience a better overall outcome with DES. The two prospective, randomized clinical trials (SOS and RRISC) comparing DES versus BMS had conflicting results. Almost all retrospective studies show a reduction in the incidence of MACE with DES during short-term follow-up. Our analysis is the first to report data that demonstrate these findings at a follow-up of 2 years. ■

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MAIN POINTS

- Saphenous vein graft (SVG) percutaneous intervention (PCI) has emerged as a positive alternative for revascularization, and with the widespread use of embolic protection devices to prevent plaque embolization, there has been a significant drop in major adverse coronary event (MACE) rates, which makes SVG PCI a sound method of treatment.
- Data from our institution showed that patients receiving bare metal stents (BMS) experienced an accelerated rate of restenosis, had nearly three times as many restenotic stents, and had a higher incidence of MACE directly and indirectly related to the stent itself.
- It appears that patients with SVG failure undergoing PCI are likely to experience a better overall outcome with drug-eluting stents (DES) than with BMS.
- The two prospective, randomized clinical trials comparing DES versus BMS had conflicting results. Almost all retrospective studies show a reduction in the incidence of MACE with DES during short-term follow-up. Our analysis is the first to report data that demonstrate these findings at a follow-up of 2 years.

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