Outcomes With Drug-Eluting Versus Bare-Metal Stents in Saphenous Vein Graft Intervention

Results From the STENT (Strategic Transcatheter Evaluation of New Therapies) Group

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Objectives This study compares outcomes of drug-eluting stents (DES) versus bare-metal stents (BMS) in patients undergoing saphenous vein graft (SVG) intervention.

Background The safety and efficacy of DES in patients undergoing SVG intervention is controversial.

Methods The STENT (Strategic Transcatheter Evaluation of New Therapies) registry is a multicenter U.S. registry evaluating outcomes with DES. Our study population includes patients undergoing PCI of SVG lesions with DES (n = 785) or BMS (n = 343) who completed 9-month or 2-year follow-up. Outcomes were adjusted with propensity analyses.

Results The DES patients had fewer emergent procedures but had smaller vessels and longer lesions. The DES patients had less death or myocardial infarction at 9 months (hazard ratio [HR]: 0.52, 95% confidence interval [CI]: 0.33 to 0.83, p = 0.006) and less death at 2 years (HR: 0.60, 95% CI: 0.36 to 0.98, p = 0.041). Target vessel revascularization (TVR) was less with DES at 9 months (7.2% vs. 10.0%, HR: 0.36, 95% CI: 0.22 to 0.61, p < 0.001) but was no different by 2 years (18.3% vs. 16.9%, p = 0.86), although adjusted TVR rates were lower (HR: 0.60, 95% CI: 0.40 to 0.90, p = 0.014). The DES reduced TVR at 9 months in SVG lesions with diameter <3.5 mm (8.0% vs. 17.2%, p = 0.013) but not ≥3.5 mm (6.0% vs. 6.6%, p = 0.74).

Conclusions Treatment of SVG lesions with DES vs. BMS is effective in reducing TVR at 9 months, although most of this advantage is lost at 2 years. The DES seem safe with less death or myocardial infarction, although selection bias might have affected these results. Our data suggest that DES might have short-term advantages over BMS in SVG lesions with diameter <3.5 mm. (J Am Coll Cardiol Intv 2009;2:1105–12) © 2009 by the American College of Cardiology Foundation

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Drug-eluting stents (DES) have been shown to be safe and more effective than bare-metal stents (BMS) in reducing the need for target vessel revascularization (TVR) in patients with noncomplex lesions undergoing elective percutaneous coronary intervention (PCI) (1,2).

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The safety and efficacy of DES for off-label use in patients undergoing PCI for lesions in saphenous vein grafts (SVG) remains controversial. There have been 2 small randomized trials (3–5) and several small registries (6–17) comparing DES with BMS in patients undergoing SVG PCI, but these studies have been limited by small numbers of patients with short-term follow-up and have had conflicting results.

The STENT (Strategic Transcatheter Evaluation of New Therapies) registry is a multicenter prospective registry designed to evaluate late outcomes with DES in the U.S. This study was designed to test the hypothesis that the use of DES compared with BMS with SVG intervention is safe and effective in reducing TVR.

**Abbreviations and Acronyms**

- **BMS** = bare-metal stent(s)
- **DES** = drug-eluting stent(s)
- **PCI** = percutaneous coronary intervention
- **SVG** = saphenous vein graft
- **TIMI** = Thrombolysis In Myocardial Infarction
- **TLR** = target lesion revascularization
- **TVR** = target vessel revascularization

**Methods**

The STENT group. The STENT Group created a multicenter registry to evaluate coronary artery stent use and outcomes in real-world clinical settings in the U.S. beginning in May 2003. Patients undergoing PCI were consented at 8 coronary interventional centers for participation including 9-month and 2-year follow-up. The STENT registry is supported by unrestricted grants from industry. Detailed methodology of this registry has been previously reported (18,19).

**Definitions.** Re-infarction was defined as a clinical event with new elevation of creatine kinase (CK) and elevation of the myocardial band fraction of CK >2 times normal and includes both ST-segment elevation and non–ST-segment elevation myocardial infarction (MI). Target vessel revascularization (TVR) was defined as a repeat procedure anywhere in the target vessel, including repeat PCI or coronary artery bypass graft surgery. Target vessel revascularization was used instead of target lesion revascularization (TLR), because determinations were assessed by the operators without a core angiographic laboratory to distinguish TLR from TVR occurring at sites other than the target lesion. Stent thrombosis was defined with a modified Academic Research Consortium definition of definite or probable stent thrombosis: angiographically documented stent thrombosis, a MI in the distribution of the target vessel, or sudden cardiac death.

**Study population.** Our study population is shown in Figure 1. Of 26,941 PCI procedures performed at 8 centers from May 2003 through June 2006, 24,384 were consented to participate in the STENT Registry (90.5%), 20,905 patients had unique procedures (first procedure in the registry), and 1,380 had SVG intervention. Of these, 348 received BMS only and 820 received DES only. Follow-up for the registry concluded June 2007. Follow-up at 9 months was obtained in 343 of the BMS patients (98.6%) and 785 of the DES patients (95.7%). Follow-up at 2 years was obtained in 252 of the BMS patients (98.1% of those eligible) and 407 of the DES patients (94.9% of those eligible).

Of the 785 patients treated with DES, 59% were treated with sirolimus-eluting stents, 38% were treated with paclitaxel-eluting stents, and 3% received both stents.

**Data collection.** All data were collected prospectively by study coordinators at participating hospitals. Procedural data, including adjunctive pharmacology, device use, reference vessel diameter, lesion length, and lesion characteristics were assessed by the operating interventional cardiologist. Post-discharge clinical follow-up was conducted by telephone interview at 9 and 24 months after the procedure. Complete hospital records were reviewed for every patient reporting a cardiac event after the index hospital stay. All data were entered into a centralized web-based database for quality control and statistical analysis (R. Stuart Dickson Institute for Health Studies, Charlotte, North Carolina). Physician investigators adjudicated all major events, including death, TVR, and stent thrombosis, and site audits were performed on 10% of the first 4,000 procedures and 5% thereafter.

**Statistical methods.** Baseline and outcome variables were compared with t tests for continuous variables and the chi-square test or Fisher exact test for categorical variables. A p value <0.05 was considered statistically significant. All analyses were performed with SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Kaplan-Meier event curves were constructed for outcome variables, and comparisons were made between DES and BMS with log-rank tests. To adjust for differences in baseline risk profile between patients treated with DES and those treated with BMS, propensity scores were calculated with a logistical regression model (20). All relevant baseline clinical and angiographic variables were included in the model. Propensity scores were then entered into the individual Cox proportional hazard regression models. These models were used to provide adjusted comparisons of event rates between DES and BMS for the outcome variables. Multivariable Cox regression analysis was used to evaluate potential predictors of TVR.
Results

Baseline clinical and angiographic variables. Patients treated with DES had a higher incidence of hypertension and hyperlipidemia but a lower incidence of ST-segment elevation MI and emergent procedures (Tables 1 and 2). The DES patients had smaller vessel size and longer lesion length (Table 2).

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Variables</th>
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<tr>
<td><strong>BMS</strong> (n = 343)</td>
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</tr>
<tr>
<td>Male</td>
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<tr>
<td>Diabetes (any)</td>
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<td>Hypertension</td>
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<td>ST-segment elevation myocardial infarction</td>
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<td>Cardiogenic shock</td>
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<td>Acute congestive heart failure</td>
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Values are mean ± SD or n (%). BMS = bare-metal stent(s); DES = drug-eluting stent(s).
Procedural and in-hospital outcomes. Patients treated with DES had less no-reflow, a higher incidence of final TIMI flow grade 3, and a higher angiographic success rate (Table 2). There were no significant differences between DES and BMS in in-hospital death (0.8% vs. 1.5%, p = 0.33) or in-hospital MI (2.0% vs. 4.1%, p = 0.16).

Propensity score adjustment. All significant univariate predictors of stent type as well as other clinically relevant variables were used in the propensity score model. The model had good fit (C = 0.825), and the model characteristics are shown in the Online Table A. All predictor variables in the propensity score model were shown to become nonsignificant after adjustment (Online Table B).

Late outcomes. Patients treated with DES compared with BMS had a significantly lower frequency of death at 2 years by unadjusted and adjusted analyses (Table 3) and had a significantly lower frequency of death or MI at 9 months and 2 years by unadjusted analyses and at 9 months by adjusted analyses (Table 3, Fig. 2). The event curves for death or MI diverged early with most of the differences occurring in the first few weeks (Fig. 2).

The TVR was lower with DES at 9 months, but by 2 years the event curves crossed, and TVR was slightly higher with DES than with BMS (Table 3, Fig. 3). After adjustments with propensity analyses, the event curves for TVR were significantly lower with DES compared with BMS both at 9 months and 2 years (Table 3, Fig. 3). When only patients who completed 2-year follow-up were analyzed, there were no significant differences in the frequency of TVR between DES and BMS by unadjusted analyses (19.0% vs. 16.5%, log rank p = 0.67) or propensity adjusted Cox regression (hazard ratio [HR]: 0.78, 95% confidence interval [CI]: 0.48 to 1.25, p = 0.30).

There were significantly fewer major adverse cardiac events (death, MI, or TVR) with DES compared with BMS at 9 months and 2 years by adjusted analyses (Table 3). Stent thrombosis was lower with DES than BMS at 9 months by adjusted analyses, but by 2 years the event curves crossed, and there were no significant differences between the 2 groups (Table 3, Fig. 4). The incidence of stent thrombosis between 9 months and 2 years was 2.0% (8 of 407) with DES and 0.4% (1 of 252) with BMS (log
rank \( p = 0.11 \) by landmark analysis). The analysis of stent thrombosis events with Cox regression modeling should be interpreted with caution, because the event rates were low.

**Predictors of TVR.** Independent predictors of TVR at 9 months by Cox regression analysis included BMS use (HR: 1.61, 95% CI: 1.04 to 2.50, \( p = 0.03 \)) and SVG reference diameter \( \geq 3.5 \text{ mm} \) (HR: 1.74, 95% CI: 1.13 to 2.67, \( p = 0.01 \)). Diabetes and long lesion length (>28 mm) were not significant predictors of TVR. In patients with 2-year follow-up, stent type and SVG reference diameter \( \geq 3.5 \text{ mm} \) were no longer significant independent predictors of TVR.

Subgroup analysis in patients with 9-month follow-up showed that TVR was less with DES than with BMS in patients with SVG reference diameter \( <3.5 \text{ mm} \) (8.0% vs. 17.2%, \( p = 0.013 \)) but not in patients with SVG reference diameter \( \geq 3.5 \text{ mm} \) (6.0% vs. 6.6%, \( p = 0.74 \)). The TVR at 9 months was not significantly different between DES and BMS in diabetic patients and in patients with long lesions (>28 mm).

**Discussion**

The “off-label” use of DES for treatment of SVG lesions has been a subject of great interest and controversy, with no
general consensus regarding whether DES have an advantage over BMS in this patient population. There have been 2 small randomized trials comparing DES with BMS in SVG intervention, with conflicting results. Brilakis et al. (3) reported the results from the SOS (Stenting Of Saphenous Vein Grafts) trial and found less restenosis and less TLR in 39 patients treated with paclitaxel-eluting stents compared with 41 patients treated with BMS at 1 year. The RRISC (Reduction in Restenosis in Saphenous vein grafts with Cypher Stent) trial found less TVR with 38 patients treated with sirolimus-eluting stents compared with 37 patients treated with BMS at 6 months, but this benefit was lost at 2 years, and mortality was higher with DES at 2 years (4,5).

There have been a number of small registries comparing DES with BMS in SVG intervention, also with conflicting results. Most (6,7,9,10,15) but not all (8,13) registries with short-term follow-up have shown less TVR with DES at 6 to 12 months. However, registries with longer follow-up have shown less consistent benefit. Two registries found less TVR with DES at 2 to 3 years (14,16), but 3 other registries found no difference in TVR at 2 to 2.5 years (11,12,17). An additional registry showed less TVR with DES at 1 year, but this benefit was lost by 2 years (11). Most registries have shown no differences in the frequency of death or MI between DES and BMS with follow-up from 6 to 30 months (6~8,11~14,17). One registry showed less death or MI with DES at 9 months (6).

Our prospective registry includes 785 patients undergoing SVG intervention who were treated with DES. The largest previously reported SVG registry included only 141 patients treated with DES (16). We found that DES, compared with BMS, reduced TVR at 9 months, but this advantage decreased over time such that at 2 years TVR rates were slightly higher with DES versus BMS (Fig. 2). Adjusted comparisons of TVR for DES versus BMS over 2 years still favored DES, and there are likely 2 explanations for this. First, DES were used in lesions at higher risk for TVR (smaller vessels, longer lesions); so after adjusting for these differences, comparisons might favor DES. Secondly, comparison of TVR event curves for DES versus BMS might primarily reflect the differences in the curves in the early months. When only patients with 2-year follow-up were evaluated with adjusted analyses, there was no significant benefit of DES over BMS in reducing TVR.

The early benefit of reduced TVR with DES was most pronounced in patients with SVG reference diameter <3.5 mm, with little apparent benefit in patients with SVG reference diameter ≥3.5 mm. The DES did not seem to have any preferential advantage over BMS in patients with long versus short lesions and in patients with and without diabetes. None of the prior registries were large enough to allow subgroup analyses, but 1 small study found a lower frequency of TVR with DES for ostial SVG lesions (14).

The late “catch-up” phenomenon in TVR seen in our study (and 2 previous studies) (5,11) whereby TVR is reduced with DES at 9 months but not at 2 years might be related to unique features of SVGs and SVG intervention (21). Once disease develops in SVGs, progression of disease is much more rapid than in native vessels (22,23). Target lesion revascularization after SVG intervention occurs much more commonly at untreated sites other than at the target lesion after the first year (22), and this might dilute the benefit of DES in reducing TVR at the lesion site (24). This progression of disease at SVG sites other than the target lesion might account for most of the TVR from 9 months to 2 years and might explain why the TVR event curves for DES and BMS merge over time. Our data do not allow us to evaluate this possibility, because we are not able to distinguish between TLR and TVR. However, data from the DELAYED RRISC (Death and Events at Long-term follow-up Analysis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) trial suggest that TVR at sites other than the target lesion might contribute to this “catch-up” phenomenon (5).

A second possible explanation for the late “catch-up” in TVR with DES is that angiographic late loss and restenosis after the first 9 months might be more common with DES than with BMS after SVG intervention. Angiographic late loss after BMS implantation in native coronary arteries generally peaks at 6 to 9 months, after which there might be some regression (25). Consequently, restenosis and TVR are uncommon with BMS after 6 to 9 months. Conversely, angiographic late loss might continue with DES after 9 months, and this might be associated with late restenosis and TLR (26). Although the frequency of late restenosis with DES in native vessels is relatively small, the frequency...
of late restenosis after SVG intervention with DES could be greater (27).

Our data suggest that DES are safe with SVG intervention. Death or MI was less frequent with DES, and there were no differences in the frequency of stent thrombosis between DES and BMS. Although propensity analysis was used to adjust for differences in baseline variables between DES and BMS, the differences in death or MI might be due to hidden selection biases that cannot be accounted for with propensity adjustments. The fact that most of the differences in death or MI between DES and BMS in our registry occurred in the first 30 to 60 days before the benefits of DES in reducing TVR are evident (Fig. 2) suggests that these differences might be due to selection biases.

Study limitations. Although our study provides an opportunity to compare “real world” outcomes with DES versus BMS in patients undergoing SVG intervention, it has the limitations of an observational database. As mentioned earlier, there might be hidden biases to choose BMS for sicker patients who might have multiple comorbidities or bleeding risks or who might be noncompliant with dual antiplatelet therapy as well as other therapies. These biases might not be accounted for by statistical adjustments. Thus, our data could overestimate the safety of DES compared with BMS with regard to death or MI and stent thrombosis. Conversely, there could be hidden biases in selecting patients for DES who have a higher chance of developing the need for TVR. These biases might not be accounted for by adjustments for variables known to affect TVR, such as diabetes, vessel size, and lesion length. Thus, our data could underestimate the benefits of DES in reducing TVR.

The SVG reference diameter, lesion length, and TIMI flow were assessed by the operators rather than by core laboratory analysis. Also, without core laboratory angiographic analysis, we are not able to distinguish between TLR and TVR. This limits our ability to evaluate the mechanisms accounting for differences in TVR between DES and BMS. We also do not have data regarding SVG age and the extent of degeneration that might impact TVR.

Our registry does not have data regarding compliance with dual antiplatelet therapy. This is an important limitation, because compliance with clopidogrel and aspirin is a major determinant of stent thrombosis and adverse events (28,29). We also do not have data regarding compliance with other adjunctive medical therapies and risk factor modification that might impact outcomes.

Clinical implications. Our data indicate that the use of DES compared with BMS in SVG intervention is effective in reducing TVR in the short term, but most of this benefit seems to have been lost by 2 years. The short-term benefit seems to be most pronounced in SVGs with small reference lumen diameter (<3.5 mm), and there seems to be little benefit in SVGs with large reference lumen diameter.

Our data indicate that SVG intervention with DES compared with BMS is safe out to 2 years, with lower rates of death or MI and similar rates of stent thrombosis. Although these differences might be due to unmeasured biases to select BMS for sicker patients, the data are reassuring in that there do not seem to be any safety concerns with the use of DES with SVG intervention.

It seems reasonable, on the basis of these data, to use DES with SVG intervention in grafts with reference diameter <3.5 mm for short-term benefit, realizing that the benefit might be attenuated at long-term follow-up. Large randomized trials powered for clinical outcomes would be required to determine whether this short-term benefit with DES will be worth the additional cost.

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REFERENCES


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