

Comparison of Sirolimus-Eluting Stents With Paclitaxel-Eluting Stents in Saphenous Vein Graft Intervention (from a Multicenter Southern California Registry)

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This study was designed to compare the safety and efficacy of sirolimus-eluting stents (SESs) to paclitaxel-eluting stents (PESs) in percutaneous intervention of saphenous vein graft (SVG) lesions. SVGs develop atherosclerosis at high rates and often require repeat revascularization. Percutaneous intervention with drug-eluting stents has become the preferred method of revascularization due to higher restenosis with bare metal stents and increased morbidity and mortality with repeat coronary artery bypass grafting. We sought to compare the rate of major adverse cardiac events and stent thrombosis between SESs and PESs in patients undergoing SVG intervention. A multicenter analysis of 172 patients with SVG lesions treated with SESs or PESs was performed. The 30-day and 1-year clinical outcomes of 102 patients receiving SESs were compared to those of 70 patients receiving PESs. There was no significant difference in baseline demographic, angiographic, and procedural characteristics between the SES and PES treatment groups. There was no statistical difference in major adverse cardiac events at 30 days and at 1 year (hazard ratio [HR] 1.58, 95% confidence interval [CI] 0.77 to 3.23, log-rank $p = 0.21$). There was also no difference in survival (HR 1.28, 95% CI 0.39 to 4.25, log-rank $p = 0.69$) or target vessel revascularization (HR 2.54, 95% CI 0.84 to 7.72, log-rank $p = 0.09$). In conclusion, this multicenter analysis of real-world patients demonstrated that SESs and PESs have similar clinical outcomes when used in SVG intervention. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;106:337–341)

Despite improvements in percutaneous revascularization, coronary artery bypass grafting (CABG) remains the preferred method of revascularization in many patients with left main coronary artery, diffuse, and multivessel disease. Although the use of arterial conduits has improved outcomes, saphenous vein grafts (SVGs) remain necessary for adequate revascularization. Unfortunately, SVGs develop intimal abnormalities as soon as 1 year after CABG, and 25% are completely occluded by 5 years.^{1–3} Repeat CABG is associated with increased operative mortality and perioperative myocardial infarction compared to first-time CABG and percutaneous SVG intervention.^{4,5} Therefore, percutaneous revascularization is often employed for treatment of SVG failure. Use of bare metal stents in SVGs results in a decrease in major cardiac events compared to angioplasty alone but may not provide significant improvement in re-

stenosis rates.^{6–8} The aim of this study was to compare the efficacy and safety of paclitaxel-eluting stents (PESs) to sirolimus-eluting stents (SESs) in SVG interventions.

Methods

Patients who underwent SVG intervention with SESs (Cypher, Cordis Corp., Miami, Florida) or PESs (Taxus, Boston Scientific Corp., Natick, Massachusetts) from April 2003 to December 2007 were included in this multicenter retrospective analysis. Participating centers in this Southern California registry include UCLA Medical Center (Los Angeles, California), Harbor-UCLA Medical Center (Torrance, California), UCSD Medical Center (San Diego, California), VA San Diego Healthcare System (San Diego, California), and Santa Barbara Cottage Hospital (Santa Barbara, California). The institutional review boards approved analysis of this database.

SVG intervention was performed according to current clinical practice. All patients received aspirin 81 to 325 mg/day indefinitely. After a loading dose of 300 or 600 mg, clopidogrel was continued for ≥ 3 months. Cardiac enzymes (creatinine kinase and creatine kinase-MB) were not routinely measured after SVG intervention unless myocardial ischemia was clinically suspected.

Patient data including baseline clinical, angiographic, and procedural characteristics and clinical outcomes were obtained from medical records and entered into a database.

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Table 1
Baseline clinical characteristics

Variable	SES (n = 102)	PES (n = 70)	p Value
Age (years), mean \pm SD	70 \pm 10	70 \pm 11	>0.95
Men	88 (86%)	57 (81%)	0.40
Diabetes	46 (45%)	37 (53%)	0.35
Hypertension	86 (84%)	60 (86%)	0.83
Chronic renal insufficiency	22 (22%)	17 (24%)	0.71
Chronic obstructive pulmonary disease	14 (14%)	11 (16%)	0.83
Peripheral arterial disease	32 (31%)	16 (23%)	0.30
Previous myocardial infarction	56 (55%)	36 (51%)	0.73
Left ventricular ejection fraction (%), mean \pm SD	50 \pm 14	47 \pm 14	0.16
Presentation with myocardial infarction	28 (27%)	28 (40%)	0.10

Surveillance angiography was not performed unless clinically indicated. Follow-up at 1 year was available in 96% of patients.

The primary end point was 1-year major adverse cardiac events (MACEs), defined as death, nonfatal myocardial infarction, and target vessel revascularization (TVR). Death was defined as death from any cause. Myocardial infarction was defined as ischemic symptoms associated with an increase of creatine kinase \geq 2 times the upper limit of normal value with an increased MB fraction and troponin I level. TVR was defined as repeat revascularization (percutaneous or surgical) for ischemia due to stenosis $>$ 50% of the luminal diameter on follow-up angiogram anywhere within the stent or SVG.

The Academic Research Consortium definition of stent thrombosis was used.⁹ Definite/confirmed stent thrombosis was defined as an acute coronary syndrome with angiographic confirmation of stent thrombus or occlusion or pathological confirmation of acute stent thrombosis. Probable stent thrombosis was defined as any unexplained death within 30 days or as target vessel myocardial infarction without angiographic confirmation of thrombosis or other identified culprit lesion. Possible stent thrombosis was defined as unexplained death after 30 days. Subacute stent thrombosis included stent thrombosis occurring within 30 days of percutaneous coronary intervention, late stent thrombosis included those occurring 31 to 365 days after percutaneous coronary intervention, and very late stent thrombosis included those occurring $>$ 365 days after the index percutaneous coronary intervention.

Binary data were presented as counts and frequencies and were compared using chi-square or Fisher's exact tests. Continuous data were expressed as mean \pm SD and compared using Student's *t* test. Freedom from clinical events was calculated using the Kaplan-Meier method, and groups were compared using log-rank test. The following variables were entered into a stepwise Cox proportional hazard regression model for 1-year MACEs: age of patient, gender, hypertension, diabetes, chronic renal insufficiency (serum creatinine \geq 1.5 mg/dl), chronic obstructive pulmonary disease, peripheral arterial disease, presentation with myocardial infarction, history of stroke, administration of glycoprotein IIb/IIIa antagonists, and stent type. A *p* value $<$ 0.05

Table 2
Baseline angiographic and procedural characteristics

Variable	SES (n = 102)	PES (n = 70)	p Value
Stents per patient	1.7 \pm 1.1	1.6 \pm 1.0	0.84
Stent diameter (mm)	3.3 \pm 0.4	3.2 \pm 0.3	0.4
Total stent length (mm)	35 \pm 25	29 \pm 16	0.20
Distal embolic protection	55 (54%)	40 (57%)	0.78
Glycoprotein IIb/IIIa antagonist	27 (26%)	18 (26%)	>0.95
Intravascular ultrasound	4 (4%)	5 (7%)	0.49
Intra-aortic balloon pump	3 (3%)	2 (3%)	>0.95

was defined as statistically significant. Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, North Carolina).

Results

A total of 172 patients underwent SVG intervention with drug-eluting stents (102 patients treated with SESs and 70 patients treated with PESs). The SES and PES groups were well matched with no significant differences in baseline demographic, angiographic, and procedural characteristics (Tables 1 and 2). The SES and PES groups had a large proportion of patients with diabetes (45% vs 53%, *p* = 0.35) and previous myocardial infarction (55% vs 51%, *p* = 0.73).

At 30 days, MACEs occurred in 3 patients (2.9%) in the SES group. One patient presented with acute myocardial infarction and died the following day from cardiogenic shock. Another died unexpectedly on day 5 from probable stent thrombosis and 1 patient had TVR on day 14 for persistent angina. MACEs did not occur in the PES group.

At 1 year, there was no significant difference between the SES and PES groups in MACEs (hazard ratio [HR] 1.58, 95% confidence interval [CI] 0.77 to 3.23, log-rank *p* = 0.21; Figure 1), survival (HR 1.28, 95% CI 0.39 to 4.25, log-rank *p* = 0.69; Figure 2), TVR (HR 2.54, 95% CI 0.84 to 7.72, log-rank *p* = 0.09; Figure 3), and stent thrombosis (HR 2.12, 95% CI 0.59 to 3.65, log-rank *p* = 0.49). By Cox regression analysis, chronic renal insufficiency was the only independent predictor of 1-year MACEs (HR 2.2, 95% CI 1.1 to 4.3, *p* = 0.03).

Discussion

The primary finding in this multicenter retrospective study is that use of SESs and PESs was not associated with any significant difference in rates of MACE, survival, TVR, and stent thrombosis.

Direct head-to-head comparisons of SESs and PESs in native coronary intervention have shown equivalent rates of mortality and myocardial infarction, but a lower risk of restenosis and TVR in patients receiving SESs.⁹⁻¹³ The Stenting Of Saphenous Vein Grafts (SOS) trial compared PESs to bare metal stents and found a decrease in restenosis at a median follow-up of 36 months with no significant difference in mortality.¹⁴ The Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent (RRISC) trial compared SESs to bare metal stents and

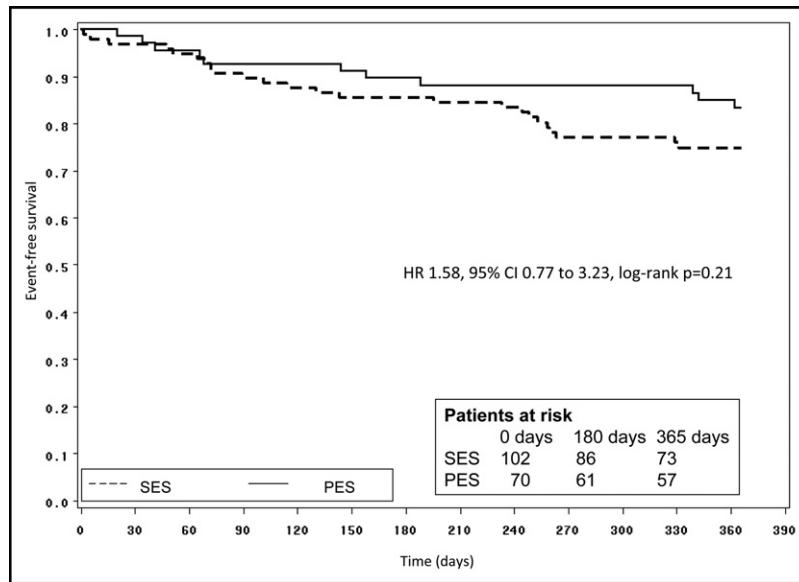


Figure 1. Kaplan-Meier estimates of probability of MACE-free survival in patients with SESs and PESs.

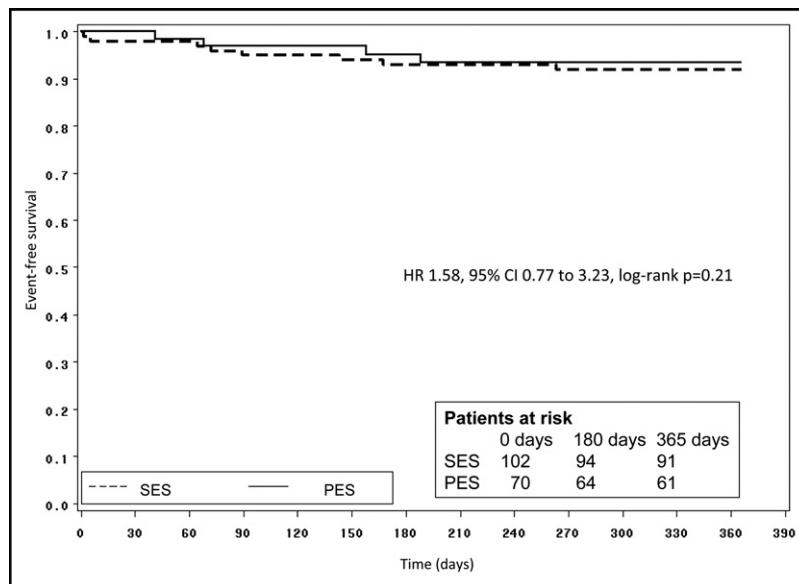


Figure 2. Kaplan-Meier estimates of probability of survival in patients with SESs and PESs.

showed a decrease in restenosis at 6 months with no difference in mortality.¹⁵ However, at secondary analysis in the Death and Events at Long-term follow-up Analysis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent (DELAYED RRISC) trial, this decrease was lost and SESs were associated with higher long-term mortality compared to bare metal stents at a median follow-up of 32 months.¹⁶ In this follow-up analysis, incidence of very late stent thrombosis was believed to play a significant role in the increased mortality in the SES group. However, it remains unclear if one type of drug-eluting stent is more effective than the other in SVG interventions due to a lack of head-to-head randomized clinical trials.

Before the present investigation, only 2 smaller single-center studies compared the use of SESs versus PESs in

SVG intervention.^{17,18} Our study is the largest and first multicenter investigation comparing SESs to PESs in SVG intervention in real-world patients. Chu et al¹⁷ prospectively studied 89 nonrandomized subjects and demonstrated no difference in MACEs and revascularization rates in the hospital, at 30 days, and at 6 months. No early or late stent thrombosis was observed in either group. Similarly, Gormez et al¹⁸ studied 71 patients in a single-center retrospective analysis and found no significant difference in MACEs and stent thrombosis 1 year after intervention. The results were similar because the 30-day rate of MACEs in our study (2.9% in SES group and 0% in PES group) was comparable to those in the studies by Chu et al (2.1% in SES group and 0% in PES group, $p = 0.96$) and Gormez et al (8% in SES group and 4.3% in PES group, $p = 0.60$). Likewise, our study found no difference in TVR between the 2 stent types.

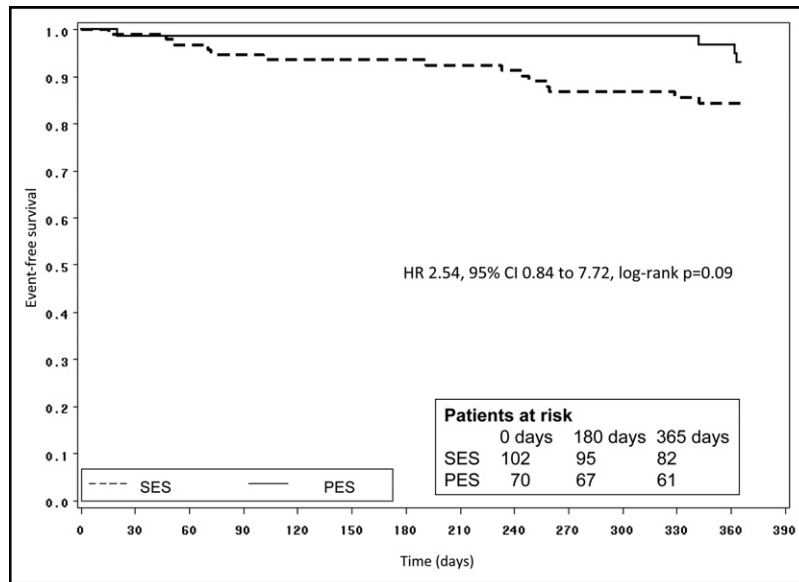


Figure 3. Kaplan-Meier estimates of probability of TVR-free survival in patients with SESs and PESs.

Although multiple studies in native coronary arteries have reported similar early and late stent thrombosis rates between bare metal stents and drug-eluting stents,^{19–22} there is evidence that drug-eluting stents may slightly increase very late stent thrombosis rates.^{23,24} In the DELAYED RRISC trial, very late stent thrombosis was implicated in the higher long-term mortality observed in the SES group.¹⁶ The present study found no significant difference in rates of stent thrombosis at 1 year, in agreement with the study by Gormez et al¹⁸ (0% in the SES group and 2.2% in the PES group, $p = 0.65$).

Limitations to this study included the relatively small sample (although larger than in previous studies), nonrandomized design, and short length of follow-up. Longer follow-up and a larger sample would have enabled evaluation of very late stent thrombosis rates. Because periprocedural cardiac enzymes were not obtained after every percutaneous coronary intervention, the true incidence of periprocedural myocardial infarction was not known. Surveillance angiography was not performed in all patients unless there was a clinical suspicion of ischemia. Therefore, the true rate of angiographic restenosis is unknown.

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