

CLINICAL RESEARCH

Sirolimus- Versus Paclitaxel-Eluting Stents for the Treatment of Cardiac Allograft Vasculopathy

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Objectives The aim of this study was to compare outcomes after percutaneous coronary intervention (PCI) with sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) in the treatment of cardiac allograft vasculopathy (CAV).

Background PCI in patients with CAV is associated with increased rates of restenosis compared with PCI in patients without CAV. There are no dedicated studies on the influence of different drug-eluting stents (DES) on the outcomes of patients with CAV.

Methods This is a retrospective observational study of 108 consecutive patients with CAV who underwent PCI with SES and PES at UCLA Medical Center and University of Padova Medical Center between 2002 and 2008.

Results Baseline characteristics were similar among SES (n = 68) and PES (n = 40) patients with the exception of older patients, larger minimal lumen diameter, and smaller diameter stenosis in the SES-treated patients. Angiographic follow-up at 1 year was high in the SES and PES groups (74% vs. 76%, p = 0.8). The SES and PES groups had similar binary restenosis rates (10% vs. 9%, p = 0.7), percent diameter stenosis ($24 \pm 24\%$ vs. $24 \pm 18\%$, p = 0.94), and late lumen loss (0.67 ± 1.03 mm vs. 0.68 ± 1.11 mm, p > 0.9). One-year clinical outcomes were not significantly different among CAV patients treated with either SES or PES (major adverse cardiac events: 10% vs. 15%, p = 0.5; death: 3% vs. 5%, p = 0.4; myocardial infarction: 3% vs. 5%, p = 0.4; target vessel revascularization: 4% vs. 8%, p = 0.3).

Conclusions In patients who underwent PCI for CAV, both SES and PES were safe and effective with no significant differences in clinical and angiographic outcomes. Randomized clinical trials comparing different DES with longer follow-up are necessary to identify the optimal treatment strategy for patients with CAV. (J Am Coll Cardiol Intv 2010;3:378–82) © 2010 by the American College of Cardiology Foundation

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Manuscript received February 1, 2010, accepted February 5, 2010.

Cardiac allograft vasculopathy (CAV) is a rapidly progressive form of atherosclerosis that can lead to allograft loss and accounts for 25% of deaths between years 1 and 10 after orthotopic heart transplantation (OHT) (1). The prevalence of CAV is 32% to 42% at 5-year follow-up (1,2). The treatment options include repeat OHT, coronary artery bypass graft surgery (CABG), or percutaneous coronary intervention (PCI), but all have their limitations. Replantation is less effective compared with the first OHT and is considered in select cases of severe coronary artery disease but is limited by a paucity of donors (3). Even when it is performed, CAV can recur in the second graft. Coronary artery bypass graft surgery has been performed but is associated with a perioperative mortality rate >30% (4,5). Clinical data for CABG in CAV are limited and outdated by over 10 years.

Percutaneous coronary intervention has been used as a palliative treatment option for CAV but is associated with worse clinical outcomes and higher rates of restenosis compared with PCI in non-CAV lesions. Several studies reported that PCI with drug-eluting stents (DES) in patients with CAV was safe and reduced the rate of angiographic restenosis compared with bare-metal stents (BMS), but no studies have reported on the influence between different DES on outcomes (6,7). We report the angiographic and clinical outcomes of lesions treated with sirolimus-eluting stents (SES) compared with paclitaxel-eluting stents (PES) in an observational study of patients with CAV.

Methods

This is a retrospective observational study of 108 consecutive patients with CAV who received SES (Cypher, Cordis, Johnson & Johnson Corporation, Miami, Florida) or PES (Taxus, Boston Scientific Corporation, Natick, Massachusetts) at the University of California at Los Angeles (UCLA) Medical Center and the University of Padova Medical Center, Padua, Italy, between 2002 and 2008. The institutional review board at each institution approved the use of the database review for this study. Thirty-nine of the 108 patients in this study were included in a previous study from UCLA Medical Center (6).

The choice of immunosuppressive therapy was at the discretion of the transplant cardiologist at the 2 institutions and included cyclosporine, prednisone, azathioprine, mycophenolate mofetil, tacrolimus, and sirolimus.

The PCI was performed with standard techniques. The choice of anticoagulation and DES and the use of hemodynamic support devices and intravascular ultrasound (Boston Scientific Corporation) were left to the operator's discretion. All patients received both aspirin and clopidogrel for a minimum of 6 months. Intracoronary nitroglycerin was prophylactically administered to decrease the risk of vasospasm.

Clinical data including baseline characteristics obtained from medical records and follow-up data were gathered retrospectively and entered into a computerized cardiovas-

cular database. Surveillance angiography was performed within the first 12 months after PCI or earlier if clinically indicated. Major adverse cardiac events were defined as the composite of cardiac death, myocardial infarction, and target vessel revascularization (TVR). Myocardial infarction was diagnosed on the basis of the presence of new Q waves in at least 2 contiguous electrocardiographic leads and elevated cardiac enzymes including creatine kinase-MB fraction. When pathologic Q waves were absent, myocardial infarction was diagnosed if the creatine kinase level increased to more than twice the upper limit of the normal range with an elevated level of creatine kinase-MB or troponin I. Target vessel revascularization was defined as a repeat revascularization driven by any lesion located in the same epicardial vessel treated at the index procedure.

The Academic Research Consortium definition of definite/confirmed stent thrombosis is an acute coronary syndrome with angiographic confirmation of stent thrombus or occlusion or pathologic confirmation of acute stent thrombosis. Probable stent thrombosis is 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 is defined as unexplained death after 30 days. Subacute stent thrombosis is defined as stent thrombosis occurring within 30 days of PCI, and late stent thrombosis occurs between 31 and 365 days after PCI.

Quantitative coronary analysis was performed with an automated edge detection computer analysis system (GE CA1000 Stenosis Analysis Application, GE Healthcare, Piscataway, New Jersey) in 69 patients who underwent PCI at UCLA Medical Center and with QCA-CMS system version 4.0 (MEDIS Medical Imaging Systems, Inc., Leyden, the Netherlands) in 39 patients who underwent PCI at University of Padova Medical Center. The contrast-filled nontapered catheter tip was used for calibration. The parameters that were measured included the reference diameter of the vessel, the minimal lumen diameter (MLD), percent diameter stenosis (difference between the reference diameter and MLD divided by the reference diameter and multiplied by 100), and late lumen loss (difference between MLD at the end of the procedure and MLD at follow-up).

Continuous variables are presented as mean \pm SD and compared with the Student *t* test. Categorical variables are

Abbreviations and Acronyms

BMS	= bare-metal stent(s)
CABG	= coronary artery bypass graft surgery
CAV	= cardiac allograft vasculopathy
DES	= drug-eluting stent(s)
MLD	= minimal lumen diameter
OHT	= orthotopic heart transplantation
PCI	= percutaneous coronary intervention
PES	= paclitaxel-eluting stent(s)
SES	= sirolimus-eluting stent(s)
TVR	= target vessel revascularization

presented as percentages and compared by chi-square or Fisher exact tests. Statistical analysis was performed with SPSS version 10.0 (SPSS, Inc., Chicago, Illinois). A value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics. Of the 108 patients who underwent PCI with DES, 68 patients received SES and 40 patients received PES (Table 1). The 2 groups were well-matched, except patients treated with SES were older (age 61 ± 14 years vs. 54 ± 19 years, $p = 0.03$).

Baseline angiographic and procedural characteristics. The SES group had a larger MLD (0.93 ± 0.45 mm vs. 0.67 ± 0.34 mm, $p = 0.01$) and a smaller diameter stenosis ($66 \pm 14\%$ vs. $76 \pm 10\%$, $p = 0.001$) compared with the PES group (Table 2). The acute gain (1.53 ± 0.53 mm vs. 1.84 ± 0.58 mm, $p = 0.02$) was larger in the PES group. The mean stent diameter was larger in the SES group (3.04 ± 0.34 mm vs. 2.88 ± 0.39 mm, $p = 0.04$) and might be explained by the availability of a 2.25-mm PES. The mean reference vessel diameter, mean lesion length, final MLD, mean stent length, and stents used per patient were similar in the 2 cohorts.

Follow-up angiography. Table 3 shows the results of the angiographic follow-up. At 1 year, angiographic follow-up was similar in both the SES and PES groups (74% vs. 76%, $p = 0.8$). The binary restenosis rates in the SES and PES

	SES (n = 68)	PES (n = 40)	p Value
Mean RVD (mm)	2.84 ± 0.60	3.03 ± 1.32	0.4
MLD (mm)	0.93 ± 0.45	0.67 ± 0.34	0.01
Diameter stenosis (%)	66 ± 14	76 ± 10	0.001
Mean lesion length (mm)	14.9 ± 7.2	15.0 ± 6.2	0.9
Lesion type			
A	18 (26)	13 (32)	0.3
B1/B2	40 (59)	21 (53)	0.5
C	25 (37)	13 (32)	0.6
Mean stent diameter (mm)	3.04 ± 0.34	2.88 ± 0.39	0.04
Mean stent length (mm)	22 ± 13	21 ± 9	0.5
Final MLD (mm)	2.48 ± 0.42	2.51 ± 0.50	0.8
Stents/patient	1.41 ± 0.85	1.20 ± 0.41	0.14
Acute gain (mm)	1.53 ± 0.53	1.84 ± 0.58	0.02
IVUS use	5 (7)	6 (15)	0.34
IABP use	3 (4)	2 (5)	0.74

Values are mean \pm SD or n (%).
IABP = intra-aortic balloon pump; IVUS = intravascular ultrasound; MLD = minimal lumen diameter; RVD = reference vessel diameter.

groups were low (10% vs. 9%, $p = 0.7$). The SES and PES groups had similar percent diameter stenosis ($24 \pm 24\%$ vs. $24 \pm 18\%$, $p = 0.9$) and late lumen loss (0.67 ± 1.03 mm vs. 0.68 ± 1.11 mm, $p > 0.9$).

One-year clinical outcomes. No significant differences were observed in major adverse cardiac events between the SES and PES groups (10% vs. 15%, $p = 0.5$) (Table 4). No significant differences in cardiac death (3% vs. 5%, $p = 0.4$) and myocardial infarction (3% vs. 5%, $p = 0.4$) were observed in the 2 groups. The SES and PES groups had low rates of TVR (4% vs. 8%, $p = 0.3$) and target lesion revascularization (3% vs. 3%, $p = 0.9$). No patients underwent repeat OHT.

Stent thrombosis. There was no significant difference in stent thrombosis between the SES and PES groups (1.5% vs. 5.0%, $p = 0.3$). Subacute stent thrombosis occurred in 1 patient who received an SES who died suddenly on day 7. Late stent thrombosis occurred on day 282 in 1 patient who received a PES and discontinued dual antiplatelet therapy before colonoscopy without the knowledge of his cardiolo-

	SES (n = 68)	PES (n = 40)	p Value
Age (yrs)	61 ± 14	54 ± 19	0.03
Male	47 (69)	28 (70)	0.7
Hypertension	49 (72)	24 (60)	0.3
Hypercholesterolemia	41 (60)	21 (53)	0.5
Diabetes	17 (25)	13 (33)	0.54
Chronic renal insufficiency	36 (53)	20 (50)	0.7
Mean ejection fraction (%)	58 ± 14	57 ± 13	0.73
Yrs post-OHT (%)	10 ± 4	10 ± 5	0.55
Clinical presentation			
Elective	57 (84)	37 (92)	0.28
UA/NSTEMI	10 (15)	2 (5)	0.21
STEMI	7 (1)	1 (3)	0.7
Immunosuppressive therapy			
Cyclosporin	43 (63)	17 (43)	0.68
Azathioprine	10 (15)	4 (10)	0.57
Mycophenolate	22 (33)	16 (40)	0.56
Prednisone	34 (50)	17 (43)	0.53
Sirolimus	19 (28)	17 (43)	0.18
Tacrolimus	15 (22)	15 (38)	0.13

Values are mean \pm SD or n (%).
NSTEMI = non-ST-segment elevation myocardial infarction; OHT = orthotopic heart transplantation; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

	SES (n = 68)	PES (n = 40)	p Value
Follow-up angiography	50 (74)	30 (76)	0.8
Binary restenosis	7 (10)	4 (9)	0.7
Percent diameter stenosis	24 ± 24	24 ± 18	0.9
Late lumen loss (mm)	0.67 ± 1.03	0.68 ± 1.11	>0.9
MLD (mm)	2.25 ± 0.78	2.31 ± 0.70	0.8

Values are n (%) or mean \pm SD.
Abbreviations as in Tables 1 and 2.

Table 4. 1-Year Clinical Outcomes

	SES (n = 68)	PES (n = 40)	p Value
Major adverse cardiac events	7 (10)	6 (15)	0.5
Cardiac death	2 (3)	2 (5)	0.4
Myocardial infarction	2 (3)	2 (5)	0.4
Target vessel revascularization	3 (4)	3 (8)	0.3
Target lesion revascularization	2 (3)	1 (3)	0.9
Stent thrombosis	1 (1.5)	2 (5)	0.3
Repeat transplantation	0 (0)	0 (0)	>0.9

Values are n (%).
 Abbreviations as in Table 1.

gist. He subsequently died from cardiogenic and septic shock. A 17-year-old female subject who was noncompliant with medication died suddenly 155 days after PCI with PES.

Discussion

The main findings of the first head-to-head comparison of 2 DES for the management of CAV are that the rates of binary restenosis and TVR were low and not significantly different at 1-year follow-up. There were also no significant differences in the rates of death, myocardial infarction, and stent thrombosis.

Cardiac allograft vasculopathy continues to represent the most common cause of late graft failure (8). The pathophysiology of CAV is different from native coronary disease in that it is characterized by diffuse intimal hyperplasia in the epicardial arteries and microcirculation (9–11). The progression to CAV seems to be multifactorial and associated with immunologic factors (Human Leukocyte Antigen donor/recipient mismatches, recurrent cellular rejection, and antibody-mediated rejection), nonimmunologic factors (hyperlipidemia, hypertension, diabetes mellitus, and hyperhomocysteinemia), and donor-related factors (older donor age and donor brain death) (12–14). Cytomegalovirus infection even in asymptomatic patients is associated with more frequent CAV (8). Patients with humoral rejection have a 10% and 36% greater incidence of CAV at 1 and 5 years, respectively (15).

In addition to aggressive control of cardiac risk factors, PCI is an essential treatment strategy for patients with CAV (8). Although PCI might be beneficial in treating CAV for focal lesions, the diffuse nature of CAV can make it difficult to treat. The late lumen loss and binary restenosis observed in our SES patients (0.67 ± 1.03 mm and 10%, respectively) were higher than that reported in patients with native coronary artery lesions in the SIRIUS (Sirolimus-Eluting Stent in de Novo Native Coronary Lesions) trial (0.17 ± 0.45 mm and 3.2%, respectively) (6). Similarly, the late lumen loss and binary restenosis in our PES patients (0.68

± 1.11 mm and 9%, respectively) was higher than that reported in patients in the TAXUS IV trial (Boston Scientific) (0.39 ± 0.50 mm and 5.5%, respectively) (17). The pro-inflammatory state of CAV leading to accelerated proliferation of the intima, media, and adventitia might help explain why restenosis rates and late lumen loss are higher in CAV patients compared with patients with native coronary artery disease.

The limited data thus far have shown that SES and PES might decrease the rate of restenosis in CAV patients compared with BMS. At a mean follow-up of 1 year, when compared with BMS, SES and PES were associated with a lower binary restenosis rate (12% vs. 30%, $p = 0.02$) (6). Similarly, a study from Columbia University reported that SES and PES had less in-stent restenosis (18.6%) compared with BMS (49%) for the treatment of CAV (7).

The SES and PES significantly reduce the rate of restenosis and subsequent need for repeat revascularization compared with BMS in native coronary arteries (16–18). A meta-analysis of 16 randomized trials reported that, compared with PES, SES was associated with a lower rate of target lesion revascularization (hazard ratio: 0.74, 95% confidence interval: 0.63 to 0.87) and lower rate of stent thrombosis (hazard ratio: 0.66, 95% confidence interval: 0.46 to 0.94) without a significant difference in the composite end point of death or myocardial infarction (19). However, SES and PES have not been previously compared for the treatment of CAV. Our analysis revealed that both SES and PES performed well with no significant difference in the rates of restenosis and TVR within the first year.

The long-term safety of DES in patients with CAV is unknown. There were no significant differences between SES and PES in terms of cardiac death (3% vs. 5%, $p = 0.4$) and myocardial infarction (3% vs. 5%, $p = 0.4$) at 1 year. Stent thrombosis might be underdiagnosed in OHT patients, because it does not always manifest in typical symptoms like chest pain due to denervation of the allografted heart. Stent thrombosis occurred in 2 patients with PES and prematurely discontinued dual antiplatelet therapy. Premature discontinuation was identified as the strongest independent predictor of stent thrombosis (20). Only 1 patient who was taking dual antiplatelet therapy experienced probable stent thrombosis. The difference in the rate of stent thrombosis was not statistically significant (1.5% vs. 5%, $p = 0.3$), but our study was not powered to detect a difference in this clinically important end point.

Sirolimus is an immunosuppressant with more utility than in the use of intracoronary stents. One study showed that, when OHT patients were switched from calcineurin inhibitors to sirolimus, there was attenuation in the progression of CAV (21). In nontransplant patients, the OSIRIS (Oral Sirolimus to Inhibit Recurrent In-stent Stenosis) trial showed that high-dose sirolimus prevented the recurrence of angiographic restenosis for the treatment of in-stent

restenosis (22). In our study, the administration of oral sirolimus as the immunosuppressant was lower in the SES group (28% vs. 43%, $p = 0.18$), and this might have been a confounding variable in our study. Future studies comparing the use of oral sirolimus in combination with DES in CAV would be interesting.

A limitation of this study was the study design. A retrospective, nonrandomized study has its cost-effectiveness yet has some drawbacks. Because selection bias was unavoidable, we were not able to appropriately adjust for treatment effect. The study was also limited by the small number of patients in each group. Although the results indicate no significant difference between the 2 types of stents in the setting of CAV, our study was not powered to detect a true difference. Because there are limited data in PCI of CAV, a large centralized database would be useful to detect possible small differences that might exist. There were significant angiographic and procedural differences between the 2 groups. The follow-up was only 1 year, and thus the long-term outcomes are unknown in patients with CAV who undergo PCI with DES. Follow-up angiography was not performed on all patients who underwent PCI. Two different computer analysis systems were used to perform quantitative coronary analysis at the institutions.

Conclusions

In the largest study of DES in CAV patients, there were no significant differences in angiographic and clinical outcomes between SES and PES at 1 year. Both stents seem to be safe and effective and seem to be good options for the treatment of CAV. Randomized clinical trials with appropriate sample size comparing different DES with longer follow-up are necessary to identify the optimal treatment strategy for patients with CAV.

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Key Words: coronary artery vasculopathy ■ drug-eluting stent ■ heart transplant.