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Comparison of Percutaneous Coronary Intervention With Bare-Metal and Drug-Eluting Stents for Cardiac Allograft Vasculopathy

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Objectives We sought to compare percutaneous coronary intervention (PCI) with bare-metal stents (BMS) and drug-eluting stents (DES) for cardiac allograft vasculopathy (CAV).

Background Cardiac allograft vasculopathy is a rapidly progressive form of atherosclerosis and is one of the main limitations to long-term survival after orthotopic heart transplantation. Percutaneous coronary intervention has been used as a palliative treatment option for CAV but is associated with worse clinical outcomes and greater rate of restenosis compared with PCI of native coronary arteries.

Methods Between 1995 and 2007, data on 82 consecutive heart transplant patients who underwent PCI with BMS and DES at the University of California at Los Angeles Medical Center were retrospectively analyzed.

Results A total of 82 lesions were treated with 98 BMS and 76 lesions were treated with 80 DES. Follow-up angiography was performed on 57 of 82 lesions (70%) treated with BMS and 58 of 76 (76%) treated with DES ($p = 0.7$) at a mean follow-up of 9.5 ± 5.5 months for BMS and 12.6 ± 8.2 months for DES ($p = 0.02$). Compared with BMS, DES was associated with a lower binary restenosis rate (12% vs. 30%, $p = 0.02$), lower percent diameter stenosis (24 ± 20 vs. 34 ± 36, $p = 0.06$), and less late lumen loss (0.24 ± 0.75 mm vs. 0.82 ± 1.03 mm, $p = 0.01$). No angiographic stent thrombosis was observed with DES.

Conclusions When compared with BMS, PCI with DES was safe and reduced the rate of angiographic restenosis in patients with CAV. A randomized clinical trial comparing BMS versus DES with longer follow-up is needed to identify the optimal long-term revascularization strategy in patients with CAV. (J Am Coll Cardiol Intv 2008;1:710–5) © 2008 by the American College of Cardiology Foundation

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Cardiac allograft vasculopathy (CAV) is a rapidly diffuse and progressive form of arterial narrowing observed in patients after orthotopic heart transplantation (OHT). It is characterized by endothelial dysfunction, intimal hyperplasia, and vascular remodeling (1). Cardiac allograft vasculopathy is one of the main limitations to the long-term survival of OHT patients and is the primary cause of allograft loss (2). At 5 years after OHT, 50% of patients have angiographic evidence of CAV (3).

The optimal treatment of CAV is unknown. Although statin therapy might decrease the incidence of CAV and graft rejection and increase long-term survival, pharmacotherapy does not reverse CAV (4,5). Repeat OHT is the only definitive therapy for CAV but is associated with higher perioperative mortality, lower long-term survival, a higher recurrence of CAV (6). Coronary artery bypass surgery is rarely performed, because CAV is associated with poor distal targets attributable to the diffuse nature of the disease and greater perioperative mortality (7–12). Percutaneous coronary intervention (PCI) has been used as a palliative treatment option for CAV but has been associated with greater procedural and long-term morbidity and mortality and higher restenosis rates compared with native coronary artery lesions (13–25).

Drug-eluting stents (DES) are associated with a significantly lower incidence of angiographic restenosis and the need for target vessel revascularization compared with bare-metal stents (BMS) in native coronary artery disease (26–28). However, the safety and efficacy of DES observed in native coronary artery disease cannot be generalized in patients with CAV, because these patients were excluded from the randomized trials. We report the angiographic outcomes of lesions treated with BMS compared with DES in an observational study of patients with CAV.

Methods

Study patients. Between 1995 and 2007, data on 82 consecutive heart transplant patients who underwent PCI procedures with BMS and DES at University of California, Los Angeles (UCLA), Medical Center were retrospectively analyzed. The 2 DES used were sirolimus-eluting stents (Cypher, Cordis, Johnson and Johnson Corporation, Miami, Florida) or paclitaxel-eluting stents (Taxus, Boston Scientific Corporation, Natick, Massachusetts). The UCLA Medical Center Institutional Review Board approved the use of the database review for this study.

The immunosuppressive regimen changed over the time course of the analysis. From the beginning of the analysis, the standard pharmacotherapy was cyclosporine, prednisone, and azathioprine. In 1996, mycophenolate mofetil replaced azathioprine. In 2000, the standard regimen was changed to tacrolimus, prednisone, and mycophenolate mofetil. As of 2002, patients with CAV were switched to sirolimus in place of mycophenolate mofetil.

PCI. Standard techniques for PCI via the femoral approach were used. The use of intra-aortic balloon counterpulsation, intravascular ultrasound (Boston Scientific Corporation), and choice of anticoagulation regimen were left to the discretion of the operator. From 1995 to 2003, BMS were used for PCI. From May 2003 when DES was first available at our institution, selection of DES or BMS and the choice of DES also were left to the discretion of the operator. Intracoronary administration of nitroglycerin was given to minimize the risk of spasm in the artery. Aspirin 325 mg/day was continued in all patients indefinitely. Clopidogrel was continued for a minimum of 1 month after PCI with BMS and a minimum of 6 months after PCI with DES after a loading dose of 300 or 600 mg. Cardiac enzymes (creatine kinase and creatine kinase-myocardial band) were routinely drawn after PCI.

Definitions. The minimal luminal diameter and percent diameter stenosis were calculated with the outer diameter of the contrast-filled catheter as the calibration standard. Reference vessel diameter was calculated as the mean of the proximal and distal shoulders of the lesion. Acute gain was calculated as the difference between the pre- and post-PCI minimal lumen diameter. Late luminal loss was calculated as the difference between post-PCI and follow-up minimal luminal diameter. Lesion length was measured as the distance from proximal to the distal shoulder of the lesion. Binary restenosis was defined as stenosis >50% of the luminal diameter on follow-up angiography. Stent thrombosis was defined as angiographic evidence of intrastent filling defect or stent occlusion associated with a clinical event.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CAV = cardiac allograft vasculopathy
DES = drug-eluting stent(s)
OHT = orthotopic heart transplantation
PCI = percutaneous coronary intervention

Data collection and follow-up. Patient demographic, medical, and procedural data were recorded in a computerized cardiovascular database. Data on clinical follow-up were obtained from institutional medical records as well as records from the referring physicians and physicians who assumed care of patients after PCI. Follow-up angiography was performed 6 to 12 months after the index procedure or earlier if clinically indicated. The primary end point was binary restenosis.

Quantitative coronary analysis. From 2005, coronary angiograms were digitally recorded and archived. All coronary angiograms that were performed before 2005 were digitalized and uploaded onto the GE Centricity Cardiology AI1000 Workstation (Fairfield, California). Digital angiograms were analyzed with an automated edge detection

computer analysis system (GE CA1000 Stenosis Analysis Application).

Quantitative coronary analysis was performed according to the American Heart Association/American College of Cardiology guidelines (29).

Statistical analysis. Continuous variables are expressed as means ± SD and compared with the Student *t* test. Discrete variables are expressed 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 p value < 0.05 was considered statistically significant.

Results

Baseline characteristics. Baseline patient characteristics and drug treatment are presented in Table 1. Of the 82 patients in the analysis, 60 (73%) were men, 17 (21%) had diabetes, 55 (67%) had hypertension, and 62 (76%) had hypercholesterolemia. Nineteen patients (23%) were treated with beta-blocker drugs, and 57 patients (70%) were treated with statin drugs.

Baseline angiographic and procedural data. A total of 82 lesions were treated with 98 BMS and 76 lesions were treated with 80 DES (Table 2). There was no difference in target artery and baseline reference vessel diameter between the 2 groups. The baseline percent diameter stenosis was 77 ± 15 in the BMS group and 73 ± 9 in the DES (p = 0.07). The baseline minimal luminal diameter was smaller in the BMS group compared with the DES group (0.61 ± 0.43 mm vs. 0.77 ± 0.28 mm, p = 0.02). The lesion length was longer in the BMS group compared with the DES group (23 ± 20 mm vs. 17 ± 8 mm, p = 0.02).

The mean diameter was 3.06 ± 0.58 mm for BMS and 2.94 ± 0.36 mm for DES (p = 0.12). The mean length was 18 ± 10 mm for BMS and 20 ± 7 mm for DES (p = 0.09). In the DES group, 58 sirolimus-eluting stents and 22 paclitaxel-eluting stents were used.

Table 1. Baseline Patient Characteristics and Drug Treatment

Male	73
Diabetes	21
Hypertension	67
Hypercholesterolemia	76
Beta-blocker drugs	23
Calcium channel blocker drugs	28
ACE inhibitor/angiotensin receptor blocker drugs	39
Statin drugs	70
Nitrates	16
Sulfonylureas	8
Metformin	1
Insulin	6

Values are %.

ACE = angiotensin-converting enzymes.

Table 2. Baseline Angiographic Data

	BMS	DES	p Value
Lesions	82	76	—
Stents	98	80	—
Sirolimus-eluting stent		58	
Paclitaxel-eluting stent		22	
Target artery (%)			0.8
Left main artery	3	9	
Left anterior descending artery	39	39	
Left circumflex artery	26	22	
Right coronary artery	31	30	
Saphenous vein graft	1	0	
Baseline reference vessel diameter (mm)	2.78 ± 0.61	2.87 ± 0.53	0.4
Baseline percent diameter stenosis	77 ± 15	73 ± 9	0.07
Baseline minimal luminal diameter (mm)	0.61 ± 0.43	0.77 ± 0.28	0.02
Lesion length (mm)	23 ± 20	17 ± 8	0.02
Stent diameter (mm)	3.06 ± 0.58	2.94 ± 0.36	0.12
Stent length (mm)	18 ± 10	20 ± 7	0.09
Post-procedure minimal luminal diameter (mm)	2.73 ± 0.67	2.58 ± 0.69	0.23
Post-procedure reference vessel diameter (mm)	3.00 ± 0.64	2.88 ± 0.61	0.34

BMS = bare-metal stent(s); DES = drug-eluting stent(s).

There was no difference in post-procedure minimal luminal diameter (BMS 2.73 ± 0.67 mm and DES 2.58 ± 0.69 mm, p = 0.23) and post-procedure reference vessel diameter (BMS 3.00 ± 0.64 mm and DES 2.88 ± 0.61 mm, p = 0.34).

Angiographic results. Follow-up angiography was performed on 57 of 82 lesions (70%) treated with BMS and 58 of 76 (76%) treated with DES (p = 0.7) at a mean follow-up of 9.5 ± 5.5 months BMS and 12.6 ± 8.2 months DES (p = 0.02) (Table 3). Patients did not have angiographic follow-up because of death or repeat OHT or because they were followed up at another institution. Compared with BMS, DES was associated with a lower binary restenosis rate (12% vs. 30%, p = 0.02), lower percent

Table 3. Follow-Up Angiographic Data

	BMS	DES	p Value
Lesions with angiographic follow-up	58/82 (71%)	55/76 (72%)	0.8
Mean duration of follow-up (months)	9.5 ± 5.5	12.6 ± 8.2	0.02
Minimal luminal diameter (mm)	1.94 ± 0.78	2.31 ± 0.78	0.045
Percent diameter stenosis	34 ± 36	24 ± 20	0.06
Late luminal loss (mm)	0.82 ± 1.03	0.24 ± 0.75	0.01
Late luminal loss index	0.07 ± 0.40	0.42 ± 0.58	0.001
Binary restenosis (% of patients)	30	12	0.02

Abbreviations as in Table 2.

diameter stenosis (24 ± 20 vs. 34 ± 36, p = 0.06), larger minimal luminal diameter (2.31 ± 0.78 mm vs. 1.94 ± 0.78 mm, p = 0.045), less late lumen loss (0.24 ± 0.75 mm vs. 0.82 ± 1.03 mm, p = 0.01), and a smaller late loss index (0.42 ± 0.58 vs. 0.07 ± 0.40, p = 0.001).

Two lesions treated with BMS were totally occluded on follow-up angiography. Because OHT patients might not experience the same symptoms as a non-OHT patient in the setting of stent thrombosis, it is unclear whether the artery was totally occluded from stent thrombosis or restenosis. Angiographic stent thrombosis did not occur in the DES group.

Clinical outcomes. Of the 82 patients in the analysis, 57 (70%) underwent repeat coronary angiography, 17 (21%) underwent target vessel revascularization, 11 (13%) underwent repeat OHT, and 18 (22%) died.

Discussion

The main finding of our study was that PCI with DES in CAV was safe, without stent thrombosis in this cohort, and reduced the risk of angiographic restenosis compared with BMS. The use of DES represents a reasonable treatment option to palliate CAV. In addition, the percent diameter stenosis, late lumen loss, and late loss index were lower with DES.

The risk factors of CAV are multifactorial, with interaction of cardiovascular risk factors, rejection, immunosuppressive therapy, and cytomegalovirus infection. There is poor long-term prognosis once CAV is diagnosed, but this can vary depending on the presence of distal arteriopathy (30,31). The current treatment options for CAV have been disappointing. Coronary artery bypass surgery is a poor treatment option for patients with CAV, because of diffuse predominantly distal disease. Furthermore, repeat sternotomy and the associated mediastinal scarring might increase the risk of complications such as infections in CAV patients on immunosuppressive therapy. The high perioperative mortality rate and the unknown long-term patency rates of bypass grafts also make bypass surgery a poor option (7–12). Repeat OHT is a viable option, but there is a shortage of donors. In addition, repeat OHT is associated with a shorter survival compared with the initial surgery, with a 1-year survival rate of 75% (32,33), and CAV recurs in the second graft in one-half of the patients (11,34).

Although OHT is a viable treatment option for patients with end-stage heart failure, CAV will continue to limit the long-term survival of the allograft. Outcomes with balloon angioplasty have been less than ideal because of the high incidence of restenosis, contributing to allograft lost, increased mortality, and increased consumption of health care resources. Although BMS represent an improvement compared with balloon angioplasty in CAV, restenosis rates still remain high (20).

The use of DES represents an improvement in terms of restenosis compared with BMS and is widely used for the treatment of native coronary artery disease. However, patients with CAV were not included in the randomized clinical trials comparing BMS with DES. In our study, the benefit of DES in terms of angiographic patency was observed in patients with CAV. The ability of sirolimus- and paclitaxel-eluting stents to decrease neointimal proliferation in CAV was evident by the lower late lumen loss (BMS 0.82 mm, DES 0.24 mm) and restenosis rate (BMS 30%, DES 12%), similar to outcomes of the randomized results in native coronary artery lesions. Although DES are associated with a lower incidence of angiographic restenosis in CAV, PCI with DES might not be feasible in all lesions, especially in diffuse small-vessel disease. The restenosis rate observed with DES is still greater compared with PCI in native coronary artery lesions. The high restenosis rates associated with PCI in CAV may be explained by the underlying inflammatory nature of CAV with intense proliferation of the intima, media, and adventitia.

Few data exist regarding the use DES in OHT patients. Tanaka et al. (18) reported a late lumen loss of 0.26 ± 0.75 mm and a restenosis rate of 19% in 25 lesions treated with DES. In another study of 17 patients treated with 28 sirolimus-eluting stents, the restenosis rate was 7% at a mean follow-up of 14 months (35). Lee et al. (25) reported on 5 patients who underwent PCI with DES of the left main artery. At a median follow-up of 518 days, all 5 patients were alive and free from myocardial infarction and target vessel revascularization. One patient underwent repeat OHT. Published data also include 3 case reports of PCI with DES for CAV, including a patient treated for in-stent restenosis of a BMS (36), a patient with significant left main disease (37), and a patient with acute myocardial infarction (38).

The safety of DES was questioned with reports of increased incidence of late stent thrombosis compared with BMS, because of delayed endothelialization, incomplete neointimal healing, or hypersensitivity reactions (39). Iakovou et al. (40) reported a 1.3% stent thrombosis rate at 9-month follow-up after PCI with DES in patients with native coronary artery disease. There is a paucity of data on the safety of DES in patients with CAV. Because OHT patients do not manifest the classic symptoms of stent thrombosis, it was difficult to determine whether stent thrombosis occurred clinically. However, the use of DES in patients with CAV was safe, with no angiographic evidence of stent thrombosis.

Study limitations. The single-center nonrandomized nature of the study limits any direct comparisons of the 2 types of stents. This study was relatively small when compared with studies involving native coronary artery lesions. However, this is the largest study in OHT patients that compared BMS and DES. However, PCI for CAV represents a small

proportion of the total patients who undergo PCI. Angiographic follow-up was not performed on all patients. Angiographic data were chosen because some patients were treated with both BMS and DES. Therefore, comparisons were made on a per-lesion basis. The BMS group had a significantly longer lesion length at baseline, which might reflect the changes in the immunosuppressive regimen over the course of the study. Although there was a trend for stent length being longer in the DES group (20 mm vs. 18 mm, $p = 0.09$), this difference is most likely due to chance. Another explanation might have been the result of a different stenting strategy used in the DES era where stent edges are implanted into normal reference segments, which might lead to the use of longer stents. Comparison between the 2 groups could not be made in terms of the incidence of myocardial infarction, repeat heart transplantation, and death.

Conclusions

Although the relative safety and efficacy of DES for the treatment of CAV has not been proven in a randomized controlled trial, our data suggest that PCI with DES is safe and provides superior angiographic results compared with PCI with BMS. A randomized clinical trial comparing BMS versus DES with an extended follow-up is needed to identify the optimal long-term revascularization strategy in this unique patient population that has high mortality and diffuse coronary disease. Until that time, PCI with DES seems to be a reasonable option for patients with CAV.

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