Safety of Drug-Eluting Stents in Patients With Left Ventricular Dysfunction Undergoing Percutaneous Coronary Intervention

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Recent studies have reported a higher incidence of late stent thrombosis in patients undergoing drug-eluting stent (DES). Reduced left ventricular (LV) ejection fraction (EF) is considered a risk factor for this complication after both bare-metal stent (BMS) and DES implantation. Therefore, the aim of this study was to evaluate the safety of DES on long-term follow-up in patients with LV dysfunction undergoing percutaneous coronary intervention. We retrospectively selected all patients with an EF <45% undergoing percutaneous coronary intervention with implantation of ≥1 sirolimus- or paclitaxel-eluting stent at our institution. The primary endpoint of the study was all-cause mortality, retrieved using both Social Security Database and hospital records. We also compared the results of this group with a historical cohort of patients with LV dysfunction undergoing BMS implantation; 121 patients who received ≥1 DES were enrolled. The mean LVEF was 36 ± 8%, with 20 patients (16%) with a LVEF ≤25%; 36 patients (30%) had diabetes mellitus, and DES implantation was considered off-label in 100 patients (83%). Survival at 1-, 2-, and 3-year follow-up was 94% (95% confidence interval [CI] 88 to 100), 90% (95% CI 82 to 98) and 88% (95% CI 80 to 96), respectively. In conclusion, the favorable results of this study demonstrate the safety of DES in patients with LV dysfunction. **(Am J Cardiol 2008;102:679–682)**

Left ventricular (LV) dysfunction represents an important clinical predictor of stent thrombosis after bare-metal stent (BMS) and drug-eluting stent (DES) implantation,[1,2] and a LV ejection fraction (EF) <25% is considered an off-label indication for DES use.[3] In patients with LV dysfunction, coronary stenting has been associated with better survival than previously reported with balloon angioplasty.[4–6] However, limited data are available about DES use in patients with LV dysfunction. In this high risk subgroup, the reduction in restenosis rate and then in the occurrence of ischemic events may improve survival more significantly than in other subsets of patients. The potential for an increased risk of stent thrombosis has to be considered. Therefore, this study evaluates the safety of DES on long-term follow-up in patients with LV dysfunction undergoing percutaneous coronary intervention (PCI).

Methods

We retrospectively selected all patients with LV dysfunction, defined as LVEF <45%, who underwent PCI with implantation of ≥1 DES between April 2003 and December 2005 at our institution. This study was approved by our local Institutional Review Board. Patients were identified from the cardiac catheterization laboratory database and baseline/procedural characteristics were evaluated using the hospital computer database and individual clinical charts. Patients were excluded if they had previous bypass surgery, previous cardiac valve replacement, or had moderate-to-severe aortic valve disease. Preprocedure LVEF was calculated within 7 days of the procedure. Based on the US Food and Drug Administration-approved DES indications, off-label use of DES was defined as acute myocardial infarction, multivessel disease with or without multivessel intervention, left main disease, bifurcation lesions, total occlusions, in-stent restenosis, long lesions requiring multiple or overlapping stenting (>36 mm), small vessel with reference diameter <2.5 mm, saphenous vein grafts disease, and LVEF <25%.[3,7] All patients were treated with aspirin, clopidogrel, and weight-adjusted heparin or 1 mg/kg enoxaparin. Stent placement was performed according to the standard protocol. Periprocedural therapy with glycoprotein IIb/IIIa inhibitors (abciximab or eptifibatide) was used at the operator's discretion. All patients received aspirin 81 to 325 mg/day indefinitely and clopidogrel 75 mg/day for ≥1 year. The procedure was considered successful if there was <20% residual stenosis in angiographic lesion, with Thrombolysis in Myocardial Infarction grade III flow. In patients with multivessel disease, the lesion deemed to be responsible of ischemia was dilated first.

In-hospital complications were considered death, Q-wave or

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Table 1
Demographic and clinical features

Variable	Patients (n = 121)
Age (yrs)	62 ± 12
Men	84 (69%)
Caucasian	67 (56%)
Diabetes mellitus	36 (30%)
Hypertension	84 (69%)
Hypercholesterolemia*	64 (53%)
Current smokers	58 (48%)
Previous myocardial infarction	40 (33%)
Previous coronary intervention	35 (29%)
Clinical presentation	
ST-elevation myocardial infarction	38 (31%)
Non–ST-elevation acute coronary syndrome	57 (47%)
Stable angina pectoris and/or inducible ischemia	26 (22%)
Co-morbidities	
Chronic obstructive pulmonary disease	19 (16%)
Chronic kidney disease	15 (12%)
Cerebrovascular disease	11 (9%)
Peripheral vascular disease	5 (4%)
Atrial fibrillation	10 (8%)
Medications	
Aspirin	111 (92%)
Clopidogrel	117 (97%)
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	99 (82%)
β blockers	108 (89%)
Calcium channels blockers	17 (14%)
Diuretics	51 (42%)
Statins	108 (89%)
Warfarin	13 (11%)

* Defined as plasma low-density lipoprotein cholesterol >130 mg/dl or on statins.

non–Q-wave myocardial infarction (defined as an elevation of creatinine kinase-MB ≥3 times the upper limit of normal), urgent coronary revascularization (urgent bypass surgery or urgent PCI). Prospective data was collected for each patient from the time of PCI for a follow-up period ranging 18 to 51 months (median 30 months).

The primary endpoint of the study was all-cause mortality. The follow-up data were retrieved using both the Social Security Database and hospital records. We also compared the results of this group of patients with a historical cohort of 113 patients with LV dysfunction treated at our institution with BMS before the introduction of DES between May 1996 and March 1999.

Statistical analysis was performed with SPSS 11.0 software for Windows (SPSS, Inc., Chicago, Illinois). Continuous variables are reported as mean ± SD; discrete variables are presented as percentages. The Student's *t* test was used to compare continuous variables, and the chi-square test (or the Fisher's exact test when indicated) was performed to compare discrete variables between the 2 groups. Kaplan-Meyer survival curves were used to compare time-dependent variables, using the Cox regression analysis for multivariable analysis. Survival rates and 95% confidence intervals (CI) are presented; 2-tailed p values of 0.05 were considered statistically significant for this analysis.

Table 2
Angiographic and procedural characteristics

Variable	Patients (n = 121)
LVEF	36 ± 8
Number of coronary arteries with narrowing >50%	
1	19 (16%)
2	15 (12%)
3	11 (9%)
Coronary artery with narrowing >50%	
Left main	3 (3%)
Left anterior descending	76 (63%)
Left circumflex	49 (40%)
Right	57 (47%)
Procedural success	120 (99%)
1-artery intervention	97 (80%)
2-artery intervention	21 (17%)
3-artery intervention	3 (3%)
No. of treated coronary arteries per patient	1.2 ± 0.5
Complete revascularization	78 (64%)
Total occlusion	24 (20%)
In-stent restenosis	17 (14%)
Number of stents	185
	Sirolimus = 171
	Paclitaxel = 14
Number of stents per patient	1.5 ± 0.8
Stent length (mm)	19.2 ± 5.1
Stent diameter (mm)	2.9 ± 0.4
Direct stenting	70 (58%)
Use of glycoprotein IIb/IIIa inhibitors	37 (31%)
Use of intra-aortic balloon pump	1 (1%)

Results

The cohort included 121 patients (84% men). Demographic and clinical features are listed in Table 1. The average age was 62 ± 12 years, 30% had diabetes, 31% underwent primary PCI for ST-elevation myocardial infarction, 47% after a non–ST-elevation acute coronary syndrome, and 22% had stable angina pectoris and/or evidence of inducible myocardial ischemia on stress test; 33% had a previous myocardial infarction, and 29% had received a previous coronary intervention.

More than 80% of patients were on angiotensin-converting enzyme inhibitors, β blockers, and statins. The mean calculated LVEF was 36 ± 8% with 20 patients (16%) having LVEF ≤25%. Multivessel coronary artery disease was present in 58% of the patients with ≥1 total occlusion in 20% of patients; 14% of patients were retreated for in-stent restenosis after BMS implantation.

Procedural success was achieved in 99% of patients; 20% had multivessel PCI. DES implantation was considered off-label in 101 patients (83%). In total, 185 DES were implanted (171 sirolimus-eluting stents and 14 paclitaxel-eluting stents). Direct stenting was performed in 70 patients (58%). The mean stent diameter was 2.9 ± 0.4 mm. Periprocedural glycoprotein IIb/IIIa antagonists were used in 37% of cases and prophylactic intra-aortic balloon pump was used only in 1 procedure. Angiographic and procedural features are reported in Table 2.

The clinical and procedural characteristics of the historical cohort of patients who underwent BMS implanta-

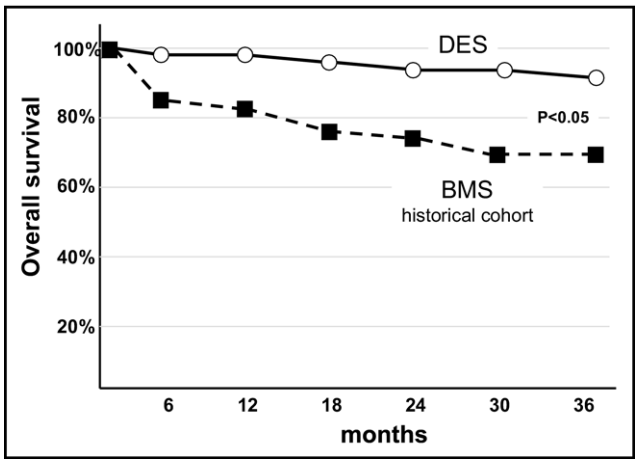

Figure 1. Kaplan Meier curves: 3-year follow-up overall survival in the DES versus BMS group.

tion were similar to the cohort of patients who underwent DES implantation. In particular, the mean calculated LVEF was 39 ± 10%, and 59% of patients had multivessel coronary artery disease; of these, 18% had multivessel PCI. A lower percentage of patients received β blockers and statins at the time of the procedure compared with the DES group (data not shown), and a prophylactic intra-aortic balloon pump was inserted in 10 patients (9%) in the BMS group. For the DES cohort, median duration of follow-up was 30 months (range 18 to 51), and there was no in-hospital death; 2 patients (2%) had myocardial infarction, and 1 of these (1%) required urgent repeat PCI for in-stent thrombosis. No patients underwent urgent coronary artery bypass surgery.

Actuarial survival curves were created showing a 1-, 2-, and 3- year survival of 94% (95% CI 88 to 100), 90% (95% CI 82 to 98), and 88% (95% CI 80 to 96), respectively. Long-term survival appeared similar in patients with LVEF ≤25% and those with LVEF 26 to 45% (5% vs 13%, p = 0.45). Figure 1 shows survival curves for the cohort of patients with DES and, for comparison, of patients with BMS.

Discussion

The present study is reassuring because it shows that despite concerns regarding an increased incidence of late stent thrombosis in patients with depressed LVEF, the use of DES appears safe and is associated with a favorable long-term outcome.

DES significantly reduce the incidence of angiographic restenosis and subsequent target vessel revascularization across a large spectrum of lesions and patients subsets.[1–6] Initial studies had suggested that rates of mortality and myocardial infarction are not reduced by DES in clinical randomized trials and observational registries, especially if DES were implanted for "off-label" indications,[3] and concerns have been raised that the lack of effects of DES on "hard" clinical end points may be explained by an increased incidence of stent thrombosis, especially late stent thrombosis.[7] Although more recent data suggest that the increase in late stent thrombosis may be less than initially described and may be offset by a beneficial impact on late ischemic events,[8,9] we considered that depressed LVEF has been shown to be an independent predictor of subacute stent thrombosis possibly due to "slow flow" within the stent[1] and, therefore, LV dysfunction and DES could have represented a risky combination. Thus, we decided to retrospectively review the cohort of patients who had received a DES. Our results are in line with the recent reports.[6,10]

Although speculative, prevention of in-stent restenosis observed with DES may lead to improvement of long-term survival, balancing potential adverse events related to stent thrombosis, especially in patients with LV dysfunction. In fact, contrary to traditional belief, in-stent restenosis is not a "benign clinical entity." Numerous studies demonstrated that 30% to 60% of cases of BMS restenosis presented as acute coronary syndromes.[11,12] The arterial injury after stent implantation and resulting neointimal proliferation may serve as a substrate for subsequent thrombus formation, leading to an acute presentation. Bossi et al[13] and the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) investigators[14] also observed a poor outcome in patients with unstable angina pectoris or myocardial infarction related to angiographic evidence of in-stent restenosis. Interestingly, LV dysfunction has been associated with an increased risk of acute presentation of stent restenosis.[12]

Several limitations of this study, such as the retrospective nature of the analysis and the relatively small number of patients, need to be acknowledged. Also the historical BMS cohort is not an ideal control for the current DES cohort, and comparisons should be interpreted cautiously. Moreover, we were not able to collect more specific data from long-term follow-up, such as incidence of myocardial infarction, repeat revascularization, and in-stent thrombosis, therefore limiting the analysis to the assessment of mortality only.

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