Results and Predictors of Angiographic Restenosis and Long-Term Adverse Cardiac Events After Drug-Eluting Stent Implantation for Aorto-Ostial Coronary Artery Disease

Duk-Woo Park, MD, Myeong-Ki Hong, MD, PhD, Il-Woo Suh, MD, Eui-Seock Hwang, MD, Se-Whan Lee, MD, Young-Hoon Jeong, MD, Young-Hak Kim, MD, PhD, Cheol Whan Lee, MD, PhD, Jae-Joong Kim, MD, PhD, Seong-Wook Park, MD, PhD, and Seung-Jung Park, MD, PhD*

The correlates of angiographic and clinical outcomes after drug-eluting stent (DES) implantation for aorto-ostial lesions remain unknown. This study evaluated long-term results of DES implantation for aorto-ostial lesions and determined risk factors for restenosis and adverse cardiac events. In total, 184 consecutive patients who underwent DES implantation for aorto-ostial lesions were investigated (DES group) compared with 172 consecutive patients treated with bare metal stents before the introduction of DESs (pre-DES group). Major adverse cardiac events (MACEs) were defined as death, Q-wave myocardial infarction, and need for target lesion revascularization. The DES group had significantly higher risk clinical and procedural profiles than the pre-DES group. Procedural success rates were 99.5% in the DES group and 100% in the pre-DES group (p = 1.0). The DES group had a significantly lower incidence of in-segment restenosis (10.5% vs 26.0%, p = 0.001) and target lesion revascularization (4.3% vs 11.6%, p = 0.011). Cumulative MACE rates at 1 year were 6.5% in the DES group and 13.4% in the pre-DES group (p = 0.03). By multivariate analysis, treatment of bypass graft, treatment of in-stent restenosis, and reference vessel diameter were predictors of restenosis, and only reference vessel diameter (hazard ratio 0.20, 95% confidence interval 0.05 to 0.75, p = 0.017) inversely correlated with 1-year MACEs after DES implantation. In conclusion, DES implantation for aorto-ostial lesions is associated with a significant decrease in restenosis and MACEs compared with the pre-DES phase. Treatment of bypass graft and in-stent restenosis and reference vessel size were identified as predictors of restenosis and/or long-term MACEs after DES implantation. **(Am J Cardiol 2007;99:760–765)**

With widespread availability of drug-eluting stents (DESs), treating physicians are currently using DESs for more challenging clinical and anatomic situations, many of which have not been evaluated in clinical trials.[1–3] The occurrence of restenosis and clinical events after DES implantation developed mainly in complex subsets, and significant clinical, angiographic, and procedural predictors of restenosis after DES implantation and adverse events have been suggested.[3,4] In the first observational study of 32 patients treated with sirolimus-eluting stents for aorto-ostial disease, more favorable angiographic and clinical results were reported[5] compared with bare metal stents (BMSs). However, the risk factors for angiographic restenosis and long-term cardiovascular events in these complex lesions remain unknown. The present study evaluated short- and long-term safety and benefits of DES implantation in a large number of patients with aorto-osital lesions and identified predictors of subsequent restenosis and 1-year major adverse cardiac events (MACEs).

Methods

Study design and patient population: From February 2003 to April 2005, we retrospectively identified 184 consecutive patients (191 lesions) who underwent DES implantation for aorto-ostial disease (DES group); sirolimus-eluting stents and paclitaxel-eluting stents were used in 163 and 28 lesions, respectively. The control group consisted of 172 consecutive patients (177 lesions) who underwent BMS implantation for aorto-ostial lesions in the period immediately before the introduction of DESs (pre-DES group). Patients were excluded if stent implantation was performed during cardiogenic shock or as a bridge to emergency bypass surgery; there was a contraindication to antiplatelet agents; or there was severe left ventricular dysfunction (ejection fraction ≤30%).

An aorto-ostial lesion was defined as a stenosis located at the aortic junction with the left main coronary artery, right coronary artery, or grafted vessel within 3 mm of the vessel origin on the view of least foreshortened angiographic pro-

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*Corresponding author: Tel: 82-2-3010-4812; fax: 82-2-475-6898.

E-mail address: sjpark@amc.seoul.kr (S.-J. Park).

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jection. This study was approved by the institutional review board, and written informed consent was obtained.

Stenting procedures and antiplatelet medications: Details of the stenting technique have been previously described.[2,6] Although the final interventional strategy was entirely left to the discretion of the operator, direct stenting (stenting without predilatation) was considered for treatment of relatively noncomplex lesions. During the procedure, patients received intravenous heparin to maintain an activated clotting time of ≥250 seconds. The use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. All patients were pretreated with ticlopidine or clopidogrel and aspirin. A loading dose of 300 mg of clopidogrel (or 500 mg of ticlopidine) was given to patients not previously taking the antiplatelet agents. After the procedure, aspirin was continued indefinitely. Clopidogrel (75 mg/day) was prescribed for ≥6 months after DES implantation and clopidogrel (75 mg/day) or ticlopidine (500 mg/day) was prescribed for ≥1 month after BMS implantation.

Angiographic analysis: Coronary angiograms were measured by 2 experienced angiographers not involved in the stenting procedure. Standard qualitative and quantitative analyses and definitions were used for angiographic analysis.[7] Using the guiding catheter for magnification calibration and an online quantitative coronary angiographic analysis system (ANCOR 2.0, Siemens, Erlangen, Germany), minimal luminal diameter, percent diameter stenosis, and reference vessel diameter were measured before and after the intervention and at follow-up from a single matched view showing the smallest minimal luminal diameter. Acute gain was calculated as the difference between minimal luminal diameters before and after the procedure. Late loss was defined as the difference between minimal luminal diameters after the procedure and at follow-up. Angiographic restenosis was defined as a diameter stenosis ≥50% by quantitative coronary angiography within a stented segment at follow-up.

Definitions and follow-up: Procedural success was defined as a Thrombolysis In Myocardial Infarction grade 3 flow and <30% residual stenosis without major procedural or in-hospital complications. A MACE was defined as death, Q-wave myocardial infarction, and need for target lesion revascularization (TLR). Deaths were classified as cardiac or noncardiac. Deaths that could not be classified were considered to be cardiac related. Q-wave myocardial infarction was defined by the postprocedural presence of new pathologic Q waves in 2 contiguous leads. Non–Q-wave myocardial infarction was defined as an increase in the MB fraction of creatinine kinase to ≥3 times the upper limit of the normal range without pathologic Q waves. TLR was defined as repeat percutaneous or surgical interventions of the stented segment. Stent thrombosis was defined as angiographic documentation of thrombotic stent occlusion associated with a clinical event, an unexplained sudden cardiac death, or myocardial infarction not clearly attributable to another coronary lesion.[8,9]

Clinical follow-up was performed by office visits or telephone interviews at 1, 3, 6, and 12 months after stenting. Angiographic follow-up was scheduled 6 to 8 months after

Table 1
Clinical, procedural, and angiographic characteristics

Characteristics	DES (n = 184)	Pre-DES (n = 172)	p Value
Age (yrs)	60 ± 12	57 ± 12	0.1
Men	113 (61%)	106 (62%)	1.0
Hypertension	98 (53%)	63 (37%)	0.002
Diabetes mellitus	60 (33%)	36 (21%)	0.013
Total serum cholesterol >200 mg/dl	41 (22%)	44 (26%)	0.5
Current smoker	51 (28%)	48 (28%)	1.0
Previous myocardial infarction	14 (8%)	5 (3%)	0.06
Previous percutaneous coronary intervention	47 (26%)	21 (12%)	0.001
Previous bypass surgery	17 (9%)	11 (6%)	0.3
Clinical presentation			
Stable angina pectoris	79 (43%)	53 (31%)	0.018
Unstable angina pectoris	83 (45%)	104 (61%)	0.004
Myocardial infarction within 2 wks	22 (12%)	15 (9%)	0.3
Mutivessel coronary disease	153 (83%)	132 (77%)	0.1
Renal failure	10 (5%)	9 (5%)	0.9
Left ventricular ejection fraction (%)	59 ± 9	61 ± 9	0.017
No. of coronary narrowings	191	177	
Treated coronary vessel			
Left main	98 (51%)	94 (53%)	0.7
Right	83 (44%)	76 (43%)	0.9
Bypass graft	10 (5%)	7 (4%)	0.6
Saphenous vein graft/free arterial graft	10/0	5/2	
Severe lesion calcium	6 (3%)	4 (2%)	0.8
In-stent restenosis	20 (11%)	7 (4%)	0.017
Total occlusion	6 (3%)	6 (3%)	1.0
Thrombus	6 (3%)	6 (3%)	1.0
Direct stenting without predilation	51 (27%)	7 (4%)	<0.001
Cutting balloon	14 (7%)	10 (6%)	0.5
Guidance with intravasular ultrasound	134 (70%)	123 (70%)	0.9
Intra-aortic balloon pump	3 (2%)	3 (2%)	1.0
Glycoprotein IIb/IIIa inhibitor	11 (6%)	8 (5%)	0.6
Use of additional high-pressure balloons	98 (51%)	35 (20%)	<0.001
Maximal balloon diameter (mm)	3.9 ± 0.4	4.3 ± 0.6	<0.001
Maximal inflation pressure (atm)	18.4 ± 3.5	15.1 ± 2.6	<0.001
Stents per lesion (no.)	1.4 ± 0.7	1.0 ± 0.1	<0.001
Total stent length per lesion (mm)	30.7 ± 21.6	13.4 ± 6.5	<0.001
Lesion length (mm)	23.1 ± 17.2	10.8 ± 7.8	<0.001
Reference vessel diameter (mm)	3.19 ± 0.55	3.84 ± 1.17	<0.001
Preprocedure MLD (mm)	1.33 ± 0.65	1.27 ± 0.66	0.4
Postprocedure MLD (mm)	3.20 ± 0.50	3.88 ± 0.71	<0.001
Follow-up MLD (mm)	2.69 ± 0.91	2.51 ± 1.24	0.3
Preprocedure diameter stenosis (%)	58.3 ± 18.3	66.2 ± 16.0	<0.001
Postprocedure diameter stenosis (%)	−1.4 ± 14.8	−4.1 ± 14.8	0.1
Follow-up diameter stenosis (%)	13.7 ± 27.9	34.0 ± 28.6	<0.001
Acute gain (mm)	1.87 ± 0.70	2.60 ± 0.80	<0.001
Late loss (mm)	0.48 ± 0.79	1.40 ± 1.03	<0.001
Restenosis (rate)	15 (10.5)	32 (26.0)	0.001

Values are reported as numbers of patients (percentages) or means ± SDs.

MLD = minimal lumen diameter.

Table 2
Incidence of adverse cardiac events

Variable	DES (n = 184)	Pre-DES (n = 172)	p Value
In-hospital outcomes			
Death	1 (0.5)	0	1.0
Q-wave myocardial infraction	0	0	NS
Non–Q-wave myocardial infarction	20 (11)	13 (8)	0.3
Stroke	0	0	NS
Urgent revascularization	0	0	NS
Stent thrombosis	0	0	NS
Cumulative 1-yr outcomes			
Death	3 (1.6)	4 (2.3)	0.7
Cardiac	3 (1.6)	3 (1.7)	1.0
Noncardiac	0	1 (0.6)	0.5
Q-wave myocardial infarction	1 (0.5)	2 (1.2)	0.6
TLR	8 (4.3)	20 (11.6)	0.011
Repeat intervention	4 (2.2)	10 (5.8)	0.1
Bypass surgery	4 (2.2)	10 (5.8)	0.1
Stent thrombosis	1 (0.5)	2 (1.2)	0.6
Total MACES	12 (6.5)	23 (13.4)	0.030

Values are reported as numbers of patients (percentages).

the procedure or sooner if clinically indicated by symptoms or documentation of myocardial ischemia. Patients who did not develop any MACE in the first month and did not present any medical contraindication were requested to have a follow-up angiogram. Four patients died within the first 6 months after the procedure, and 10 were considered to have a medical contraindication (4 with end-stage renal disease on dialysis, 2 with severe allergic contrast reaction, 1 with disabling stroke, 2 with malignancy, and 1 with Eisenmenger syndrome). Therefore, 177 patients (96%) in the DES group and 165 (96%) in the pre-DES group were eligible for angiographic restudy ($p = 0.9$).

Statistical analysis: Categorical variables were presented as frequencies (percentages) and compared with chi-square statistics or Fisher's exact test. Continuous variables were presented as mean ± SD and compared with Student's *t* test. Logistic regression analysis was used to determine the independent predictors of angiographic restenosis. The Cox proportional hazards regression model was used to identify independent predictors of MACEs at 1-year follow-up. All clinical, procedural, and angiographic variables (listed in Table 1) with a p value <0.10 by univariate analyses were included in multivariate analyses using the forward stepwise selection process. A p value <0.05 was considered statistically significant, and all statistical tests were 2-tailed. Statistical analyses were performed with SPSS 12.0 (SPSS, Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics: Baseline clinical, lesion, and procedural characteristics are presented in Table 1. The DES group had a higher incidence of hypertension, diabetes, and previous coronary intervention and a lower ejection fraction than the pre-DES group. Recent myocardial infarction (within 2 weeks) was the indication for the procedure in 10% of overall patients.

Seven patients in the DES group and 5 in the pre-DES group underwent stenting in left main and right coronary ostial lesions. The 2 groups were well matched for lesion location and characteristics, except that restenotic lesions were more often included for stenting in the DES group. Patients treated with DESs had significantly more direct stenting without predilatation, a higher final balloon pressure, a larger number of used stents, and longer stent length per lesion. There were no cases of coronary perforation or residual dissection after stenting in either group.

Angiographic and clinical results: Angiographic data and clinical outcomes are presented in Tables 1 and 2, respectively. The DES group had a smaller reference diameter and a longer lesion than the pre-DES group. Postprocedure minimal luminal diameter was significantly larger in the pre-DES group due to greater acute gain.

During hospitalization, 1 patient in the DES group died compared with no patients in the pre-DES group ($p = 1.0$). This patient presented with unstable angina and occlusive aorto-ostial disease of the saphenous vein graft, which was anastomosed to the left anterior descending artery. The patient died 4 days after successful stenting because of ventricular fibrillation. Periprocedural non–Q-wave myocardial infarction occurred in 20 patients (11%) in the DES group and in 13 patients (8%) in the pre-DES group ($p = 0.3$). Procedural success rates were 99.5% in the DES group and 100% in the pre-DES group ($p = 1.0$).

Follow-up angiography was performed in 138 patients in the DES group (78% of eligible patients) and 118 in the pre-DES group (72% of eligible patients, $p = 0.2$). There was no significant difference in mean time to angiographic follow-up (7.0 ± 3.2 vs 6.9 ± 4.5 months, $p = 0.96$). Late lumen loss (0.48 ± 0.79 vs 1.40 ± 1.03 mm, $p < 0.001$) and binary restenosis rate (10.5% vs 26.0%, $p = 0.001$) were significantly lower in the DES group than in the pre-DES group (Table 1). In the DES group, the angiographic pattern of in-stent restenosis was focal in 12 lesions (in-stent 10, distal edge 2), diffuse in 1 lesion, and totally occluded in 2 lesions. Of the 15 restenotic lesions in the DES group, 8 (53%) compromised the 3-mm segment from the aortic junction. In the pre-DES group, the restenotic pattern was focal in 17 lesions (in-stent 15, distal edge 2), diffuse in 14 lesions, and totally occluded in 1 lesion.

At 1-year follow-up (available in all patients), the incidence of MACEs was significantly lower in the DES group than in the pre-DES group (6.5% vs 13.4%, $p = 0.030$). Three patients (1.6%) in the DES group died compared with 4 (2.3%) in the pre-DES group ($p = 0.7$). All 3 patients in the DES group were classified as having cardiac death; 1 died after discontinuation of antiplatelet therapy due to colonic polypectomy 172 days after left main stenting, 1 died as a result of pneumonia and pump failure, and 1 died during hospitalization. The DES group had a significantly lower rate of TLR compared with the pre-DES group (4.3% vs 11.6%, $p = 0.011$). Stent thrombosis developed in 1 patient (0.5%) in the DES group and in 2 patients (1.2%) in the pre-DES group ($p = 0.6$).

Predictors of restenosis and cardiac events after DES implantation: Figure 1 shows the univariate correlation between the incidence of in-segment restenosis and clinical, procedural, and angiographic variables in patients treated with DESs. Covariates included in the multivariable model

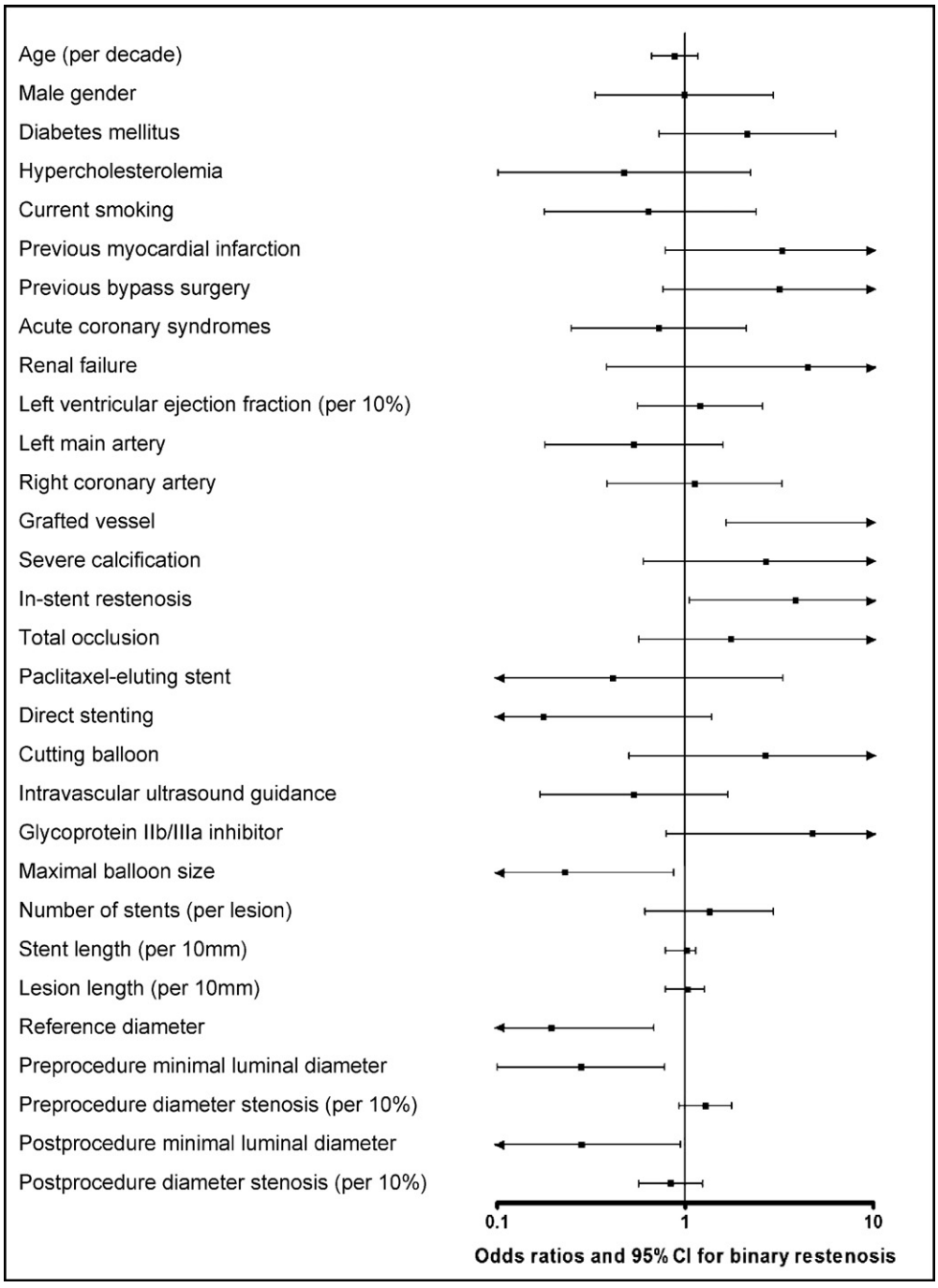

Figure 1. Univariate analysis of binary in-segment restenosis after DES implantation in aorto-ostial lesions according to clinical, procedural, and angiographic parameters. The ORs are shown on a logarithmic scale with their 95% CIs.

were treatment of bypass graft (odds ratio [OR] 15.53, 95% confidence interval [CI] 1.66 to 57.42, p = 0.018), treatment of in-stent restenosis (OR 3.87, 95% CI 1.05 to 14.20, p = 0.042), direct stenting (OR 0.18, 95% CI 0.02 to 1.38, p = 0.099), glycoprotein IIb/IIIa inhibitor use (OR 4.77, 95% CI 0.80 to 28.59, p = 0.087), maximal balloon diameter (OR 0.23, 95% CI 0.06 to 0.87, p = 0.030), reference vessel diameter (OR 0.19, 95% CI 0.06 to 0.68, p = 0.011), preprocedure minimal luminal diameter (OR 0.28, 95% CI 0.10 to 0.78, p = 0.015), and postprocedure minimal lumi-

Table 3
Multivariate predictors of angiographic restenosis after drug-eluting stent implantation

Variables	Multivariate Analysis		
	OR	95% CI	p Value
Treatment of bypass graft	10.09	1.18–45.26	0.037
Treatment of in-stent restenosis	4.38	1.12–19.39	0.048
Reference vessel diameter (mm)	0.15	0.03–0.63	0.010

Table 4
Univariate and multivariate predictors of major adverse cardiac events after drug-eluting stent implantation

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Treatment of in-stent restenosis	3.12	0.85–11.68	0.085			
Glycoprotein IIb/IIIa inhibitor use	5.22	1.14–23.92	0.034			
Lesion length (mm)	1.03	1.002–1.06	0.034			
Reference vessel diameter (mm)	0.23	0.06–0.83	0.025	0.20	0.05–0.75	0.017
Preprocedure MLD (mm)	0.36	0.14–0.93	0.035			

HR = hazard ratios; other abbreviation in Table 1.

nal diameter (OR 0.28, 95% CI 0.08 to 0.95, p = 0.041). In multivariate analysis, treatment of bypass graft, treatment of in-stent restenosis, and reference vessel diameter were identified as independent predictors of angiographic restenosis (Table 3).

Univariate and multivariate predictors of cumulative MACEs at 1 year in patients treated with DESs are listed in Table 4. At multivariate analysis, only reference vessel diameter (hazard ratio 0.20, 95% CI 0.05 to 0.75, p = 0.017) inversely correlated with occurrence of MACEs during 1-year follow-up.

Discussion

The major findings of this study are that (1) utilization of DES to treat aorto-ostial lesions appears safe and feasible with a very high procedural success rate (99.5%); (2) a marked benefit with respect to rates of restenosis (60% relative risk decrease) and MACEs (51% relative risk decrease) emerged in patients with DESs compared with those with BMSs, thus confirming previous observations[5]; and (3) treatment of bypass graft, treatment of in-stent restenosis, and smaller reference vessel were independent predictors of angiographic restenosis and/or long-term MACEs after DES implantation.

In a previous study of patients with complex lesions and "off-label" indications, ostial lesions had a relatively high restenosis rate (14.7%) and were identified as independent predictors of restenosis after DES implantation.[4] Several recent reports using DESs have shown encouraging angiographic and clinical results in coronary ostial lesions, including aorto-ostial and left anterior descending ostial lesions.[5,10,11] Compared with the BMS group, use of DESs on relatively complex aorto-ostial lesions involving diffuse long segments and a less restrictive stenting strategy for more complete lesion coverage led to a significant increase in the number and length of stents implanted. Despite these lesion and procedural complexities, our present findings are in keeping with previous observations. However, to date, no data are available about the correlates of restenosis and cardiac events in aorto-ostial lesions after DES implantation due to the limited number of patients.

In our study, treatment of bypass graft and in-stent restenosis with DESs in an aorto-ostial location was an independent predictor of angiographic restenosis after adjustment for other significant covariates. Percutaneous intervention of saphenous vein graft is associated with a higher rate of periprocedural complications and late angiographic and clinical restenosis.[12] Ostial location had an especially higher restenosis rate than nonostial location after BMS implantation.[13] Although DES has achieved more predictable results and lower restenosis rates in saphenous vein graft disease,[14] we found that the aorto-ostial involvement was still prone to higher restenosis after DES implantation. Higher elastic recoil and lesion rigidity might be a possible explanation for this finding. In addition, the unavailability of a DES >3.5 mm may lead to discrepancies between stent and vessel sizes, which preclude optimal lumen geometry and homogenous drug delivery.

Although a DES has a low incidence of recurrent restenosis after treatment of noncomplex restenotic lesions,[15,16] its efficacy in treating more complicated restenotic lesions remains to be established. The higher incidence of restenosis observed after treating in-stent restenosis of aorto-ostial lesions may be due to a modification of the vessel wall in response to repeated injury and to local elements specific to the aorto-ostial junction, thus decreasing responsiveness to antiproliferative drugs.

By multivariate analysis, reference vessel size was identified as a predictor of restenosis as well as long-term MACEs, similar to previous reports in real practice with different complex lesions[17] and in relatively large vessels, such as the left main artery.[18–20] Because coronary restenosis resulted mostly from neointimal hyperplasia, binary restenosis and need for revascularization may be more likely to occur in patients with smaller reference diameters.

Because aorto-ostial lesions usually have a very large reference vessel size despite the small intraluminal lesion diameter, more appropriate or larger stents, not yet available, may be needed to ensure more complete apposition of the stent strut to the vessel wall and more uniform drug distribution. This issue therefore deserves further investigation.

This study is subject to some limitations. (1) It is a retrospective, single-center study and lacks the clear advantages of a randomized trial. (2) The DES group included 2 different types of DESs. (3) Sirolimus-eluting stents were more commonly used. (4) Angiographic follow-up was not performed in all patients, possibly resulting in selection bias. (5) This study was underpowered to show a difference in the incidence of stent thrombosis, death, or Q-wave myocardial infarction between patients with DESs and those with BMSs. Further studies with larger samples are required to investigate the differential effect of DESs (sirolimus- vs paclitaxel-eluting stents) in prespecified subgroups accord-

ing to clinical presentation (stable vs acute coronary syndromes) and lesion locations (left main vs right coronary artery vs grafted vessel).

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