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Comparison of Sirolimus-Eluting Stent, Paclitaxel-Eluting Stent, and Bare Metal Stent in the Treatment of Long Coronary Lesions

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Objective: This study compared the efficacy of the sirolimus-eluting stent (SES), the paclitaxel-eluting stent (PES), and the bare metal stent (BMS) for long coronary lesions. Background: The outcome of drug-eluting stent (DES) implantation in long coronary lesions remains unclear. Methods: The study involved 527 patients with de novo long coronary lesions (≥24 mm), which were treated with long (≥28 mm) SESs (223 lesions), PESs (194 lesions), or BMSs (201 lesions). Results: Lesions in the SES (36.0 ± 14.9 mm, *P* < 0.001) and PES (36.3 ± 14.5 mm, *P* < 0.001) groups were longer than those in the BMS group (32.0 ± 12.3 mm), meaning the two DES groups had longer stented segments than did the BMS group. Six-month angiographic follow-up showed the SES (9.3%, *P* < 0.001) and PES (21.3%, *P* < 0.001) groups had lower in-segment restenosis rates than that of the BMS group (42.5%). The rate of major adverse cardiac events (MACE) including death, myocardial infarction, and target lesion revascularization at 9 months was higher in the BMS group (26.6%) than that in the SES (13.0%, *P* < 0.001) and PES (15.7%, *P* < 0.001) groups. *Posthoc* analysis of the two DES groups showed that the in-segment restenosis rate was lower for the SES than that for the PES group (*P* = 0.002), while the MACE rate was similar. Conclusions: The use of DESs for long coronary lesions appears to be safe and more effective than the use of BMSs in terms of restenosis and adverse clinical events. SES use was associated with lower late luminal loss and a lower angiographic restenosis rate compared with PES use. © 2006 Wiley-Liss, Inc.

Key words: stent; restenosis; coronary artery disease

INTRODUCTION

Long coronary lesions comprise up to 20% of current interventional practice and are considered difficult both technically and in terms of achieving successful clinical outcomes [1–7]. The long stented segment of bare metal stents (BMSs) correlates with a risk of restenosis when used for diffuse coronary lesions [1–7]. In contrast, promising results obtained when using drug-eluting stents (DESs) make long coronary lesions an inviting target for percutaneous coronary intervention [8–11]. Recently, several randomized studies were conducted comparing the safety and efficacy of the two leading DESs,

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the sirolimus-eluting stent (SES, Cordis, Johnson & Johnson) and the paclitaxel-eluting stent (PES, Boston Scientific) [12–16]. However, few data are available that specifically address the safety and efficacy of these two DESs in long coronary lesions.

Therefore, the present study compared clinical and angiographic outcomes when using SESs, PESs, and BMSs for treatment of de novo long coronary lesions.

MATERIALS AND METHODS

Study Design and Population

This nonrandomized prospective study was performed at eight cardiac centers in Korea. The study was approved by the institutional review boards of all participating centers and informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Eligible patients were at least 18 years, had a history or evidence of coronary ischemia, and underwent SES, PES, or BMS implantation using stents of $\geq$28-mm total length between April 2003 and February 2004. Angiographic inclusion criteria specified de novo coronary lesions with a diameter stenosis $\geq$ 70%, a reference diameter $\geq$ 2.5 mm and a lesion length $\geq$ 24 mm as estimated visually using angiography. Exclusion criteria were acute myocardial infarction within the previous 48 hr, an ejection fraction $\leq$ 40%, a left main coronary lesion, bifurcation stenting, chronic total occlusion, or an inability to follow the protocol. Patients who met the inclusion criteria and had multiple lesions treated with the same type of stent were also included in angiographic analysis.

Enrollment and Data Management

The study prospectively included patients from investigating centers. The Korean Food and Drug Administration approved the SES in February 2004 and the PES in August 2004. Therefore, the SES was used exclusively until the PES was approved, after which the PES was exclusively used. The BMS group was formed throughout the study period as a control group. Stent selection was not specifically predetermined by the study protocol. In total, 527 patients were included in the study with 184 patients (223 lesions) treated with SESs, 166 patients (194 lesions) with PESs, and 177 patients (201 lesions) with BMSs. At each participating center, patient data were recorded prospectively on standard case report forms. Independent event committee blinded to the treatment groups adjudicated all adverse clinical events.

All patients were evaluated clinically by office visits or telephone interviews at 30, 90, 180, and 270 days. Repeat coronary angiography was routinely recommended 6 months after stenting or earlier if indicated by clinical symptoms or evidence of myocardial ischemia.

Stenting Procedure

Lesions were treated using standard interventional techniques [17]. There was no limit on the number of stents used to achieve complete lesion coverage. The decision of either predilation or direct stenting was made by the operator involved. Intravascular ultrasound (IVUS) guidance was strongly encouraged. Before and after the procedure, all patients received aspirin (200 mg daily) and clopidogrel (a loading dose of 300 mg 24 hr before the procedure and then 75 mg daily for 1 month in the BMS group and for 6 months in the DES groups). The use of intravenous glycoprotein IIb/IIIa inhibitors was at the operators' discretion.

Study Endpoints

The primary endpoint was in-segment angiographic restenosis at 6 months. Secondary endpoints included angiographic in-segment late luminal loss at 6 months and major adverse cardiac events (MACE) including death from any cause, myocardial infarction (Q-wave or non-Q-wave), and target lesion revascularization (TLR) at 9 months. TLR was performed in patients who had restenosis at the target lesion with evidence of recurrent myocardial ischemia as assessed by symptoms or myocardial stress test. Q-wave myocardial infarction was defined by the postprocedural presence of new Q-waves of greater than 0.04 sec in two contiguous leads. Non-Q-wave myocardial infarction was defined as a creatine kinase MB fraction greater than three times the normal upper limit.

Quantitative Angiographic Analysis

Coronary angiograms were obtained prior to the procedure (baseline), after the procedure and at follow-up, and were submitted to the angiographic analysis center (Asan Medical Center, Seoul, Korea) where they were analyzed by two independent angiographers. Quantitative coronary angiographic measurements of target lesions were obtained for both the "in-stent" region including the stented segment only, and the "in-segment" region including the stented segment as well as the margins 5 mm proximal and distal to the stent. Late luminal loss was defined as the difference in minimal luminal diameter (MLD) between postprocedure and follow-up measurements. Angiographic restenosis was defined as $>$50% diameter stenosis.

Statistical Analysis

Data are expressed as mean $\pm$ SD for continuous variables, and as frequencies for categorical variables. Comparisons were performed using Pearson's χ^2-tests, unpaired *t*-tests, and standard ANOVA with *posthoc* comparison using the Bonferroni correction. TLR- and MACE-free survival distributions in the three groups were estimated using the Kaplan–Meier method, and were com-

TABLE I. BASELINE CHARACTERISTICS OF PATIENTS

	SES	PES	BMS	*P*-value
Patients	184	166	177	
Age (years)	61.5 ± 9.2	61.6 ± 10.4	60.1 ± 10.0	0.133
Male	130 (70.7)	123 (74.1)	136 (76.8)	0.408
Left ventricular ejection fraction (%)	58.5 ± 8.3	59.4 ± 9.6[‡]	56.6 ± 9.6	0.036
Hypertension	105 (57.1)	93 (56.0)	97 (54.8)	0.910
Diabetes mellitus	57 (31.0)	53 (31.9)	57 (32.2)	0.966
Current smoker	57 (31.0)[†]	55 (33.1)[‡]	88 (49.7)	<0.001
Hypercholesterolemia (total cholesterol ≥ 200 mg/dL)	50 (27.2)	52 (31.3)	61 (34.5)	0.323
Previous percutaneous coronary intervention	22 (12.0)	24 (14.5)	23 (13.0)	0.786
Previous bypass surgery	3 (1.6)	6 (3.6)[‡]	0 (0)	0.035
Clinical diagnosis				0.653
Stable angina	100 (54.3)	83 (50.0)	89 (50.3)	
Unstable angina	68 (37.0)	63 (38.0)	64 (36.2)	
Acute myocardial infarction	16 (8.7)	20 (12.0)	24 (13.6)	
Medications at discharge				
ACE inhibitor	37 (20.1)	32 (19.3)	46 (26.0)	0.253
β-Blocker	128 (69.6)	131 (78.9)	124 (70.1)	0.092
Statin	61 (33.2)	64 (38.6)	69 (39.0)	0.442

BMS, bare metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.
Values given are either mean ± SD or *n* values (and percentages in parentheses).
[†,‡]These represent $P < 0.05/3$ between the SES and the BMS groups, and between the PES and the BMS groups, respectively.

pared using log-rank tests. The influence of baseline and procedural variables on angiographic restenosis was evaluated using multiple logistic regression analysis per lesion. Age, sex, clinical, and angiographic variables with a *P*-value ≤ 0.2 on univariate analysis were entered into the model. A *P*-value < 0.05 was considered to indicate a significant difference. Statistical analysis was performed using commercially available software (SPSS ver.11 for Windows, SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

Patient baseline clinical characteristics are shown in Table I. There were no significant differences between the SES, PES, and BMS groups other than current smoking habits, left ventricular ejection fraction, and prior history of bypass surgery. Angiographic characteristics before the procedure are shown in Table II. Reference vessel diameter was smallest in the SES group and largest in the BMS group. Lesion lengths in the two DES groups were similar and longer than those in the BMS group.

Procedural Results

Procedural characteristics for the three groups are summarized in Table III. Since the two DES groups had longer mean lesion lengths than did the BMS group, they had more stents implanted per lesion and underwent more IVUS guidance than did the BMS group. There were no significant differences between the SES and PES groups in terms of procedural techniques and stented lengths. Adverse events during hospitalization are listed in Table IV. Cardiac death occurred in one PES patient and one BMS patient. The patient in the PES group died from procedure-related cardiac tamponade during multivessel intervention, while the patient in the BMS group had no reflow after stenting at the infarct-related artery and died from Q-wave myocardial infarction and cardiogenic shock. The frequencies of non-Q-wave myocardial infarction and MACE during hospitalization were similar for the three groups. Quantitative angiographic measurements after the procedure are shown in Table II. The SES group achieved less acute gain than did the PES and BMS groups. Postprocedural MLD was largest in the BMS group and least in the SES group.

Follow-Up Results

Angiographic follow-up data are shown in Table II. Angiographic follow-up at 6 months was performed in 172 lesions (77.1%) of the SES group, 150 lesions (77.3%) of the PES group, and 160 lesions (79.6%) of the BMS group. The duration of angiographic follow-up was 6.1 ± 1.0 months in the SES group, 6.4 ± 1.1 months in the PES group, and 6.3 ± 1.7 months in the BMS group ($P = 0.259$). The two DES groups showed less in-segment and in-stent late luminal losses than did the BMS group, and late luminal losses were less in the SES group than those in the PES group. Therefore, in-segment and in-stent MLD were greatest in the SES group and least in the BMS group. According to the different late losses in the three

TABLE II. ANGIOGRAPHIC CHARACTERISTICS OF LESIONS

	SES	PES	BMS	*P*-value
Patients	184	166	177	
Lesions	223	194	201	
Diseased vessels				0.821
1 vessel	48 (26.1)	42 (25.3)	47 (26.7)	
2 vessel	72 (39.1)	74 (44.6)	69 (39.2)	
3 vessel	64 (34.8)	69 (39.2)	60 (34.1)	
Lesion location				0.088
Left anterior descending artery	126 (56.5)	93 (47.9)	89 (44.3)	
Left circumflex artery	37 (16.6)	31 (16.0)	41 (20.4)	
Right coronary artery	60 (26.9)	70 (36.1)	71 (35.3)	
Before procedure				
Lesion length	36.0 ± 14.9†	36.3 ± 14.5‡	32.0 ± 12.3	0.002
Mean reference diameter (mm)	2.73 ± 0.41*,†	2.90 ± 0.48‡	3.10 ± 0.54	<0.001
Minimal luminal diameter (mm)	0.76 ± 0.48	0.77 ± 0.49	0.78 ± 0.54	0.948
Diameter stenosis (%)	72.1 ± 16.7	73.6 ± 16.2	74.4 ± 17.0	0.351
After procedure				
Mean reference diameter (mm)	2.73 ± 0.42*,†	2.92 ± 0.46‡	3.09 ± 0.50	<0.001
Minimal luminal diameter (mm)				
In-segment	2.35 ± 0.43*,†	2.50 ± 0.45	2.60 ± 0.50	<0.001
In-stent	2.64 ± 0.44*,†	2.78 ± 0.43‡	2.90 ± 0.55	<0.001
Diameter stenosis (%)				
In-segment	8.5 ± 10.6†	9.8 ± 11.1	11.8 ± 11.2	0.008
In-stent	2.6 ± 13.3	4.2 ± 13.5	5.7 ± 12.2	0.051
Acute gain (mm)	1.88 ± 0.59†	2.01 ± 0.57	2.12 ± 0.67	<0.001
Follow-up				
Lesions	172	150	160	
Mean reference diameter (mm)	2.69 ± 0.38†	2.78 ± 0.41	2.86 ± 0.49	0.002
Minimal luminal diameter (mm)				
In-segment	2.21 ± 0.60*,†	1.90 ± 0.71‡	1.56 ± 0.69	<0.001
In-stent	2.40 ± 0.66*,†	1.98 ± 0.77‡	1.58 ± 0.71	<0.001
Diameter stenosis (%)				
In-segment	14.9 ± 20.0*,†	31.0 ± 24.0‡	45.4 ± 22.4	<0.001
In-stent	10.1 ± 22.8*,†	29.3 ± 25.8‡	45.0 ± 22.7	<0.001
Late loss (mm)				
In-segment	0.14 ± 0.53*,†	0.56 ± 0.62‡	1.02 ± 0.67	<0.001
In-stent	0.26 ± 0.62*,†	0.78 ± 0.72‡	1.35 ± 0.74	<0.001
Restenosis				
In-segment	16 (9.3)*,†	32 (21.3)‡	68 (42.5)	<0.001
In-stent	13 (7.6)*,†	24(16.0)‡	65 (40.6)	<0.001

BMS, bare metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.
Values given are either mean ± SD or *n* values (and percentages in parentheses).
*,†,‡These represent $P < 0.05/3$ between the SES and the PES groups, between the SES and the BMS groups, and between the PES and the BMS groups, respectively.

TABLE III. PROCEDURAL CHARACTERISTICS

	SES	PES	BMS	*P*-value
Lesions	223	194	201	
Multivessel intervention	101 (54.9)	90 (54.2)	98 (55.4)	0.977
Number of stents per lesion	1.69 ± 0.72†	1.63 ± 0.70‡	1.28 ± 0.49	0.009
Multiple stents per lesion	126 (56.5)†	100 (51.5)‡	52 (25.9)	<0.001
Use of glycoprotein IIb/IIIa	1 (0.5)	2 (1.2)	7 (4.1)	0.038
Intravascular ultrasound guidance	170 (76.2)†	144 (74.2)‡	96 (47.8)	<0.001
Maximal inflation pressure (atm)	15.4±3.6*,†	13.2±3.9‡	12.0±3.3	<0.001
Maximal device diameter (mm)	3.36±0.39	3.40±0.41	3.47±0.52	0.056
Total stent length (mm)	44.4±16.7†	43.1±16.4‡	36.0±11.4	<0.001

BMS, bare metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.
Values given are either mean ± SD or *n* values (and percentages in parentheses).
*,†,‡These represent $P < 0.05/3$ between the SES and the PES groups, between the SES and the BMS groups, and between the PES and the BMS groups, respectively.

TABLE IV. CLINICAL OUTCOMES DURING HOSPITALIZATION AND AT 9-MONTH FOLLOW-UP

	SES	PES	BMS	*P*-value
Patients	184	166	177	
In-hospital outcomes				
Death	0 (0)	1 (0.6)	1 (0.6)	0.583
Myocardial infarction	16 (8.7)	16 (9.6)	15 (8.5)	0.923
Q myocardial infarction	0 (0)	0 (0)	1 (0.6)	0.371
Non-Q myocardial infarction	16 (8.7)	16 (9.6)	14 (7.9)	0.851
Target lesion revascularization	0 (0)	0 (0)	0 (0)	1.0
MACE	16 (8.7)	17 (10.2)	15 (8.5)	0.827
9-month outcomes				
Death	2 (1.1)	1 (0.6)	1 (0.6)	0.817
Myocardial infarction	16 (8.7)	16 (9.6)	15 (8.5)	0.923
Q myocardial infarction	0 (0)	0 (0)	1 (0.6)	0.371
Non-Q myocardial infarction	16 (8.7)	16 (9.6)	14 (7.9)	0.851
Target lesion revascularization	7 (3.8)†	10 (6.0)‡	34 (19.2)	<0.001
MACE	24 (13.0)†	26 (15.7)‡	47 (26.6)	<0.001

BMS, bare metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

Values given are either mean ± SD or *n* values (and percentages in parentheses). †,‡ These represent $P < 0.05/3$ between the SES and the BMS groups, and between the PES and the BMS groups, respectively.

TABLE V. PATTERNS OF IN-SEGMENT RESTENOSIS USING THE MEHRAN CRITERIA

	SES ($n = 16$)	PES ($n = 32$)	BMS ($n = 68$)	*P*-value
Focal	15 (93.8)*,†	14 (43.8)	21 (30.9)	<0.001
1A	0	0	0	1.0
1B	3 (18.8)	7 (21.9)‡	3 (4.4)	0.021
1C	12 (75.0)*,†	5 (15.6)	17 (25.0)	<0.001
1D	0	2 (6.3)	1 (1.5)	0.291
Diffuse				
II	0*,†	10 (31.3)	30 (44.1)	0.003
III	1 (6.3)	7 (21.9)	13 (19.1)	0.392
IV (total occlusion)	0	1 (3.1)	4 (5.9)	0.539

BMS, bare metal stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

*,†,‡ These represent $P < 0.05/3$ between the SES and the PES groups, between the SES and the BMS groups, and between the PES and the BMS groups, respectively.

groups, in-segment and in-stent restenosis rates were lowest in the SES group and highest in the BMS group. Different patterns of restenoses were found in the three groups as in Table V [18]. A focal restenosis pattern was observed more frequently in the SES group than that in the other two groups ($P < 0.001$). Multivariate analysis showed DES implantation, in-stent MLD after the procedure, and smoking habits were independent determinants of in-segment restenosis (Table VI). In patients treated with DESs, PES implantation, long lesions, and small in-stent MLD after the procedure were independent predictors of in-segment restenosis.

TABLE VI. INDEPENDENT PREDICTORS OF IN-SEGMENT RESTENOSIS

	Relative risk	95% CI	*P*-value
All groups			
DES implantation	0.20	0.12–0.32	<0.001
In-stent MLD after procedure	0.35	0.21–0.57	<0.001
Current smoker	1.75	1.11–2.75	0.016
DES group			
PES implantation	3.08	1.57–6.07	0.001
In-stent MLD after procedure	0.31	0.14–0.67	0.003
Lesion length per 10 mm	1.29	1.05–1.58	0.014

DES, drug-eluting stent; MLD, minimal luminal diameter; PES, paclitaxel-eluting stent.

Clinical follow-up information at 9 months was collected for all patients. After discharge, there were no cases of myocardial infarction in any of the three groups (Table IV). There were two postdischarge deaths in the SES group, one from a traffic accident and the other where an end stage renal disease patient experienced a rapid decline. Angiography showed no patients in any of the three groups had evidence of stent thrombosis. TLR was performed more frequently in the BMS group than that in the two DES groups, with the TLR rate being similar for both the PES and SES groups. Consequently, the 9-month MACE rate was lower in the two DES groups than that in the BMS group, and was similar for both DES groups. The MACE-free survival rate at 9 months was lower in the SES (87.0% ± 2.5%, $P = 0.002$) and PES (84.3% ± 2.8%, $P = 0.019$) groups than that in the BMS group (73.5% ± 3.3%), and was similar for the two DES groups ($P = 0.485$). The TLR-free survival curves at 9 months for the three groups are shown in Fig. 1.

DISCUSSION

This prospective nonrandomized multicenter study of long coronary lesion treatment demonstrated that, compared with conventional BMSs, DES implantation reduced the risk of clinical and angiographic restenosis without increment of stent thrombosis. Moreover, the SES was superior to the PES in terms of lower late luminal loss and angiographic restenosis.

The selected inclusion of long coronary lesions in this study resulted in a mean lesion length of 36 mm, which is longer than the lesions studied in recent clinical trials comparing the outcomes of two DESs, such as 19 mm in the SIRTAX study, 17 mm in the REALITY study, and 14 mm in the ISAR-DIABETES study [12,13,15]. Analysis of pooled data from 10 recent randomized studies comparing DESs and BMSs showed that stent length was strongly linked to the rate of stent thrombosis [19]. However, the present study found long DES implantation was safe and without any incidence of stent thrombosis. Relatively high rates of non-Q myocardial infarction in the three groups

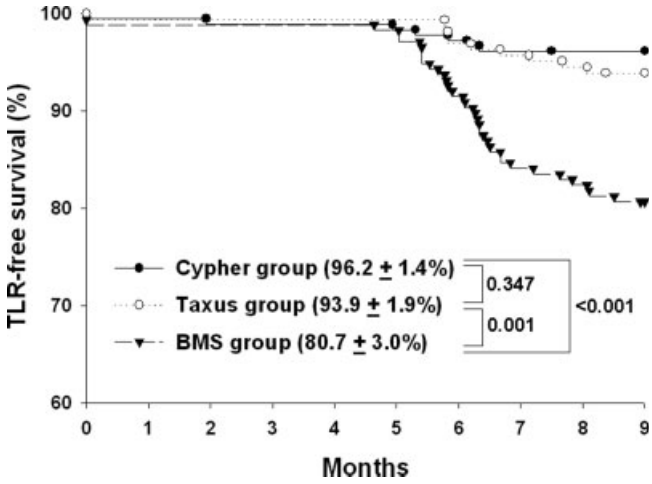

Fig. 1. Kaplan–Meier survival curves displaying cumulative rates of freedom from TLR during a 9-month follow-up. TLR = target lesion revascularization.

were resulted by the periprocedural cardiac enzyme elevation during the treatment of long segments. Strict recommendation of combined antiplatelet therapy for 6 months and use of IVUS-guided procedures may explain the lack of stent thrombosis in the current study [20–22]. In addition to the safety associated with the two DESs in the present study, use of these stents remarkably reduced the restenosis rate and the late luminal loss compared with the use of BMSs. The in-segment restenosis rate when using the SES and the PES was 83% and 50% less than that when using the BMS, respectively. This decrease in the occurrence of restenosis resulted in 9-month MACE rates being in the single digits after DES implantation in these long coronary lesions. This result was consistent with registry data showing the feasibility of DESs in very long coronary lesions [10,11].

The present study found that the SES was associated with a lower angiographic restenosis rate and a lower late luminal loss compared with that of the PES. These findings are consistent with recent randomized studies reporting that SESs provided superior angiographic benefits compared with those of PESs [12–14]. The SIR-TAX (6.7% vs. 11.9%, $P = 0.02$) and ISAR-DIABETES (6.9% vs. 16.5%, $P = 0.03$) studies reported lower in-segment restenosis rates when using the SES when compared with the use of PES when treating native coronary lesions [12,13]. Moreover, the ISAR-DESIRE study involving patients with in-stent restenosis also indicated that the SES was more effective than that of the PES in reducing the need for TLR (8.0% vs. 19.0%, $P = 0.02$) [14]. A metaanalysis of six head-to-head clinical trials showed that the SES was associated with a significantly lower risk of restenosis and TLR when compared with that of the PES [23]. However, there is still controversy surrounding the possible differing benefits of the different DESs. In the unpublished REALITY study and the small randomized TAXi study, the incidences of angiographic restenosis and adverse cardiac events were similar for both SESs and PESs [15,16].

Although the present study found the two DESs were associated with different restenosis rates, the mechanisms underlying this difference are yet to be identified. Less late luminal loss for the SES might be partly attributed to its lower restenosis rate when compared with that for the PES [24]. An alternative explanation is that the nonrandomized study design resulted in patient selection for PES implantation possibly biasing the outcomes. However, despite similar lesion and stent lengths for the two DES groups, the PES group had a larger reference vessel and achieved greater lumen gain—traditionally protective factors against restenosis—when compared with those of the SES group. These observations argue against selection bias explaining our data.

Despite the different angiographic outcomes, the SES and the PES did not differ in terms of the clinical endpoints of MACE and TLR. Only 10 (34%) of 29 restenoses in the PES group underwent TLR. This discrepancy between angiographic and clinical outcomes may be partly explained by our strategy that the decision to perform a TLR was clinically driven based upon careful observation of symptoms or objective evidence of ischemia. Otherwise, a small study population may not have enough statistical power to show significant differences between the two DESs in terms of clinical events.

Several potential limitations of the present study should be acknowledged. These include a nonrandomized study design, choice of treatment being influenced by patient and/or physician preference, and the institution's influence on selection of stent type or procedural technique. Furthermore, 6-month angiographic follow-up in a limited study population may influence the outcomes.

In conclusion, compared with the BMS, the DES dramatically reduced angiographic restenosis and the need for TLR, and did not increase the incidence of hazardous cardiac events when used for treatment of long coronary lesions. In addition, the SES appears superior to the PES in terms of angiographic outcomes in the treatment of such lesions.

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