Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 12, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.11.047

Randomized Trial of Optimal Treatment Strategies for In-Stent Restenosis After Drug-Eluting Stent Implantation

Hae-Geun Song, MD,* Duk-Woo Park, MD,* Young-Hak Kim, MD,* Jung-Min Ahn, MD,* Won-Jang Kim, MD,* Jong-Young Lee, MD,* Soo-Jin Kang, MD,* Seung-Whan Lee, MD,* Cheol Whan Lee, MD,* Seong-Wook Park, MD,* Seungbong Han, PHD,† In-Whan Seong, MD,‡ Nae-Hee Lee, MD,§ Bong-Ki Lee, MD,‖ Keun Lee, MD,¶ Seung-Wook Lee, MD,# Deuk-Young Nah, MD,** Seung-Jung Park, MD*

Seoul, Daejeon, Bucheon, Chuncheon, Kwangju, and Gyeongju, Korea

Objectives The purpose of this study is to compare the efficacy of the treatment strategies for in-stent restenosis (ISR) of drug-eluting stents (DES) according to the morphologic pattern of restenosis.

Background Optimal treatment strategies for ISR within DES have not been adequately addressed yet.

Methods Patients with ISR of DES were randomized according to the lesion length to compare outcomes of sirolimus-eluting stent (SES) versus cutting balloon angioplasty for focal type (≤10 mm) and SES versus everolimus-eluting stent (EES) for diffuse type (>10 mm). The primary endpoint was in-segment late loss at 9 months. Overall 162 patients, 96 with focal ISR and 66 with diffuse ISR, were enrolled.

Results In focal lesions, in-segment late loss was significantly higher in the cutting balloon group (n = 48) than in the SES group (n = 48; 0.25 mm, interquartile range [IQR]: −0.01 to 0.68 mm vs. 0.06 mm, IQR: −0.08 to 0.17 mm; p = 0.04). Consequently, in-segment restenosis rate tended to be higher in the cutting balloon group than in the SES group (20.7% vs. 3.1%, p = 0.06) with comparable incidences of the composite of death, myocardial infarction, or target vessel revascularization at 12 months of clinical follow up (6.3% vs. 6.3%, p > 0.99). In 66 cases of diffuse ISR, in-segment late loss (0.11 mm, IQR: −0.02 to 0.30 mm; vs. 0.00 mm, IQR: −0.08 to 0.25 mm; p = 0.64), in-segment restenosis rate (5.0% vs. 14.3%, p = 0.32), and the composite incidence of death, myocardial infarction, or target lesion revascularization (9.6% vs. 8.8%, p > 0.99) did not differ between SES group (n = 32) and EES group (n = 34).

Conclusions For lesions of focal DES restenosis, repeat implantation of SES is more effective in reducing late luminal loss and subsequent restenosis rate than cutting balloon angioplasty. For diffuse DES restenosis, implantation of SES or EES is comparably effective in terms of angiographic and clinical outcomes. (J Am Coll Cardiol 2012;59: 1093–100) © 2012 by the American College of Cardiology Foundation

Although drug-eluting stents (DES) have dramatically reduced the rates of restenosis compared with bare-metal stents (BMS), in-stent restenosis (ISR) of DES still exists, and it has become a clinically significant problem due to its considerable prevalence in complex coronary lesions (1,2). However, the optimal management strategy for DES restenosis remains undefined because clinical investigations have been hampered by the low incidence of DES restenosis. Moreover, determining a generalized optimal treatment strategy for DES restenosis is difficult because etiology is diverse and prognosis is different according to the morphologic pattern (3,4).

For the focal type ISR, cutting balloon angioplasty has been regarded as an attractive option because of its convenience, cost effectiveness, and safety in the era of BMS (5,6). However, few studies to date have compared repeat DES

From the *Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; †Division of Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; ‡Chungnam National University Hospital, Daejeon, Korea, §Soonchunhyang University Bucheon Hospital, Bucheon, Korea; ‖Kangwon National University Hospital, Chuncheon, Korea; ¶Seoul Veterans Hospital, Seoul, Korea; #Kwangju Christian Hospital, Kwangju, Korea; and the **Donguk University Gyeongju Hospital, Gyeongju, Korea. This study was supported by funds from the Cardiovascular Research Foundation, Seoul, Korea, and by a grant from the Korea Health 21 R&D Project, Ministry of Health and Welfare, Korea (0412-CR02-0704-0001). The authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 11, 2011; revised manuscript received October 18, 2011, accepted November 8, 2011.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
IQR = interquartile range
ISR = in-stent restenosis
MI = myocardial infarction
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

treatment with cutting balloon angioplasty in the focal type DES restenosis. Also, for the diffuse type ISR, there have been no studies comparing the new generation DES with the established first-generation DES. Therefore, the aim of this randomized clinical trial was to elucidate the optimal treatment option according to the morphologic pattern of ISR within DES; to compare the effectiveness of cutting balloon (Boston Scientific, Natick, Massachusetts) angioplasty with sirolimus-eluting stent (SES [Cypher Select, Cordis, Johnson & Johnson, Miami Lakes, Florida]) implantation for the focal restenosis, and to compare the effectiveness of everolimus-eluting stent (EES [XIENCE V, Abbott Vascular, Santa Clara, California]) with SES implantation for the diffuse restenosis.

Methods

Study design and population. This prospective, randomized, open-label, multicenter study was performed at 7 centers in South Korea between July 2008 and March 2011. The study protocol was approved by the institutional review board at each participating center. All patients provided written, informed consent for participation in this trial.

The eligible patients were consecutively enrolled with stable angina or acute coronary syndrome or inducible ischemia in the presence of restenosis ≥50% diameter stenosis in the stented segment with or without edge involvement by quantitative coronary angiography. Patients were excluded if they had acute ST-segment elevation myocardial infarction (MI) necessitating primary percutaneous coronary intervention; severely compromised ventricular dysfunction (ejection fraction <30%) or cardiogenic shock; allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, everolimus or sirolimus; left main coronary artery disease (defined as stenosis of >50%); chronic renal failure (serum creatinine level ≥2.0 mg/dl or dependence on dialysis); terminal illness; elective surgery planned within 6 months after the procedure, necessitating discontinuation of antiplatelet agent; participation in another coronary device study or inability to follow the protocol.

Randomization, procedures, and adjunct drug therapy. Patients who met the inclusion and exclusion criteria were randomized after diagnostic angiography and before angioplasty, with stratification by lesion length. Patients with ISR lesions ≤10 mm in length by visual estimation were enrolled in the "focal ISR cohort" and were randomly assigned 1:1, using an interactive web response system, to receive either SES implantation or cutting balloon angioplasty. In contrast, patients with ISR length >10 mm were enrolled in the "diffuse ISR cohort" and randomly allocated to SES or EES implantation. The allocation sequence was computer-generated and further stratified according to participating center. Patients, but not investigators, were unaware of the treatment assignment.

All procedures were performed with standard interventional techniques. Cutting balloon dilation using cutting balloons of 10 mm to 15 mm in length with the same or 0.25 mm to 0.5 mm larger diameter than the reference vessel was attempted in all ISR lesions at the recommended maximal pressure of 8 to 12 atm with or without additional balloon inflation. Balloon angioplasty was regarded as successful if the final residual stenosis was <30% with TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 and absence of serious dissection. If the balloon angioplasty was ultimately unsuccessful, additional stenting was attempted at the operator's discretion. The number and lengths of stents to be implanted were at the operator's discretion, but the recommendation was to fully cover the restenotic lesion. The choice of direct stenting or stenting after predilation was at the operator's discretion. It was recommended that all procedures were guided by intravascular ultrasonography.

During the coronary intervention, patients received anticoagulation therapy with unfractionated heparin. Use of adjunctive devices or glycoprotein IIb/IIIa inhibitors was at the operator's discretion. All patients were pretreated with aspirin. Patients who were not already on a maintenance dose of clopidogrel after the initial stent implantation were also administered a loading dose of 300 mg of clopidogrel within 12 h before the procedure. After intervention, patients received aspirin (100 mg daily) indefinitely and clopidogrel (75 mg daily) for at least 6 months after DES implantation. Standard post-intervention care was recommended for all patients (7).

Study endpoints and definitions. The primary endpoint of this study was late luminal loss in the analysis segment 9 months after the index procedure. The secondary endpoints were angiographic parameters including binary restenosis, in-stent late loss at 9 months, and clinical outcomes including death, MI, target lesion revascularization (TLR), target vessel revascularization (TVR), stent thrombosis, and composite of major adverse cardiac events, including death, MI, and TVR within 12 months.

All deaths were considered to have been from cardiac causes unless a noncardiac cause could be identified. Myocardial infarction was defined as an elevation of creatine kinase-myocardial band (CK-MB) or troponin to the upper reference limit, and periprocedural MI was defined as an elevation of CK-MB or troponin to at least 3 times the upper reference limit during the first 48 h after percutaneous coronary intervention (8). Target lesion revascularization and TVR were defined as any revascularization procedure involving target lesion and target vessel due to luminal narrowing in the presence of symptoms or objective signs of ischemia. Stent thrombosis was defined as definite or probable thrombosis by the Academic Research Consortium

definitions (9). Device success was defined as final stenosis of <30% of the vessel diameter after treatment.

Patient follow-up and data management. A 12-lead electrocardiogram was obtained and CK and its MB isoenzyme levels were measured before and at both 8 to 16 h and 18 to 24 h after the procedure. Clinical follow-up was scheduled at 30 days, 6 months, and 12 months after the procedure with monitoring of clinical status, rehospitalizations or recatheterization, cardiac-related medications, and occurrence of adverse events. All eligible patients were asked to return for an angiographic follow-up 9 months after the procedure, or earlier if anginal symptoms occurred.

Clinical, angiographic outcome and procedural data were collected using a dedicated electronic case report form by specialized personnel at the clinical data management center. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee, whose members were blinded to the assigned treatment. An independent data and safety monitoring board reviewed the data periodically to identify potential safety issues, but there were no formal stopping rules.

Quantitative coronary angiography. Coronary angiograms were digitally recorded at baseline, immediately after the procedure, and at follow-up, and were assessed off line in the angiographic core laboratory (Asan Medical Center, Seoul, Korea) using an automated edge-detection system (CAAS V, Pie Medical Imaging, Maastricht, the Netherlands) by experienced assessors. All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin. Standard qualitative and quantitative analyses and definitions were used for angiographic analysis (10). All quantitative angiographic measurements were obtained within the stented segment (in-stent) and over the entire segment including the stent and its 5 mm proximal and distal margins (in-segment). Angiographic variables included absolute lesion length, stent length, reference vessel diameter, minimum lumen diameter, percent diameter stenosis, binary restenosis rate, immediate gain, late loss, and patterns of recurrent restenosis. The reference diameter was determined by interpolation. Binary restenosis was defined as percent diameter stenosis of 50% or greater on follow-up angiography, and patterns of angiographic restenosis were quantitatively assessed with the Mehran classification (11).

Statistical analysis. Sample size was calculated separately for the focal and diffuse ISR cohorts with the same primary endpoint of in-segment late loss. In the focal ISR cohort, we assumed a mean in-segment late loss of 0.25 ± 0.3 mm in the SES group and 0.5 ± 0.3 mm in the cutting balloon angioplasty group (12–15). Using 2-sided α-level of 0.05 and a statistical power of 90%, expecting approximately 25% of the patients would not receive follow-up angiography, a total of 90 patients (n = 45 per group) was needed. In the diffuse ISR cohort, we assumed a mean in-segment late loss of 0.5 ± 0.3 mm in the SES group, and 0.2 ± 0.3 mm in the EES group (16,17). Using 2-sided α-level of 0.05 and a statistical power 90%, expecting approximately 25% of the patients would not receive follow-up angiography, a total of 60 patients (n = 30 per group) was needed to fulfill the primary endpoint. Sample size was calculated with the use of PASS software (NCSS, Kaysville, Utah).

All analyses were based on the intention-to-treat principle. The statistician was blinded to treatment options in each cohort during statistical analysis. All values are expressed as the median (interquartile range [IQR]) for continuous variables or as counts and percentages for categorical variables. Differences in clinical, angiographic, procedural characteristics, and outcomes between treatment groups were evaluated by the Mann-Whitney *U* test for continuous variables and by the chi-square test or Fisher's exact test for categorical variables. Cumulative frequency distribution curves in each group were compared with Kolmogorov-Smirnov test. To adjust the baseline angiographic findings of each group, a multivariable regression model was constructed using angiographic covariates with $p < 0.1$. To carry out the multivariable regression analysis, the robust linear regression model and the generalized linear model with gamma distribution were fitted (18).

All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, North Carolina) and R software, version 2.10.1, by a statistical analyst who was unaware of the type of stent implanted. A 2-sided p value of <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics and procedural results. In the focal cohort, a total of 96 patients was randomly assigned to receive SES (n = 48) or cutting balloon angioplasty (n = 48). In the diffuse cohort, a total of 66 patients was randomly assigned to receive SES (n = 32) or EES (n = 34). Table 1 shows the baseline clinical characteristics of the study population. The lesion and procedural characteristics are shown in Table 2. Most of clinical, lesion, and procedural characteristics were well matched between the 2 groups in both the focal and the diffuse ISR cohorts.

Angiographic outcomes. FOCAL ISR COHORT. Quantitative angiographic results at baseline, post-procedure, and at follow-up in the focal cohort are shown in Tables 3 and 4. Device success rates were 95.8% in the cutting balloon group and 100% in the SES group (p = 0.16). Follow-up angiography was performed in 29 patients (60%) in the cutting balloon group and 32 patients (67%) in the SES group (p = 0.58) at the median of 276 days (IQR: 261 to 308 days) in the SES group and 282 days (IQR: 271 to 339 days) in the cutting balloon group (p = 0.23) after the procedure, respectively. Between patients with and without angiographic follow-up, clinical or procedural characteristics did not differ. Immediately after the procedure, in-segment acute gain was similar between the 2 groups (SES 1.91 mm, IQR: 1.55 to 2.21 mm; vs. cutting balloon group 1.66 mm,

JACC Vol. 59, No. 12, 2012
March 20, 2012:1093–100

Table 1 Baseline Clinical Characteristics of the Patients

	Focal Lesion (≤10 mm)			Diffuse Lesion (>10 mm)		
	SES Group (n = 48)	CBA Group (n = 48)	p Value	SES Group (n = 32)	EES Group (n = 34)	p Value
Age, yrs	61.5 (55.3–66.8)	65.0 (57.3–70.0)	0.11	60.5 (54.3–67.0)	65.0 (54.7–69.0)	0.33
Male	35 (72.9)	36 (75.0)	0.87	15 (46.9)	19 (55.9)	0.63
Diabetes mellitus	18 (37.5)	15 (31.2)	0.36	8 (25.0)	12 (35.3)	0.63
Hypertension	28 (58.3)	32 (66.7)	0.63	18 (56.3)	19 (55.8)	0.98
Hyperlipidemia	25 (52.1)	25 (52.1)	1.00	22 (66.8)	30 (75.0)	0.07
Smoking	16 (33.3)	23 (47.9)	0.43	2 (6.3)	6 (17.6)	0.26
Previous myocardial infarction	8 (16.7)	2 (4.2)	0.15	4 (12.5)	3 (8.8)	0.71
Left ventricular ejection fraction, %	60.0 (60.0–65.0)	60.0 (55.0–64.0)	0.06	60.0 (57.8–61.0)	60.0 (55.0–64.3)	0.85
Multivessel disease	12 (25.0)	15 (31.2)	0.75	8 (25.0)	12 (35.3)	0.63
Clinical indication			0.47			0.08
Stable angina	32 (66.7)	37 (77.1)		15 (46.8)	23 (67.6)	
Acute coronary syndrome	16 (31.3)	11 (22.9)		17 (53.1)	11 (32.4)	

Values are median (IQR) or n (%).
CBA = cutting balloon angioplasty; EES = everolimus-eluting stent(s); SES = sirolimus-eluting stent(s).

IQR: 1.37 to 2.05 mm). (Fig. 1) As a primary study endpoint, in-segment late loss was lower in the SES group (0.06 mm, IQR: −0.08 to 0.17 mm]) than in the cutting balloon group (0.25 mm, IQR: −0.01 to 0.68 mm; p = 0.04). (Fig. 2) When the primary endpoint was fitted in the regression model with angiographic covariates, the regression coefficient for in-segment late loss was −1.31 (95% confidence interval: −1.86 to −0.75; p = 0.02) for cutting balloon angioplasty compared with SES. These trends of the result were not changed even after the angiographic covariate adjustments in the multivariate regression analysis. Accordingly, at follow-up, the SES group had larger in-

Table 2 Baseline Lesion and Procedural Characteristics

	Focal Lesion (≤10 mm)			Diffuse Lesion (>10 mm)		
	SES Group (n = 48)	CBA Group (n = 48)	p Value	SES Group (n = 32)	EES Group (n = 34)	p Value
Lesion characteristics						
Target vessel			0.32			0.28
Left anterior descending	28 (58.3)	28 (58.3)		18 (56.3)	23 (67.6)	
Left circumflex	2 (4.2)	6 (12.5)		1 (3.1)	3 (8.8)	
Right coronary	18 (37.5)	14 (29.2)		13 (40.6)	8 (23.5)	
Bifurcation lesions	10 (20.8)	12 (25.0)	0.85	4 (12.5)	5 (14.7)	0.99
Ostial lesion	6 (12.5)	2 (4.2)	0.23	3 (9.4)	3 (8.8)	0.94
Calcification	2 (4.2)	4(8.3)	0.70	2 (6.3)	5 (14.7)	0.43
Stent fracture	0	0	NA	0	0	NA
Angiographic pattern of restenosis*						
Focal			0.13			
IA (articulation or gap)	0	0		—	—	
IB (margin)	13 (27.1)	7 (14.6)		—	—	
IC (focal body)	24 (50.0)	35 (72.9)		—	—	
ID (multifocal)	11 (22.9)	6 (12.5)		—	—	
Diffuse						0.96
II (intrastent)	—	—		19 (59.4)	19 (55.9)	
III (proliferative)	—	—		8 (25.0)	9 (26.5)	
IV (total occlusion)	—	—		5 (15.6)	6 (17.6)	
Procedural characteristics						
Diameter of balloon or stent, mm	3.0 (3.0–3.5)	3.0 (2.9–3.5)	0.28	3.5 (3.0–3.5)	3.5 (3.0–3.5)	0.09
Maximal pressure of balloon or stent, atm	15.0 (12.0–18.0)	10.0 (10.0–14.0)	0.61	16.0 (12.0–19.5)	13.5 (10.0–18.0)	0.19
Glycoprotein IIb/IIIa antagonists	0	0	NA	0	0	NA
Number of stents	1.0 (1.0–1.0)	—		1.0 (1.0–1.75)	1.0 (1.0–2.0)	0.16
Length of stents, mm	18.0 (13.0–23.0)	—		28.0 (23.0–33.0)	28.0 (23.0–28.0)	0.16

Values are n (%) or median (interquartile range). *Classified using the Mehran criteria (13).
NA = not available; other abbreviations as in Table 1.

Table 3 Quantitative Angiographic Analysis Pre-Procedure and Post-Procedure

	Focal Lesion (≤10 mm)			Diffuse Lesion (>10 mm)		
	SES Group (n = 48)	CBA Group (n = 48)	p Value	SES Group (n = 32)	EES Group (n = 34)	p Value
Before procedure						
Lesion length, mm	8.63 (6.45–12.25)	7.45 (4.70–8.72)	0.03	22.24 (16.34–27.96)	22.46 (15.40–35.95)	0.89
Reference vessel diameter, mm	3.18 (2.83–3.40)	2.93 (2.72–3.23)	0.05	3.19 (2.83–3.48)	3.43 (3.08–3.71)	0.08
Minimal luminal diameter, mm	0.68 (0.50–0.86)	0.80 (0.53–1.00)	0.09	0.94 (0.55–1.27)	0.75 (0.37–1.27)	0.43
Diameter stenosis, %	78.0 (70.3–83.0)	72.0 (63.0–81.0)	0.09	71.5 (55.3–83.3)	72.0 (62.8–89.3)	0.19
Immediately after procedure						
Minimal luminal diameter, mm						
In segment	2.62 (2.23–2.84)	2.54 (2.04–2.79)	0.42	2.30 (2.19–2.64)	2.43 (2.02–2.93)	0.65
In stent	2.78 (2.45–3.02)	2.68 (2.23–2.96)	0.30	2.78 (2.49–3.00)	2.87 (2.47–3.32)	0.65
Diameter stenosis, %						
In segment	6.0 (5.0–12.8)	7.0 (6.0–9.0)	0.40	18.0 (12.0–23.8)	18.0 (10.5–25.0)	0.36
In stent	4.0 (3.0–6.75)	5.0 (4.0–7.0)	0.03	6.0 (4.0–9.75)	7.0 (3.8–11.0)	0.55
Acute gain, mm						
In segment	1.91 (1.55–2.21)	1.66 (1.37–2.05)	0.10	1.43 (0.96–1.97)	1.48 (0.99–2.32)	0.36
In stent	2.09 (1.68–2.35)	1.81 (1.51–2.17)	0.05	1.93 (1.28–2.35)	1.89 (1.41–2.66)	0.32

Values are median (IQR).
Abbreviations as in Table 1.

stent minimal luminal diameter and lower in-stent diameter stenosis than the cutting balloon group. Subsequently, there was tendency toward higher angiographic in-segment restenosis rate in the cutting balloon group (20.7%) than in the SES group (3.1%, p = 0.06). (Table 4).

DIFFUSE ISR COHORT. In the diffuse cohort, baseline clinical and angiographic characteristics were similar between both groups. Device success rates were 97.9% for SES and 95.7% for EES group (p = 0.16). Follow-up angiography was performed in 20 patients (62.5%) in the SES group and 21 patients (62.0%) in the EES group (p = 0.91) at the median of 302 days (IQR: 274 to 384 days) in the SES group and 272 days (IQR: 219 to 286 days) in the EES group (p = 0.17). Patients' clinical and procedural characteristics were not different between patients with and without follow-up angiography. Immediately after the procedure, in-segment acute gain was similar between the 2 groups (SES 1.43 mm, IQR: 0.96 to 1.97 mm; cutting balloon group 1.48 mm, IQR: 0.99 to 2.32 mm; p = 0.36). (Fig. 1) As a primary study endpoint, in-segment late luminal loss were comparable between the SES group (0.11 mm, IQR: −0.02 to 0.30 mm) and the EES group (0.00 mm, IQR: −0.08 to 0.25 mm; p = 0.64) (Fig. 2) When the primary endpoint was fitted in the regression model with the angiographic covariates, the regression coefficient of EES for in-segment late loss was 0.81 (95% confidence interval: −0.40 to 2.02; p = 0.50) compared with SES. These trends of the result were not changed even after adjustments in the multivariate regression analysis. The rates of angiographic in-segment restenosis were 5.0%

Table 4 Quantitative Angiographic Analysis at 9-Month Follow-Up

	Focal Lesion (≤10 mm)			Diffuse Lesion (>10 mm)		
	SES Group (n = 48)	CBA Group (n = 48)	p Value	SES Group (n = 32)	EES Group (n = 34)	p Value
Late luminal loss, mm						
In segment	0.06 (−0.08 to 0.17)	0.25 (−0.01 to 0.68)	0.04	0.11 (−0.02 to 0.30)	0.00 (−0.08 to 0.25)	0.64
In stent	0.02 (−0.09 to 0.10)	0.30 (0.08 to 0.80)	<0.001	0.13 (−0.01 to 0.36)	0.07 (−0.01 to 0.35)	0.88
Minimal luminal diameter, mm						
In segment	2.37 (2.13 to 2.74)	2.13 (1.42 to 2.55)	0.04	2.17 (2.00 to 2.40)	2.30 (2.00 to 2.78)	0.45
In stent	2.57 (2.31 to 2.89)	2.08 (1.58 to 2.61)	0.002	2.58 (2.30 to 2.87)	2.71 (2.36 to 2.98)	0.58
Diameter stenosis, %						
In segment	12.5 (4.5 to 24.5)	16.5 (8.3 to 42.3)	0.04	25.0 (9.0 to 36.3)	18.0 (13.0 to 31.0)	0.88
In stent	5.5 (1.0 to 16.0)	16.0 (6.0 to 37.5)	0.001	16.0 (7.0 to 26.3)	18.0 (7.0 to 25.0)	0.81
Angiographic restenosis						
In segment	1 (3.1)	6 (20.7)	0.06	1 (5.0)	3 (14.3)	0.32
In stent	1 (3.1)	5 (17.2)	0.10	1 (5.0)	3 (14.3)	0.32

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

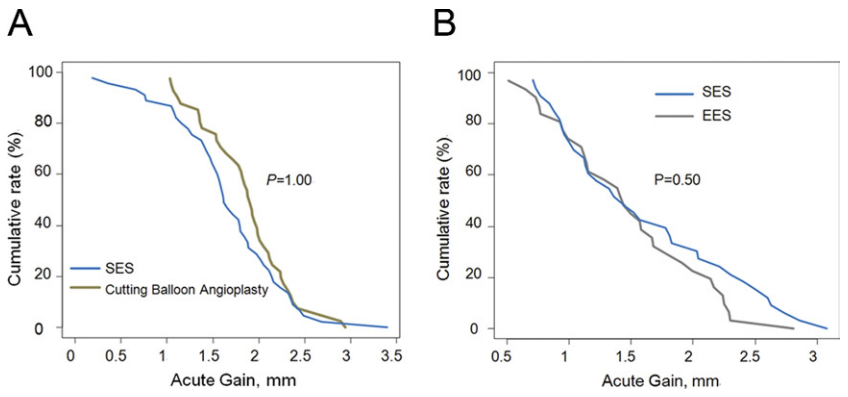

Figure 1 Cumulative Frequency Distribution Curves for In-Segment Acute Gain in Focal and Diffuse ISR Group

(A) Focal in-stent restenosis (ISR). **Blue line** = sirolimus-eluting stent(s) (SES); **brown line** = cutting balloon angioplasty. **(B)** Diffuse in-stent restenosis. **Blue line** = SES; **gray line** = everolimus-eluting stent(s) (EES).

in the SES group and 14.3% in the EES group (p = 0.32) (Table 4).

Clinical outcomes. Major clinical events during follow-up are shown in Table 5. Clinical follow-up at 1 month and 12 months were completed for all patients. In the focal cohort, the incidence of clinical events including major adverse cardiac events and individual endpoints of major adverse cardiac events at 1 and 12 months did not differ between the SES and the cutting balloon group. Three patients in the cutting balloon group underwent repeated TLR, and 1 patient in the SES group had stent thrombosis during 12 months. In the diffuse cohort, the incidence of clinical events at 1 and 12 months was also similar between the SES and EES groups. During 12 months of follow-up, in the SES group, 1 patient died (18 days after procedure) of cardiac causes, and 1 patient underwent repeated TLR. In the EES group, 2 patients underwent repeat TLR, and there was no death or stent thrombosis.

Discussion

This randomized trial was designed to compare the efficacy of the treatment strategies for ISR of DES according to the morphologic pattern of restenosis, known as the most important predictor of clinical outcomes. In the cases of focal type DES restenosis, repeat implantation of SES showed more effective trend for preventing late luminal loss compared to cutting balloon angioplasty. However, in the cases of diffuse type DES restenosis, SES and EES implantation showed similar angiographic and clinical outcomes.

In the era of BMS, the angiographic pattern of restenosis was prognostically important to predict TLR (11). Similarly, the angiographic pattern of restenosis after DES implantation has also been considered an important predictor of long-term angiographic and clinical outcomes (4,19,20). On the basis of these studies, it was proposed that short DES placement or balloon angioplasty using the

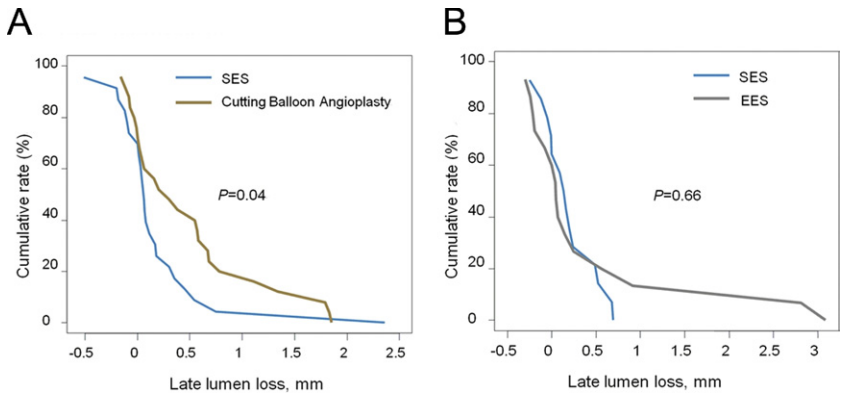

Figure 2 Cumulative Frequency Distribution Curves for In-Segment Late Luminal Loss in Focal and Diffuse ISR Groups

(A) Focal in-stent restenosis (ISR). **Blue line** = sirolimus-eluting stent(s) (SES); **brown line** = cutting balloon angioplasty. **(B)** Diffuse in-stent restenosis. **Blue line** = SES; **gray line** = everolimus-eluting stent(s) (EES).

Table 5 Clinical Events at 1-Month and 12-Month Follow-Up

	Focal Lesion (≤10 mm)			Diffuse Lesion (>10 mm)		
	SES Group (n = 48)	CBA Group (n = 48)	p Value	SES Group (n = 32)	EES Group (n = 34)	p Value
Follow-up at 1 month						
Death	0	0	NA	1 (3.1)	0	0.49
Myocardial infarction	2 (4.3)	0	0.26	1 (3.1)	1 (2.9)	1.00
Death or myocardial infarction	2 (4.3)	0	0.26	2 (6.2)	1 (2.9)	0.61
Stent thrombosis	1 (2.1)	0	0.50	0	0	NA
Target lesion revascularization	0	1 (2.1)	0.50	0	0	NA
Target vessel revascularization	0	1 (2.1)	0.50	0	0	NA
Major adverse cardiac events	2 (4.3)	1 (2.1)	0.63	2 (6.2)	1 (2.9)	0.61
Follow-up at 12 months						
Death	0	0	NA	1 (3.1)	0	0.49
Myocardial infarction	3 (6.3)	0	0.13	1 (3.1)	1 (2.9)	1.00
Death or myocardial infarction	3 (6.3)	0	0.13	2 (6.2)	1 (2.9)	0.61
Stent thrombosis	1 (2.1)	0	0.48	0	0	NA
Target lesion revascularization	0	3 (6.3)	0.27	1 (3.1)	2 (5.8)	0.59
Target vessel revascularization	0	3 (6.3)	0.27	1 (3.1)	2 (5.8)	0.59
Major adverse cardiac events*	3 (6.3)	3 (6.3)	1.00	3 (9.6)	3 (8.8)	1.00

Values are n (%). *The pre-specified major adverse cardiac events were defined as a composite of all-cause death, myocardial infarction, and target vessel revascularization.
Abbreviations as in Tables 1 and 2.

cutting, scoring or drug-eluting balloon was recommended for the treatment of focal type ISR. On the contrary, for diffuse type of DES restenosis, repeat DES placement or bypass surgery was recommended (3). However, there have been few randomized studies comparing treatment modalities according to angiographic patterns. We compared cutting balloon angioplasty with repeat DES implantation in the focal type of DES restenosis cohort because cutting balloon may have better efficacy to extrude fibrous residual neointimal plaque out of the stent strut and also have some procedural advantages, such as use of fewer balloons, less requirement for additional stenting and lower incidence of balloon slippage compared with plain balloon angioplasty (6,21). In our study of the focal restenosis cohort, late luminal loss in the analysis segment, which was primary endpoint, was lower in the SES group (0.06 mm, IQR: −0.08 to 0.17 mm) than in the cutting balloon group (0.25 mm, IQR: −0.01 to 0.68 mm) with numerically lower restenosis rate in the SES group (3.1%) compared to the cutting balloon group (20.7%). This result indicates that repeat implantation of DES is still more effective than cutting balloon angioplasty in reducing neointimal hyperplasia and preventing recurrent restenosis even for focal type DES restenosis.

The lack of benefit of cutting balloon angioplasty even for focal DES restenosis was contrasted with the results of BMS restenosis. For focal BMS restenosis, cutting balloon angioplasty showed comparable or more effective outcomes compared with BMS reimplantation or plain balloon angioplasty (5,22,23). The reasons for the differential effectiveness of cutting balloon angioplasty in patients with DES and BMS restenosis are not clear. However, theoretically, it may be related with the different tissue components, and subsequently different tissue reaction after balloon inflation, between DES and BMS restenosis. Studies using the pathologic specimen of stent restenosis reported that neoatherosclerosis was more frequently observed in DES restenosis and occurred earlier than in BMS restenosis (24–26). It might be considered that those pathologic characteristics of DES restenosis could have more aggressive responses during surgical cutting of neointima than BMS restenosis.

With regard to the diffuse type DES restenosis, there have been few studies comparing the first-generation DES with new-generation DES. In this study, we demonstrated statistically comparable late luminal loss and angiographic restenosis rate between the 2 different types of DES. Previous studies have been considered repeat SES treatment for diffuse DES restenosis is more effective compared to repeat paclitaxel-eluting stent implantation, plain balloon angioplasty and brachytherapy (27–29). However, we hypothesized that the reduced strut thickness and a thinner polymer coating in conjunction with improved biocompatibility of polymer of the EES would have more favorable effect on neointimal hyperplasia than SES. In contrast, however, in-segment late luminal loss at 9 months was comparable between the SES group (0.11 mm, IQR: −0.02 to 0.30 mm) and the EES group (0.00 mm, IQR: −0.08 to 0.25 mm; $p = 0.64$) with comparable angiographic and clinical outcomes. Despite our small sample size, the favorable long-term outcomes we observed may have been due to the extensive use of intravascular ultrasonography (SES 89.3%, EES 100%; $p = 0.09$), even though we enrolled very long ISR lesions.

Study limitations. First, because of lower angiographic follow-up rates, a follow-up bias may have been introduced the results. However, because repeated angiographic follow-up of patients with DES restenosis is difficult in real world settings, our results may at least stand for the actual

outcomes of patients. Second, despite power calculation, our sample size was still underpowered to detect the minor differences in the angiographic and clinical outcomes across the different groups. However, this limitation may not hamper the value of our study because a large-scale study would be very difficult because of the very low incidence of DES restenosis. Third, we included the lesions depending on the angiographic findings without consideration of the ISR mechanism. Therefore, we cannot exclude the possibility that the mechanical factors of restenosis significantly contributed to the result, such as under-expansion or stent fracture. Because of these limitations of our study, a collaborative, larger multicenter study is required to provide the results of diverse treatment modalities of DES restenosis.

Conclusions

In the focal DES restenosis, repeat SES implantation is more effective for reducing late loss and subsequent angiographic restenosis than cutting balloon angioplasty. However, in the diffuse type DES restenosis, the second-generation EES is not more effective than the first-generation SES in improving angiographic or clinical outcomes.

Reprint requests and correspondence: Dr. Seung-Jung Park, Department of Cardiology, University of Ulsan College of Medicine, Cardiac Center, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sjpark@amc.seoul.kr.

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Key Words: angioplasty ■ coronary disease ■ stent.