JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 4, NO. 2, 2011

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2010.10.012

CLINICAL RESEARCH

Effectiveness of Paclitaxel-Eluting Balloon Catheter in Patients With Sirolimus-Eluting Stent Restenosis

Seiji Habara, MD, Kazuaki Mitsudo, MD, Kazushige Kadota, MD, Tsuyoshi Goto, MD, Satoki Fujii, MD, Hiroyuki Yamamoto, MD, Harumi Katoh, MD, Naoki Oka, MD, Yasushi Fuku, MD, Shingo Hosogi, MD, Akitoshi Hirono, MD, Takeshi Maruo, MD, Hiroyuki Tanaka, MD, Yoshikazu Shigemoto, MD, Daiji Hasegawa, MD, Hiroshi Tasaka, MD, Mana Kusunose, MD, Suguru Otsuru, MD, Yoji Okamoto, MD, Naoki Saito, MD, Yuki Tsujimoto, MD, Haruki Eguchi, MD, Koshi Miyake, MD, Mitsuru Yoshino, MD

Kurashiki, Japan

Objectives The aim of this study was to investigate the efficacy of a paclitaxel-eluting balloon (PEB) for the treatment of sirolimus-eluting stent (SES) restenosis.

Background Because drug-eluting stents (DES) are being used in increasingly complicated settings, DES restenosis is no longer an uncommon phenomenon, and its optimal treatment is unknown.

Methods This study was a prospective single-blind randomized trial conducted in 50 patients with SES restenosis. Patients were randomly assigned to a PEB group (n = 25) or a conventional balloon angioplasty (BA) group (n = 25). The primary end point was late lumen loss at 6-month follow-up. Secondary end points included the rate of binary restenosis (in-segment analysis) and major adverse cardiac events (MACE) at 6-month follow-up.

Results At 6-month angiographic follow-up (follow-up rate: 94%), in-segment late lumen loss was lower in the PEB group than in the BA group (0.18 ± 0.45 mm vs. 0.72 ± 0.55 mm; p = 0.001). The incidence of recurrent restenosis (8.7% vs. 62.5%; p = 0.0001) and target lesion revascularization (4.3% vs. 41.7%; p = 0.003) was also lower in the PEB group than in the BA group. The cumulative MACE-free survival was significantly better in the PEB group than in the BA group (96% vs. 60%; p = 0.005).

Conclusions In patients with SES restenosis, PEB provided much better clinical, angiographic outcomes than conventional BA. (J Am Coll Cardiol Intv 2011;4:149–54) © 2011 by the American College of Cardiology Foundation

From the Department of Cardiology, Kurashiki Central Hospital, Kurashiki, Japan. All authors have reported that they have no relationships to disclose.

Manuscript received August 10, 2010; revised manuscript received October 14, 2010, accepted October 17, 2010.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 4, NO. 2, 2011
FEBRUARY 2011:149–54

Drug-eluting stents (DES) have dramatically reduced the restenosis risk compared with bare-metal stents (BMS) and conventional balloon angioplasty (BA) (1,2). Because DES are being used in increasingly complicated settings, DES restenosis is no longer an uncommon phenomenon, and its optimal treatment is unknown. Recently, DES have come to be considered the standard treatment for coronary in-stent restenosis (ISR). However, recent studies with DES have demonstrated higher rates of recurrent restenosis and recurrent target lesion revascularization (TLR) when used for the treatment of DES restenosis compared with the treatment of de novo lesions (3–5). Furthermore, repeat stenting for DES restenosis is associated with a high risk of treatment failure (6). In a pilot prospective double-blind randomized trial, the treatment of BMS restenosis with a paclitaxel-eluting balloon (PEB) catheter revealed a surprisingly lower late lumen loss at 6 months and fewer major adverse cardiac events (MACE) for up to 2 years compared with conventional BA (7,8). However, currently no data are available to support PEB in the treatment of DES restenosis. The aim of this study was to investigate the efficacy of PEB for the treatment of sirolimus-eluting stent (SES) restenosis.

Abbreviations and Acronyms

BA = balloon angioplasty
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
ISR = in-stent restenosis
MACE = major adverse cardiac event(s)
MLD = minimal lumen diameter
PEB = paclitaxel-eluting balloon
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Methods

Patient selection and study design. Patients with ISR after SES implantation treated at our institute between September 2008 and November 2009 were enrolled in this study. Eligible patients were not younger than 18 years of age and had clinical evidence of stable angina. Patients with acute coronary syndrome, severe renal insufficiency (glomerular filtration rate <30 ml/min), prior stent implantation within 6 months, severe concomitant systemic illness, and conditions likely to preclude follow-up angiography were excluded. The target lesion had to be the first ISR after SES implantation with a restenosis length of <26 mm in a vessel 2.5 to 3.5 mm in diameter. Lesions in the left main coronary artery and ostial, bifurcated, or totally occluded lesions were not regarded as target lesions.

Patients were randomly assigned to a PEB group or a conventional BA group by means of sealed envelopes containing a randomization schedule generated by a computer before the beginning of the study. This study was designed as a single-blind study, and the patients were blinded to the treatment assignment during the study. The study was conducted in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the institutional review board, and written informed consent was obtained from all patients before randomization. All patients were requested to undergo repeat angiography 6 months after a successful procedure.

Interventional procedure. All patients received prior treatment of aspirin (100 mg daily) and ticlopidine (200 mg/day)/clopidogrel (75 mg/day). Aspirin treatment was prescribed for life. Ticlopidine/clopidogrel treatment was recommended for at least 3 months. During interventions, heparin was administered to maintain an activated clotting time of more than 250 s. Pre-dilation was performed at all sites of ISR lesions. The recommended inflation time for PEB was 60 s. A paclitaxel-eluting PTCA balloon (SeQuent Please balloon catheter; B. Braun Melsungen AG, Vascular Systems, Berlin, Germany) was available in 15-, 20-, 26-, and 30-mm lengths and in diameters of 2.5, 3.0, and 3.5 mm.

Angiographic analysis. Serial coronary angiography was performed at baseline (before and after intervention) and at 6-month follow-up. Quantitative coronary angiographic analysis was performed with QCA-CMS (Medis Medical Imaging Systems, Leiden, the Netherlands). All angiograms were analyzed in a random sequence by 2 experienced observers who were blinded to the clinical characteristics of the patients. Coronary angiograms were obtained in multiple views after intracoronary nitrate. Reference diameter, minimal lumen diameter (MLD), percentage diameter stenosis, and lesion length were measured before and after intervention and at follow-up. Acute gain was defined as MLD immediately after the procedure minus MLD at baseline. Late lumen loss was defined as MLD immediately after the procedure minus MLD at angiographic follow-up. Measurements included the stenotic area (from shoulder to shoulder where the balloon was dilated; in-lesion analysis) and the total treated area plus 5 mm of the edge (in-segment analysis).

Follow-up and definition. Clinical and angiographic follow-up was performed routinely 6 months after a successful procedure. The follow-up angiogram was obtained earlier if clinically indicated. Binary restenosis at follow-up was defined as a stenosis occupying more than 50% of diameter. The ISR was classified as focal (type I, ≤10 mm in length), diffuse (type II, >10 mm in length), proliferative (type III, >10 mm in length and extending outside the stent), or totally occluded (type IV) according to the Mehran classification (9). The TLR was defined as any repeat percutaneous coronary intervention or aortocoronary bypass surgery due to restenosis (percentage diameter stenosis ≥50%) associated with symptoms or objective signs of ischemia. Death from any cause, nonfatal repeat acute myocardial infarction, and TLR were considered MACE. Stent thrombosis was defined according to Academic Research Consortium guidelines (10).

Study end points. The primary end point was late lumen loss at 6-month follow-up. Secondary end points included

the rate of binary restenosis (in-segment analysis) and MACE at 6-month follow-up.

Statistical analysis. Continuous variables are expressed as mean ± SD. Values are reported as numbers with relative percentage or SD. For continuous data, groups were compared with a parametric Student *t* test or a nonparametric Mann-Whitney *U* test according to the distribution of the data. Categorical variables were compared with a chi-square test. A p value of <0.05 was considered statistically significant. Survival curves were constructed by the Kaplan-Meier method. The SPSS statistical software (version 17.0, SPSS, Inc., Chicago, Illinois) was used for all statistical calculations.

Results

Baseline and procedural data. Fifty patients with ISR of SES were enrolled and randomly assigned to a PEB group (n = 25) or BA group (n = 25) (Fig. 1). Table 1 shows baseline clinical, angiographic, and procedural characteristics. No significant differences were observed in clinical characteristics between the 2 groups except for sex. Forty-two percent of the lesions had nonfocal ISR. The types of ISR in the PEB group were similar to those in the BA group. Post-intervention MLD was also similar (1.99 ± 0.26 mm vs. 2.00 ± 0.51 mm; p = 0.912) between the groups. Procedural success was obtained in all patients (100%). No major events occurred during hospital stay.

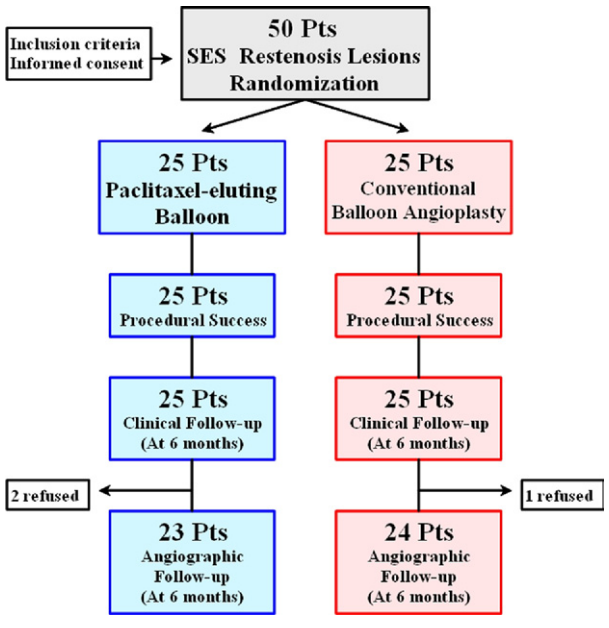

Figure 1. Flow Chart of Patients Enrolled in Trial and Patients Receiving Angiographic and Clinical Follow-Up

Pts = patients; SES = sirolimus-eluting stent(s).

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

	PEB Group (n = 25)	BA Group (n = 25)	p Value
Age, yrs	69.9 ± 11.0	68.9 ± 9.9	0.74
Male	19 (76)	24 (96)	0.049
Risk factors			
Diabetes mellitus	14 (56)	17 (68)	0.38
Hypertension	15 (60)	17 (68)	0.56
Hyperlipidemia	15 (60)	16 (64)	0.77
Current smoker	1 (4)	0 (0)	0.50
Previous MI	8 (32)	14 (56)	0.09
Target lesion			0.22
Left anterior descending	16 (64)	11 (44)	
Left circumflex	2 (8)	6 (24)	
Right	7 (28)	8 (32)	
Classification of ISR	0.67		
Type I	13 (52)	16 (64)	
Type II	9 (36)	8 (32)	
Type III	3 (12)	1 (4)	
Type IV	0 (0)	0 (0)	
Procedural characteristics			
Angiographic success	25 (100)	25 (100)	1.00
Pre-dilation			
Balloon diameter (mm)	2.78 ± 0.39	2.91 ± 0.48	0.39
Balloon length (mm)	16.0 ± 2.2	16.0 ± 3.0	0.91
Paclitaxel-eluting balloon			
Balloon diameter (mm)	2.74 ± 0.39		
Balloon length (mm)	20.5 ± 4.1		
TIMI flow grade 3 after procedure	25 (100)	25 (100)	1.00

Values are mean ± SD or n (%), unless otherwise indicated.
BA = conventional balloon angioplasty; ISR = in-stent restenosis; MI = myocardial infarction; PEB = paclitaxel-eluting balloon; TIMI = Thrombolysis In Myocardial Infarction.

Angiographic results. Follow-up angiography was performed in 47 patients at an average of 184 ± 27 days after intervention (follow-up rate: 94%); 3 remaining patients refused follow-up angiography. Quantitative coronary angiographic results are summarized in Table 2. The incidence of recurrent restenosis was 8.7% (2 of 23 lesions) in the PEB group and 62.5% (15 of 24 lesions) in the BA group (p = 0.0001) (Fig. 2). The incidence of TLR was 4.3% (1 of 23 lesions) in the PEB group and 41.7% (10 of 24 lesions) in the BA group (p = 0.003) (Fig. 2). The in-segment late lumen loss was lower in the PEB group than in the BA group (0.18 ± 0.45 mm vs. 0.72 ± 0.55 mm; p = 0.001). Recurrent restenosis occurred in 7 of 8 nonfocal restenosis lesions in the BA group and in 2 of 11 lesions in the PEB group (Fig. 2). With regard to both focal and nonfocal restenosis, the cumulative incidence in the PEB group was significantly lower than that in the BA group (Fig. 3).

Clinical outcomes. A complete clinical follow-up at 6 months was conducted for all 50 patients (100%). All

Table 2. Quantitative Coronary Angiographic Analysis Results

	PEB Group (n = 25)	BA Group (n = 25)	p Value
Before procedure			
Percentage diameter stenosis (%)	64.1 ± 9.9	68.4 ± 16.9	0.77
MLD	0.99 ± 0.32	0.92 ± 0.51	0.84
Reference diameter	2.69 ± 0.36	2.90 ± 0.47	0.11
Lesion length	12.7 ± 5.3	13.2 ± 5.5	0.66
After procedure			
Percentage diameter stenosis (%)	25.7 ± 7.2	31.0 ± 8.9	0.024
MLD	1.99 ± 0.26	2.00 ± 0.51	0.91
Reference diameter	2.74 ± 0.34	2.90 ± 0.46	0.25
Acute gain	1.03 ± 0.31	1.10 ± 0.54	0.71
6-month follow-up	23/25 (92%)	24/25 (96%)	
Percentage diameter stenosis (%)	34.2 ± 15.2	58.0 ± 22.7	0.0001
MLD (in-lesion)	1.82 ± 0.54	1.28 ± 0.80	0.010
MLD (in-segment)	1.81 ± 0.54	1.28 ± 0.80	0.011
Reference diameter	2.74 ± 0.36	2.98 ± 0.47	0.09
Late luminal loss (in-lesion)	0.17 ± 0.45	0.72 ± 0.56	0.001
Late luminal loss (in-segment)	0.18 ± 0.45	0.72 ± 0.55	0.001
Binary restenosis	2 (8.7)	15 (62.5)	0.0001
Target lesion revascularization)	1 (4.3)	10 (41.7)	0.003

Values are mean ± SD or n (%), and are given in millimeters, unless otherwise indicated.
MLD = minimal lumen diameter; abbreviations as in Table 1.

patients had received aspirin (100 mg/day) and ticlopidine (200 mg/day)/clopidogrel (75 mg/day) during the 6-month follow-up period. No death, myocardial infarction, or stent thrombosis occurred in any group. The Kaplan-Meier MACE-free survival curve is shown in Figure 4. The cumulative MACE-free survival was significantly better in the PEB group than in the BA group (log-rank test; p = 0.005). The MACE-free rate during 6-month follow-up in the PEB and BA groups was 96% and 60%, respectively, and all MACE were due to repeated revascularization procedures.

Discussion

This randomized study demonstrated that PEB for treatment of SES restenosis was effective and resulted in a low late lumen loss and a low incidence of recurrent restenosis.

In a previous study, Scheller et al. (7,8) treated BMS restenosis with PEB or conventional BA and compared the angiographic outcomes. Compared with conventional BA, PEB exhibited a significant reduction in 6-month late lumen loss and angiographic restenosis. In addition, PEB was associated with a significant reduction in MACE. There are no published data concerning the effects of PEB on DES restenosis. In our study, we found an incidence of angiographic restenosis of 8.7% and 62.5% (p = 0.0001) and a mean late lumen loss of 0.18 mm and 0.72 mm (p = 0.001) in the PEB and BA groups, respectively. In a previous randomized trial in patients with BMS restenosis, the angiographic restenosis rate was 6% to 7% and 51%, and the mean late lumen loss was 0.11 to 0.17 and 0.81 mm, in the PEB and conventional BA groups, respectively (7,8,11). The results of our study are consistent with those of the aforementioned publications. Our study suggests that PEB could be effective for different biological responses after DES restenosis.

Taking angiographic patterns of restenosis into consideration is important when assessing DES restenosis. Patients with a nonfocal pattern of DES restenosis have a higher rate of repeat DES implantation than those with a focal pattern (12). In our study, 42% of lesions were nonfocal restenosis. In nonfocal lesions, there was a highly significant difference in recurrent restenosis between the 2 groups (18% in the PEB group vs. 88% in the BA group; p =

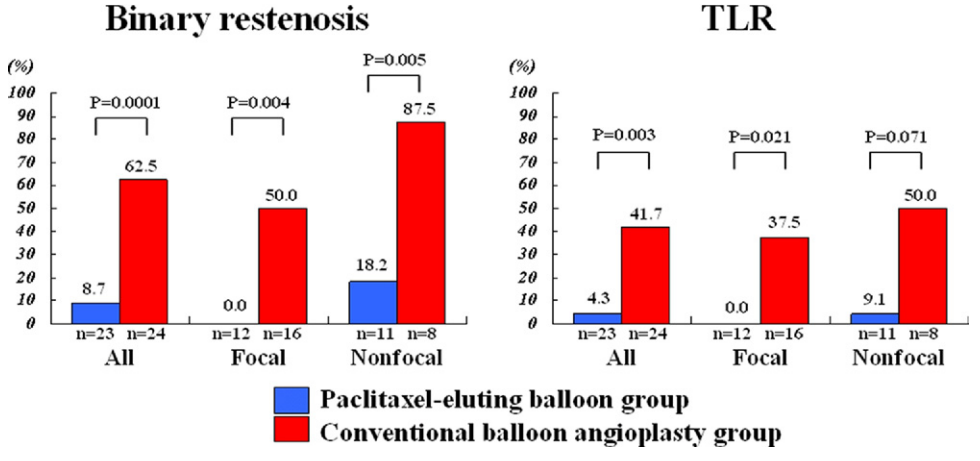

Figure 2. Angiographic Restenosis and TLR

TLR = target lesion revascularization.

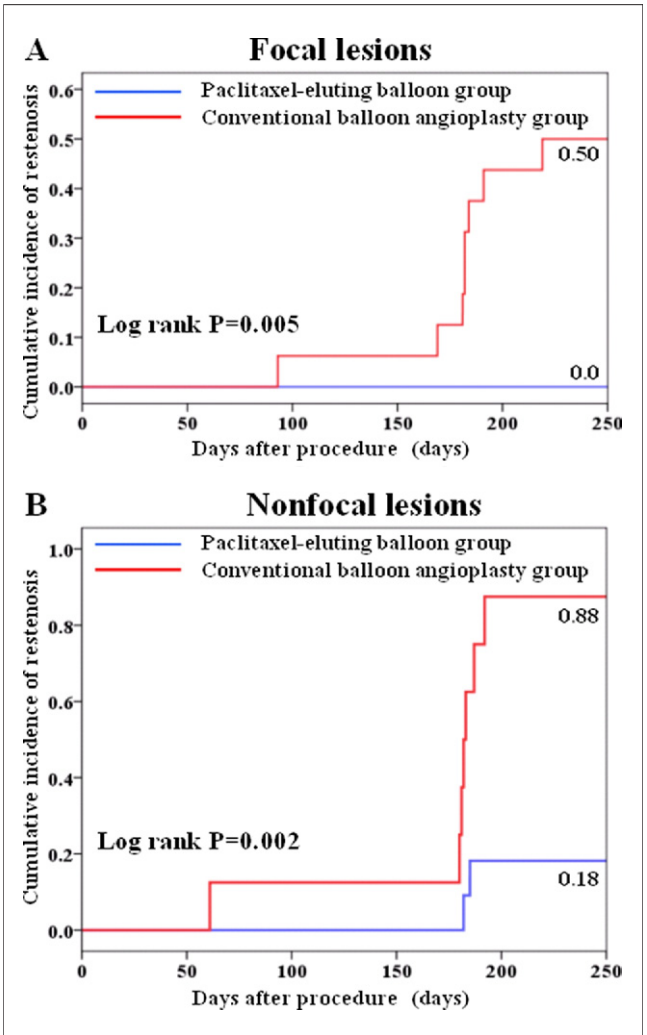

Figure 3. Cumulative Incidence of Restenosis During 6-Month Follow-Up Period

Cumulative incidence of restenosis during the 6-month follow-up period: focal **(A)** versus nonfocal **(B)** lesions.

0.005). In the PEB group, no recurrence was observed in focal restenosis. The PEB might be more effective for the treatment of nonfocal DES restenosis.

Post-DES restenosis is associated with poorer outcomes than post-BMS restenosis (13,14). The DES is an excellent treatment for patients with BMS restenosis but not always for patients with DES restenosis. The mechanisms of DES restenosis are similar to those of BMS restenosis, including stent underexpansion, stent fracture, stent malapposition, and nonuniform strut distribution (15–18). In addition, the particular mechanisms of DES restenosis include several drug-specific factors, such as localized hypersensitivity, nonuniform drug deposition, polymer disruption due to difficult stent delivery, and drug resistance (19).

A number of studies have investigated repeat DES implantation for patients with DES restenosis, and the procedure is currently considered an option for DES restenosis treatments. However, repeat stenting has the following limitations: 1) nonresorbable polymers trigger chronic inflammation and hypersensitivity reactions that might contribute to increased risks of late stent thrombosis and late restenosis (20,21); 2) repeat stenting might lead to uneven distribution of drug release and suboptimal stent geometry (18); 3) repeat stenting might cause insufficient stent expansion, which has been shown to be predictive of recurrent restenosis (22); and 4) repeat stenting is problematic because treatment of recurrent restenosis is limited, because of multiple layers of metal in the coronary artery. A PEB allows for immediate and homogenous drug transfer to the vessel wall without any polymers or sustained-release mechanism. The absence of a stent ensures that the original anatomy of the arteries is not altered. A PEB could be used multiple times if recurrent restenosis occurred. From this point of view, PEB might be the next preferred strategy for the treatment of DES restenosis.

Study limitations. This was a single-center randomized trial with a relatively small number of patients. In a pilot prospective double-blind randomized trial, PEB treatment was associated with fewer MACE than conventional BA at 6- to 24-month follow-ups (8). Therefore, we followed up our patients for 6 months. However, the optimal time point for evaluation of PEB efficacy for DES restenosis remains to be defined. The clinical and angiographic follow-ups were limited to 6 months, and further long-term information is eagerly awaited.

We regarded the patients receiving conventional BA as the control group in this study, because the optimal treatment strategy for DES restenosis has not yet been adequately defined. In a previous study with SES restenosis, the restenosis rate was 19% to 20%, and the mean late lumen loss was 0.38 to 0.40 mm in the repeat stenting group (23).

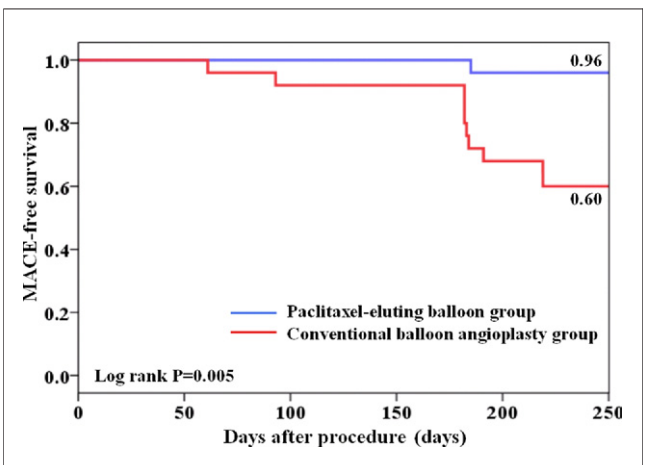

Figure 4. Kaplan-Meier MACE-Free Survival Curve for 6-Month Follow-Up

MACE = major adverse cardiac event(s).

This suggested that PEB could be more effective for DES restenosis than repeat stenting. However, we should conduct a randomized study to compare PEB with repeat stenting for the management of DES restenosis.

Conclusions

This randomized clinical study suggested that PEB provided much better clinical, angiographic outcomes than conventional BA in patients with SES restenosis.

Acknowledgment
The authors thank Noriko Makita (clinical research coordinator) for supporting this study.

Reprint requests and correspondence: Dr. Seiji Habara, Department of Cardiology, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki-shi, Okayama 710-8602, Japan. E-mail: sh10461@kchnet.or.jp.

REFERENCES

1. Holmes DR Jr., Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109:634–40.
2. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–23.
3. Cosgrave J, Melzi G, Corbett S, et al. Repeated drug-eluting stent implantation for drug-eluting stent restenosis: the same or a different stent. Am Heart J 2007;153:354–9.
4. Garg S, Smith K, Torguson R, et al. Treatment of drug-eluting stent restenosis with the same versus different drug-eluting stent. Catheter Cardiovasc Interv 2007;70:9–14.
5. Lee SS, Price MJ, Wong GB, et al. Early- and medium-term outcomes after paclitaxel-eluting stent implantation for sirolimus-eluting stent failure. Am J Cardiol 2006;98:1345–8.
6. Mishkel GJ, Moore AL, Markwell S, Shelton MC, Shelton ME. Long-term outcomes after management of restenosis or thrombosis of drug-eluting stents. J Am Coll Cardiol 2007;49:181–4.
7. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med 2006;355:2113–24.
8. Scheller B, Hehrlein C, Bocksch W, et al. Two-year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. Clin Res Cardiol 2008;97:773–81.
9. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8.
10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
11. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986–94.
12. Cosgrave J, Melzi G, Biondi-Zoccai GG, et al. Drug-eluting stent restenosis: the pattern predicts the outcome. J Am Coll Cardiol 2006;47:2399–404.
13. Whan-Lee C, Kim SH, Suh J, et al. Long-term clinical outcomes after sirolimus-eluting stent implantation for treatment of restenosis within bare-metal versus drug-eluting stents. Catheter Cardiovasc Interv 2008;71:594–8.
14. Steinberg DH, Gaglia MA Jr., Pinto-Slottow TL, et al. Outcome differences with the use of drug-eluting stents for the treatment of in-stent restenosis of bare-metal stents versus drug-eluting stents. Am J Cardiol 2009;103:491–5.
15. Fujii K, Mintz GS, Kobayashi Y, et al. Contribution of stent underexpansion to recurrence after sirolimus-eluting stent implantation for in-stent restenosis. Circulation 2004;109:1085–8.
16. Iakovou I, Stankovic G, Montorfano M, et al. Is overdilatation of 3.0 mm sirolimus-eluting stent associated with a higher restenosis rate? Catheter Cardiovasc Interv 2005;64:129–33.
17. Sianos G, Hofma S, Ligthart JM, et al. Stent fracture and restenosis in the drug-eluting stent era. Catheter Cardiovasc Interv 2004;61:111–6.
18. Takebayashi H, Mintz GS, Carlier SG, et al. Nonuniform strut distribution correlates with more neointimal hyperplasia after sirolimus-eluting stent implantation. Circulation 2004;110:3430–4.
19. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.
20. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation 2004;109:701–5.
21. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
22. Kastrati A, Dibra A, Mehilli J, et al. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. Circulation 2006;113:2293–300.
23. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. J Am Coll Cardiol 2010;55:2710–6.

Key Words: drug-eluting balloon ■ in-stent restenosis (ISR) ■ sirolimus-eluting stent (SES) restenosis.