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Difference of Neointimal Formational Pattern and Incidence of Thrombus Formation Among 3 Kinds of Stents

An Angioscopic Study

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Objectives The purpose of this study is to compare the neointimal formational pattern and incidence of thrombus formation among sirolimus-eluting (SES), paclitaxel-eluting (PES), and bare-metal stents (BMS) with coronary angioscopy.

Background Neointimal formation and incidence of mural thrombus are different with the type of stent.

Methods One hundred successive patients who received 43 SES, 40 PES, or 32 BMS implantation underwent 6-month follow-up coronary angioscopy. We evaluated angioscopic parameters, including minimum and maximum neointimal grade; presence and number of red mural thrombus; neointimal grade around thrombus; and heterogeneity score, which is defined by subtracting minimum from maximum grade within 1 stent by classifying angioscopic neointimal coverage grades into 4 categories. We compared these parameters among 3 kinds of stent groups.

Results Heterogeneity scores of SES, PES, and BMS were 0.79 $\pm$ 0.60, 1.27 $\pm$ 0.75, and 1.03 $\pm$ 0.82, respectively ($p = 0.011$). The PES showed the highest incidence of angioscopic red mural thrombus (50% in PES, 12% in SES, and 3% in BMS, $p < 0.001$), and the number of thrombus observed within 1 stent in the PES group tended to be larger than those in the SES and BMS groups.

Conclusions At 6 months after stent implantation, PES showed the most heterogeneous neointimal formation and the highest incidence of thrombus formation compared with SES and BMS. (J Am Coll Cardiol Intv 2010;3:215–20) © 2010 by the American College of Cardiology Foundation

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Strong evidence of benefits with first-generation drug-eluting stent (DES) compared with bare-metal stent (BMS) both for on- and off-label indications have led to the use of DES in the majority of percutaneous coronary interventions (1,2). However, the risk of stent thrombosis after DES implantation remains a serious concern. One of the possible mechanisms for an increased risk of stent thrombosis in DES is delayed arterial healing and high incidence of mural thrombus, which have been revealed by several postmortem pathological studies and real-time imaging studies such as optical coherence tomography or coronary angioscopy (3–5). Moreover, neointimal formation is different with the type of DES (6,7).

The purpose of this study is to compare the neointimal coverage pattern and incidence of thrombus formation among sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), and cobalt alloy BMS with coronary angioscopy.

Methods

Patients. The study patients consisted of 100 successive patients who underwent single type stent implantation for de novo lesions, with SES (Cypher, Cordis, Miami Lakes, Florida), PES (Taxus Express2, Boston Scientific, Natick, Massachusetts), or BMS (Vision, Abbott, Saint-Laurent, Canada; and Driver, Medtronic, Santa Rosa, California). They all accepted 6-month angiographic follow-up with angioscopic assessment of the stent. We compared patient and lesion characteristics, late lumen loss with quantitative coronary angiography, and coronary angioscopic parameters among these 3 kinds of stent groups. Major adverse cardiac events (cardiac death, nonfatal myocardial infarction, or target vessel revascularization) were also assessed at 1 year after coronary angioscopy.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)

All SES were implanted between September 2006 and May 2007, because SES was the only DES available in Japan during the period, and all PES were implanted between June 2007 and December 2007 in the same manner. The PES was approved for clinical use from May 2007 in Japan and became available in June 2007 at our institution. The decision to use either a BMS or DES was at the discretion of the attending physician, on the basis of the relative advantages and disadvantages of each type of stent (8). We defined late lumen loss as the difference between the minimum lumen diameter immediately after stenting and that at 6-month angiographic follow-up with quantitative coronary angiography with QAngio XA (Medis Medical Imaging Systems, Leiden, the Netherlands).

The ethics committee at Osaka Rosai Hospital approved this study, and written informed consent was obtained from all patients before catheterization.

Antiplatelet regimen. All patients received 100 mg aspirin during the follow-up period. Ticlopidine (200 mg) was given additionally as a dual antiplatelet regimen for at least 3 months after stent implantation in the SES group, for at least 6 months in the PES group, and for at least 2 weeks in the BMS group. The drug was changed to cilostazol (200 mg) if side effects were present. Dual antiplatelet therapy was ceased at attending physician's discretion.

Angioscopic technique and analysis. Angioscopy (Fiber Catheter, Fiber Tech, Chiba, Japan) was performed after follow-up coronary angiography after intravenous administration of 5,000 U heparin. The optical fiber was manually pulled back from the distal part of the stent to the proximal part under careful angioscopic and angiographic guidance to evaluate as many parts of stents as possible. Angioscopic images were recorded on digital video discs for subsequent analysis.

We classified neointimal coverage grade into 4 categories. Grade 0 represents stent struts without endothelialization showing glistening metallic luster similar to that immediately after stent implantation. Grade 1 represents stent struts with very thin neointimal coverage and visible metallic color but without metallic luster. Grade 2 represents stent struts without metallic color but not fully embedded in neointima. Grade 3 represents invisible stent struts with full neointimal coverage (Fig. 1). The best-covered segment was defined as the maximum grade, the worst-covered was the minimum grade, and heterogeneity score was defined by subtracting the minimum from maximum grade within 1 stent.

We also evaluated the incidence and number of red mural thrombus and neointimal coverage grade around thrombus. Red mural thrombus was defined as an isolated coalescent red superficial or protruding mass that could not be flushed out by dextran solution injection. Overlapping stent area was excluded from evaluations of this study. Two independent observers who were unaware of the clinical information analyzed the images.

Statistical analysis. Statistical analysis was performed with SPSS for Windows, version 11.0 (SPSS, Inc., Chicago, Illinois). We assumed that the data were approximately normally distributed. Continuous and ordinal variables were presented as mean ± SD. We employed analysis of variance for the evaluation of continuous variables and Kruskal-Wallis test for the evaluation of ordinal variables. Post hoc multiple comparisons were additionally performed for assessing neointimal coverage grade and heterogeneity score with Tukey's test or Games-Howell test after Levene's test for equality of variance, because a nonparametric multiple comparison test was not available with the statistical soft-

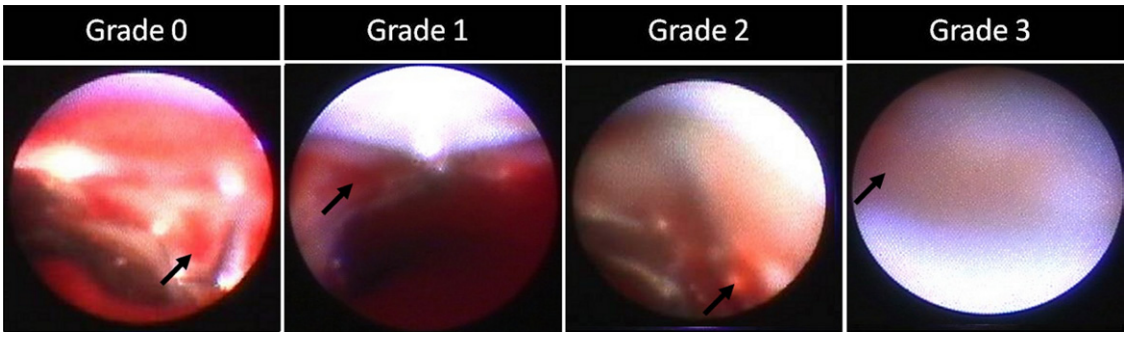

Figure 1. Neointimal Coverage Grade Around Red Mural Thrombus

Arrows indicate red mural thrombi next to focusing neointimal coverage grade. Grade 0 represents stent struts without endothelialization showing glistening metallic luster similar to that immediately after stent implantation. Grade 1 represents stent struts with very thin neointimal coverage and visible metallic color but without metallic luster. Grade 2 represents stent struts without metallic color but not fully embedded in neointima. Grade 3 represents invisible stent struts with full neointimal coverage.

ware we used. Categorical variables were presented as frequencies and analyzed by the chi-square test. A p value <0.05 was considered statistically significant. We also assessed independent predictors for the presence of red mural thrombus with multiple logistic regression analysis with all available variables as independent variables. The inter-rater reliability for the number of mural thrombi was evaluated with intraclass correlation coefficient. The inter-rater reliabilities for other angioscopic parameters were assessed with Cohen's kappa coefficient. Cohen's kappa coefficient >0.80 was considered to be almost perfect agreement. When stents were the unit of analysis, no correction was made for correlated observations within individuals.

Results

Patient and lesion characteristics. Thirty-five patients underwent 43 SES, 35 patients underwent 40 PES, and 30 patients underwent 32 BMS (7 Vision and 25 Driver stents) implantations. Patient and lesion characteristics are shown in Table 1. There were some significant differences in these demographic data. No signs of thrombi were revealed by angiography at the day of follow-up. However, 1 patient who received implantation with PES was admitted to the hospital, due to late stent thrombosis approximately 2 months after coronary angioscopy (Fig. 2).

Angioscopic findings. Angioscopic findings are shown in Figure 3 and Table 2. Heterogeneity scores of SES, PES, and BMS were 0.79 ± 0.60, 1.27 ± 0.75, and 1.03 ± 0.82, respectively ($p = 0.011$). Neointimal coverage of BMS is much greater than that of DES, whereas heterogeneity score was highest in PES. In addition, incidence of red mural thrombi in PES was much higher than in SES or BMS. We detected angioscopic red mural thrombus in 5 (12%) SES. Two of them were undergoing dual antiplatelet therapy at the day of follow-up. We also found red mural thrombi in 20 (50%) PES and 1 (3%) BMS, although all of these patients were undergoing dual antiplatelet therapy at the day of follow-up. The number of thrombi and neointimal coverage grade

Table 1. Patient and Lesion Characteristics

	SES	PES	BMS	p Value
Patient characteristics	n = 35	n = 35	n = 30	
Age	68 ± 8	69 ± 8	66 ± 11	0.284
Male	27 (77)	32 (91)	28 (93)	0.096
Major coronary risk factors				
Hypertension	27 (77)	31 (89)	25 (83)	0.444
Diabetes mellitus	12 (34)	12 (34)	6 (20)	0.360
Smoking	18 (51)	22 (63)	17 (57)	0.627
Dyslipidemia	32 (91)	31 (89)	29 (97)	0.481
Serum markers				
Hemoglobin A1c (%)	5.8 ± 0.9	5.8 ± 1.1	5.5 ± 0.6	0.168
LDL cholesterol (mg/dl)	112 ± 25	104 ± 27	89 ± 24	0.002
HDL cholesterol (mg/dl)	48 ± 11	47 ± 10	43 ± 11	0.175
hs-CRP (mg/dl)	0.21 ± 0.35	0.22 ± 0.41	0.22 ± 0.33	0.988
e-GFR (ml/min/1.73 m^2)	91 ± 22	86 ± 23	93 ± 25	0.519
MACE at 1 year after angioscopy	0 (0)	1 (3)	0 (0)	0.391
Lesion characteristics	n = 43	n = 40	n = 32	
Follow-up period (days)	199 ± 32	190 ± 20	193 ± 20	0.355
ACS	9 (21)	1 (3)	23 (72)	<0.001
Stent diameter (mm)	3.0 ± 0.4	3.1 ± 0.3	3.5 ± 0.4	<0.001
Stent length (mm)	25.1 ± 5.8	24.6 ± 6.6	19.0 ± 4.9	<0.001
Late lumen loss (mm)	0.11 ± 0.11	0.36 ± 0.26	0.93 ± 0.28	<0.001
Dual antiplatelet therapy at the day of angioscopy	23 (54)	40 (100)	9 (28)	<0.001

Data are presented as mean ± SD or n (%).

ACS = acute coronary syndrome; BMS = bare-metal stent(s); e-GFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high sensitive C-reactive protein; LDL = low-density lipoprotein; MACE = major adverse cardiac events; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

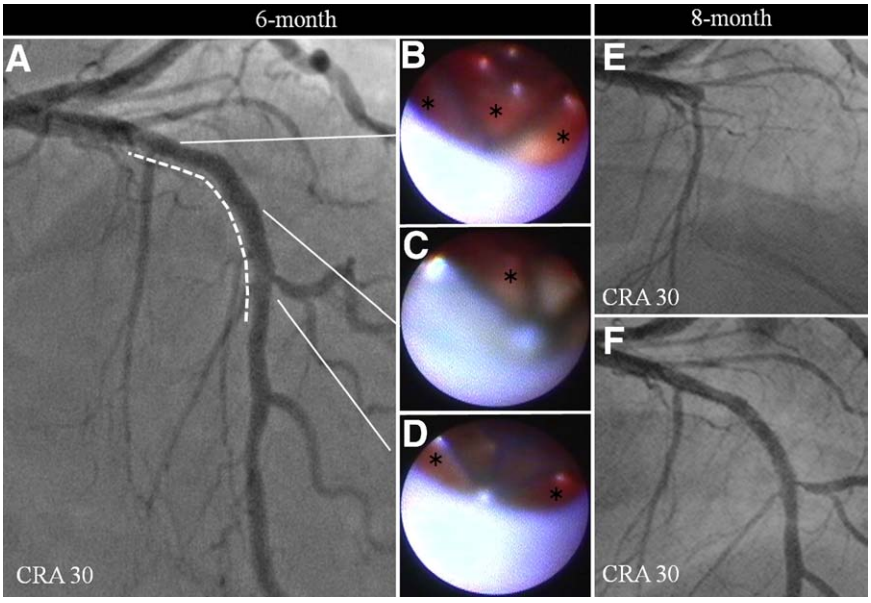

Figure 2. Case of Late Stent Thrombosis

A 62-year-old man who received implantation of a 3.0 × 32 mm paclitaxel-eluting stent in the middle portion of the left anterior descending coronary artery. At 6-month follow-up **(A to D)**, coronary angioscopy showed grade 1 to 2 neointimal coverage at the whole stent **(B to D)** with multiple red mural thrombi **(*)**. The patient discontinued ticlopidine immediately after the discharge. At 2 months after angioscopy and cessation of ticlopidine, he was admitted to the hospital due to nonfatal myocardial infarction **(E)**. Emergent percutaneous coronary intervention was successfully performed with thrombectomy followed by balloon angioplasty **(F)**. Pathological evaluation of aspiration substrate caused us to reach the diagnosis of late stent thrombosis.

around thrombi demonstrated in these 26 stents were shown in Table 2. The number of thrombi in the PES group tended to be larger than those in the SES and BMS groups. In addition, red mural thrombi were revealed along stent struts with even grade 3 neointimal coverage in the PES group. Intraclass correlation coefficient for the number of mural thrombus was 0.97. Cohen's kappa coefficients for the evaluation of inter-rater reliability were 0.95, 0.90, 0.86, and 0.95 for minimum grade, maximum grade, heterogeneity score, and presence of red mural thrombi, respectively.

Predictors for red mural thrombus. Multiple logistic regression analysis revealed the relationship between the presence of red mural thrombus and non-PES, minimum neointimal coverage grade, and estimated glomerular filtration rate with

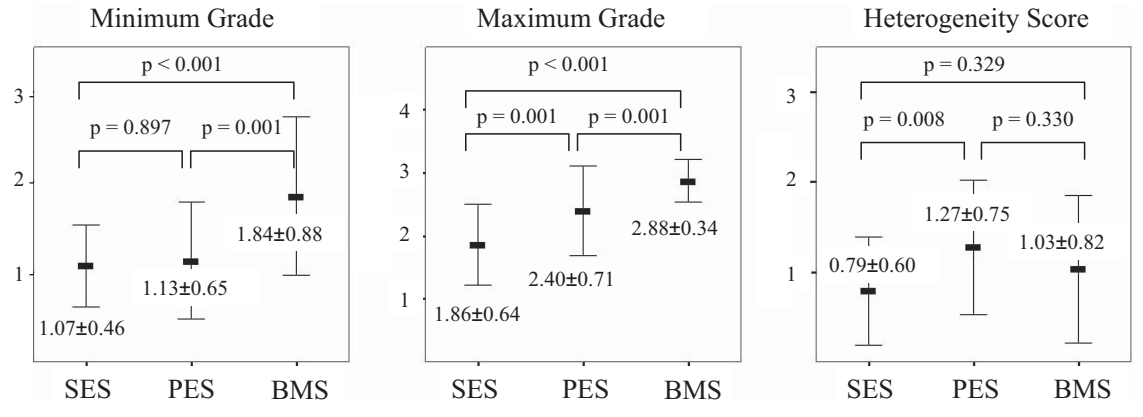

Figure 3. Comparison of Angioscopic Parameters

Data are presented as mean ± SD and analyzed by Kruskal-Wallis test with post-hoc comparison. BMS = bare-metal stent(s); PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

Table 2. The Presence of Thrombus

	SES (n = 43)	PES (n = 40)	BMS (n = 32)	p Value
Incidence of thrombus	5 (12)	20 (50)	1 (3)	<0.001
Total thrombi	10	148	1	
Thrombi/stent	2.0 ± 1.0	7.4 ± 8.2	1.0	0.296
Neointimal coverage grade around thrombi				
Grade 0/1/2/3	4 (40)/2 (20)/4 (40)/0 (0)	8 (5)/26 (18)/111 (75)/3 (2)	1 (100)/0 (0)/0 (0)/0 (0)	

Data are presented as n (%), n, or mean ± SD
Abbreviations as in Table 1.

adjusted odds ratio (95% confidence interval) of 0.039 (0.009 to 0.176, $p < 0.001$), 0.088 (0.021 to 0.361, $p = 0.001$), and 1.035 (1.007 to 1.063, $p = 0.015$), respectively.

Discussion

In the present study, we found that the minimum and maximum neointimal coverage grades of BMS were higher than those of SES. We also found that heterogeneity score of PES is higher than that of SES. Incidence of red mural thrombus of BMS was lower than that of SES, and that of PES was higher than SES. These findings were consistent with the previous clinical studies (5,6). Besides, we also revealed the differences in angioscopic parameters between PES and BMS, and the number of thrombi observed within 1 stent in the PES group tended to be larger than those in SES and BMS.

Neointimal coverage pattern and incidence of thrombus formation. We demonstrated that the incidence of thrombus formation of PES is much higher than that of SES and BMS. Because there is strong correlation between uncovered stent struts and thrombus formation (3,4), this difference of incidence of thrombus formation between SES and PES is difficult to understand, because there were no significant differences in minimum grade between SES and PES in this study. There are 3 possible mechanisms of this phenomenon. First, heterogeneity of PES might have led to a higher incidence of stent struts without endothelialization and resulted in the high incidence of thrombus formation of PES. In other words, because red mural thrombi covered stent struts without endothelialization next to struts with neointimal coverage, we found red mural thrombi along stent struts with even grade 3 neointimal coverage. Second, there is a possibility of neointimal dysfunction for preventing thrombus formation (9,10), even though there are no pathological supporting data that demonstrate supra-neointimal thrombus formation so far. The neointimal function of SES for preventing thrombus formation might be superior to that of PES at 6 months after stent implantation. Finally, high incidence of thrombus formation might be one of the healing processes after stent implantation. We demonstrated a red mural thrombus along stent struts with even grade 3 neointimal coverage, and this thrombus looked whitish (Fig. 1), which made us imagine the red mural thrombus might be covered with neointima.

At any rate, because many of our study patients did not show any evidence of thrombotic events during the 18-month follow-up period and many large clinical trials and registries have not shown a significant difference in the incidence of clinical stent thromboses between SES and PES (11–14), we speculated that most of these angioscopic red mural thrombi are subclinical. The clinical impact of these differences in neointimal heterogeneous property and incidence of thrombus formation at 6 months after DES implantation is low, at least under the treatment of dual antiplatelet therapy.

Study limitations. There are several limitations in this study. First, this is a nonrandomized observational study and has a small number of patients. Second, although the inter-rater reliability of the study was considered to be almost perfect by statistical analysis, the coronary angioscopic evaluation is subjective with limited viewing field. In addition, the definition of heterogeneity score, which was calculated by simply subtracting minimum from maximum grade, has the possibility to overestimate the value in cases when a single strut was heavily covered but the rest of the stent uncovered or in case a single strut was uncovered but the rest of the stent was heavily covered, although we did not experience that situation in this study. Third, patient and lesion characteristics were different in some parameters, partly because the decision regarding which stent (DES vs. BMS) to place was left to the operator. This could lead to biased results and reminds us to interpret the data with caution. Finally, the relationship between angioscopic neointimal coverage and pathological endothelialization was not validated.

Conclusions

At 6 months after stent implantation, PES showed the most heterogeneous neointimal formation and the highest incidence of thrombus formation compared with SES and BMS.

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Key Words: angioscopy ■ heterogeneity ■ neointimal dysfunction ■ stent ■ thrombus.