High incidence of thrombus formation at 18 months after paclitaxel-eluting stent implantation: Angioscopic comparison with sirolimus-eluting stent

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Background Difference of neointimal formational pattern and incidence of thrombus formation between sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) at 18 months after stent implantation has not previously been reported.

Methods We retrospectively enrolled 35 event-free patients who received SES (15 patients, 18 stents) or PES (20 patients, 23 stents) implantation with 18-month follow-up coronary angioscopy. We divided our patients into SES or PES groups and compared neointimal coverage pattern and incidence of red mural thrombus formation between the 2 groups. Neointimal coverage grades were classified into 4 categories. Minimum neointimal coverage grade, maximum grade, and heterogeneity score were assessed in each stent. Heterogeneity score was calculated by subtracting minimum from maximum grade within one stent.

Results Minimum neointimal coverage grade of PES was significantly lower than that of SES (0.70 ± 0.64 vs 1.33 ± 0.69, $P = .005$), whereas maximum grade was not significantly different (2.48 ± 0.73 vs 2.22 ± 0.73, $P = .218$). Heterogeneity score and incidence of red mural thrombus of PES were higher than those of SES (1.78 ± 0.80 vs 0.89 ± 0.76, $P = .002$ and 70% vs 11%, $P < .001$).

Conclusions The present study revealed that PES shows more heterogeneous neointimal coverage and higher incidence of thrombus formation as compared with SES at 18 months after stent implantation. (Am Heart J 2010;159:905-10.)

Based upon the marked reductions in restenosis and target lesion revascularization with drug-eluting stents (DESs) compared with bare-metal stents,[1,2] DESs have been used in the majority of patients who undergo percutaneous coronary interventions.[3] However, very late stent thrombosis (>12 months) has been raised as one of the serious safety concerns of DESs because it may present as death or myocardial infarction.[4-6] This restenosis benefit and the possibly increased risk of very late stent thromboses of DESs compared with bare-metal stents are believed to result from inhibition of in-stent neointimal hyperplasia and thrombus formation.[6]

Sirolimus-eluting (SES) and paclitaxel-eluting stent (PES) are widely used first-generation DESs.[4-7] Although arterial healing process and incidence of mural thrombus are different between SES and PES at 6 months after stent implantation,[8] incidence of very late stent thrombosis (>12 months) may be similar between SES and PES.[4-7] The aim of this study is to evaluate and compare neointimal coverage pattern and incidence of thrombus formation between SES and PES at 18 months after stent implantation with coronary angioscopy.

Methods

Study population

We retrospectively enrolled 35 patients who underwent 18-month angioscopic evaluation of SES (Cypher; Cordis, Miami Lakes, FL) or PES (Taxus Express[2]; Boston Scientific, Natick, MA) between May 2007 and July 2009. We encourage as many patients as possible to participate in 18-month follow-up angiography after DES implantation in a daily clinical practice to evaluate angiographic outcomes of DESs. In addition, patients who had 18-month follow-up angiographic evaluation of DESs during the period were basically study candidates for angioscopic evaluation. Thus, the study cohort included the previously reported 6-month angioscopic follow-up patients,[8] but was not prespecified. The decision to request cooperation of angioscopic evaluation was at the discretion of the attending physician.

Inclusion criteria of this retrospective study were event-free patients who underwent elective DES implantation for de novo lesions under intravascular ultrasound (IVUS) guidance. Thus, all

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stents were implanted for the treatment of stable angina pectoris between April 2005 and December 2007; and DES implantations for acute coronary syndrome were excluded. Patients with major adverse cardiac events (cardiac death, nonfatal myocardial infarction, or target vessel revascularization) during the follow-up period were also excluded from this study. All SESs were implanted before Jun 2007, and all PESs were implanted after Jun 2007 in the same manner because SES was the only DES available at our institution before June 2007. Paclitaxel-eluting stent was approved for clinical use from May 2007 in Japan and from June 2007 at our institution. Paclitaxel-eluting stent was used exclusively as DES from June through December 2007 at our institution to minimize selection bias of DES for comparing clinical outcomes between SES and PES. A total of 368 patients with stable angina pectoris underwent SES implantation between April 2005 and May 2007, and 90 of these patients underwent 18-month follow-up angiography. On the other hand, 128 patients underwent PES implantation between June and December 2007, and 70 of these patients underwent 18-month follow-up angiography.

We divided our patients into SES group (15 patients, 18 stents) and PES group (20 patients, 23 stents) and compared patient and lesion characteristics, and coronary angioscopic and IVUS parameters between the 2 groups. All serum parameters shown in Table I were measured at the day of follow-up.

The ethics committee at Osaka Rosai Hospital approved this study, and written informed consent was obtained from all patients before catheterization. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the paper.

Antiplatelet regimen

All patients took 100 mg aspirin daily during the follow-up period. Ticlopidine (200 mg) was given additionally as a dual-antiplatelet regimen for at least 3 months after SES implantation and at least 6 months after PES implantation. Ticlopidine was replaced by clopidogrel (75 mg) from October 2007 when clopidogrel become available for clinical use in Japan. Replacement from ticlopidine to clopidogrel or cessation of dual-antiplatelet therapy was at the attending physician's discretion.

Quantitative IVUS analysis

All DESs were implanted with IVUS (Galaxy 2, Boston Scientific) guidance. Intravascular ultrasound was performed with an automated pullback system at 1.0 mm/s using a 40-MHz ultrasound probe. All data were recorded on digital video discs and analyzed off-line. For cross-sectional parameters, 1.0-mm consecutive cross-sections were analyzed by semiautomatic contour tracing system equipped with IVUS in the stented segment. Lesion length, minimal and maximal stent diameter and area immediately after stenting, and the existence of incomplete stent apposition were compared between the two groups. *Incomplete stent apposition* was defined as 1 or more stent struts clearly separated from the vessel wall. Reference vessel or lumen parameters could not be assessed in some patients because IVUS probe did not pass the lesion because of severe calcification. In such a case, lesion length was calculated as the length of stented segment. Thus, reference vessel or lumen parameters were excluded from the comparison.

Table I. Patient and lesion characteristics

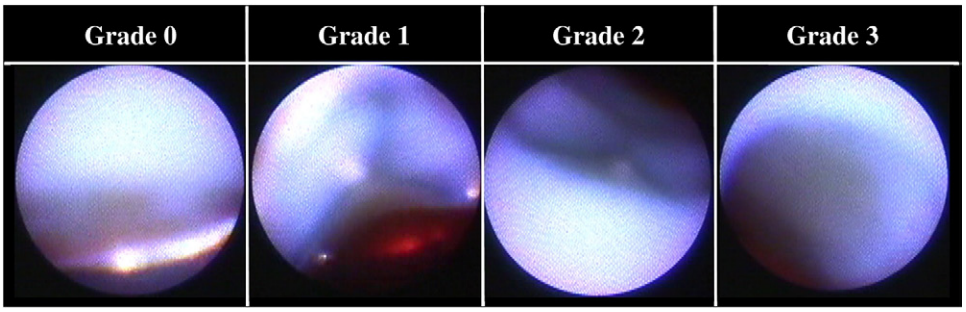
	SES	PES	*P* value
Patient characteristics	n = 15	n = 20	
Age	72 ± 7	70 ± 8	.512
Male	11 (73)	17 (85)	.332
Follow-up period (d)	532 ± 189	554 ± 22	.172
Major coronary risk factors			
Hypertension	13 (87)	16 (80)	.481
Diabetes mellitus	10 (67)	7 (35)	.064
Smoking	10 (67)	14 (70)	.560
Dyslipidemia	13 (87)	17 (85)	.640
Serum markers			
Hemoglobin A_{1c} (%)	6.5 ± 0.9	6.0 ± 1.0	.064
LDL cholesterol (mg/dL)	102 ± 17	87 ± 21	.032
HDL cholesterol (mg/dL)	50 ± 13	45 ± 11	.175
High-sensitivity CRP (mg/dL)	0.36 ± 0.51	0.29 ± 0.73	.186
Estimated GFR (mL/[min 1.73 m^2])	80 ± 21	93 ± 29	.153
No. of stents per patient	1.2 ± 0.4	1.2 ± 0.4	.702
Duration of dual-antiplatelet therapy at the day of follow-up (d)	391 ± 240	378 ± 173	.729
Lesion characteristics	n = 18	n = 23	
Target lesion			.616
LMT	2 (11)	1 (4)	
LAD	7 (39)	6 (26)	
LCx	1 (6)	2 (9)	
RCA	8 (44)	14 (61)	
Lesion type			.387
B1	4 (22)	2 (9)	
B2	4 (22)	4 (17)	
C	10 (56)	17 (74)	
Stent diameter (mm)	3.11 ± 0.37	3.20 ± 0.25	.524
Stent length (mm)	24.1 ± 4.7	25.6 ± 6.4	.231
Maximum inflation pressure (atm)	17.3 ± 3.0	13.7 ± 3.2	.002
IVUS data			
Lesion length (mm)	26.8 ± 13.7	28.5 ± 11.7	.699
Minimum stent diameter (mm)	2.47 ± 0.41	2.51 ± 0.31	.733
Maximum stent diameter (mm)	3.47 ± 0.47	3.59 ± 0.44	.608
Minimum stent area (mm^2)	5.79 ± 1.71	6.09 ± 1.20	.411
Maximum stent area (mm^2)	8.41 ± 2.16	8.73 ± 2.14	.887
Incomplete stent apposition	0 (0)	0 (0)	–
Late lumen loss (mm)	0.13 ± 0.15	0.35 ± 0.30	.008
Dual-antiplatelet therapy at follow-up	9 (50)	10 (44)	.678

Data are presented as mean ± SD or the number (percentage). *HDL*, High-density lipoprotein; *CRP*, C-reactive protein; *GFR*, glomerular filtration rate; *LMT*, left main trunk; *LAD*, left anterior descending artery; *LCx*, left circumflex artery; *RCA*, right coronary artery.

Angioscopic technique and analysis

Detailed methodology has also previously been reported elsewhere.[8] We used angioscopy (Fiber Catheter; Fiber Tech, Chiba, Japan) after 5,000 units of intravenous heparin administration. All procedures were performed with a transradial approach using 6.0F guide catheters. The optical fiber, which can demonstrate a clear 6,000-pixel image, was contained in a 4.0F catheter. The optical fiber was manually pulled back from the distal part of the stented segment to the proximal part under careful angioscopic and angiographic guidance. Angioscopic

Figure 1



Neointimal coverage grade. Grade 0: stent struts showing glistening metallic luster without neointima. Grade 1: stent struts with thin neointima with visible metallic color but no metallic luster. Grade 2: stent struts without metallic color but not fully embedded in neointima. Grade 3: full neointimal coverage without visible strut.

Table II. Predictors of angioscopic thrombus formation: Multiple logistic regression analysis

	Adjusted odds ratio	95% CI	*P* value
SES	0.057	0.005-0.634	.020
Minimum grade	0.286	0.056-1.475	.135
Maximum grade	0.875	0.217-3.527	.851
Absence of dual-antiplatelet therapy	0.086	0.001-13.294	.340
Duration of dual-antiplatelet therapy at the day of follow-up	0.992	0.976-1.008	.309
Diabetes mellitus	0.585	0.086-3.961	.583
High-sensitivity CRP	0.949	0.225-4.002	.943
Stent length	1.023	0.856-1.222	.802

images were recorded on digital video discs for subsequent off-line analysis. One of the limitations of this coronary angioscopy system is that a 4.0F catheter may limit viewing field in some parts of coronary arteries. Neointimal coverage grade was classified into 4 grades: 0, stent struts without endothelialization showing glistening metallic luster similar to that immediately after stent implantation; 1, stent struts with very thin neointimal coverage and visible metallic color but without metallic luster; 2, stent struts without metallic color but not fully embedded in neointima; and 3, invisible stent struts with full neointimal coverage (Figure 1). The analysis has subjective and semiquantitative aspects. The grade of the best-covered strut was defined as the *maximum grade*, and the worst-covered strut was the *minimum grade* in each stent. *Heterogeneity score* was defined by subtracting the minimum from maximum grade within one stent as a representative of heterogeneous property of neointimal formation. Thus, higher heterogeneity score means more heterogeneous neointimal formation. We proposed the use of heterogeneity score to compare neointimal formational pattern between SES and PES, not for predicting the risk of thrombus formation. We defined *red mural thrombus* as a coalescent red superficial or protruding mass that cannot be flushed out by dextran solution injection. We evaluated the incidence and number of red mural thrombus. There were 3 overlapping stent segments in both the SES and PES groups, and overlapping segments were 1 to 3 mm in all cases according to IVUS analysis.

The angioscopic analysis was performed off-line by 2 independent observers (observers 1 and 2). If there was a disagreement between observers 1 and 2, it was resolved by a consensus with a third observer. They are experienced to assess angioscopic findings at our institution and were blinded to the patient and stent information during the analysis. The observers can in many cases determine the type of stent by the appearance of the strut design. The consensus report is presented in this manuscript.

Statistical analysis

Continuous and ordinal variables were presented as mean ± SD. We used Student *t*, Welch *t*, or Mann-Whitney test for statistical analysis after Shapiro-Wilk test for normal distribution and Levene test for equality of variance. Categorical variables were presented as frequencies and analyzed by the χ^2 test. $P < .05$ was considered statistically significant. We also assessed independent predictors for the presence of red mural thrombus using multiple logistic regression analysis. Multiple logistic regression analysis was performed with fixing variable method using variables shown in Table II as independent variables.

To determine the consistency and reproducibility of angioscopic parameters, the interrater reliability between observers 1 and 2 was evaluated by Cohen κ coefficient. Cohen κ coefficient >0.80 was considered to be almost perfect agreement. All statistical analyses were performed using SPSS for Windows, version 11.0 (SPSS Inc, Chicago, IL).

Results

Patient and lesion characteristics

Patient and lesion characteristics are shown in Table I. There were no significant differences in patient and lesion characteristics between SES and PES groups, except low-density lipoprotein (LDL) cholesterol, maximum balloon inflation pressure during stent implantation, and late lumen loss. LDL cholesterol and maximum

Table III. Coronary angioscopic findings

	SES (n = 18)	PES (n = 23)	*P* value
Minimum grade	1.33 ± 0.69	0.70 ± 0.64	.005
Grade 0	1 (6)	9 (39)	
Grade 1	11 (61)	12 (52)	
Grade 2	5 (28)	2 (9)	
Grade 3	1 (6)	0 (0)	
Maximum grade	2.22 ± 0.73	2.48 ± 0.73	.218
Grade 0	0 (0)	0 (0)	
Grade 1	3 (17)	3 (13)	
Grade 2	8 (44)	6 (26)	
Grade 3	7 (39)	14 (61)	
Heterogeneity score	0.89 ± 0.76	1.78 ± 0.80	.002
Score 0	6 (33)	1 (4)	
Score 1	8 (44)	7 (30)	
Score 2	4 (22)	11 (48)	
Score 3	0 (0)	4 (17)	
Incidence of thrombus	2 (11)	16 (70)	<.001
Total no. of thrombi	6	103	
No. of thrombi per stent	3.0 ± 1.4	6.4 ± 3.3	.176

Data are presented as mean ± SD or the number (percentage). Neointimal coverage grade was classified into 4 grades: 0, stent struts without endothelialization showing glistening metallic luster similar to that immediately after stent implantation; 1, stent struts with very thin neointimal coverage and visible metallic color but without metallic luster; 2, stent struts without metallic color but not fully embedded in neointima; and 3, invisible stent struts with full neointimal coverage.

balloon inflation pressure of SES group were significantly higher than those of PES group, whereas late lumen loss was significantly lower in SES group than in PES group.

Angioscopic findings

As shown in Table III, minimum neointimal coverage grade of PES was significantly lower than that of SES, whereas there was no significant difference in maximum grade between the 2 groups. In addition, heterogeneity score and the incidence of red mural thrombus of PES group were higher than those of SES group. The number of thrombus observed within one stent in PES group tended to be larger than that in SES group. Cohen κ coefficients for the evaluation of interrater reliability were 0.916, 0.960, 0.895, and 1.000 for minimum grade, maximum grade, heterogeneity score, and presence of red mural thrombus, respectively. Representative cases are shown in Figure 2.

Table II shows the results of multiple logistic regression analysis. There was negative correlation between SES and the presence of thrombus formation. Dual-antiplatelet therapy at the day of follow-up and all other variables shown in Table II did not show a relationship with the presence of thrombus formation in this study.

Discussion

In the present study, we found that PES showed lower minimum neointimal coverage grade, higher heterogeneity score, and higher incidence of thrombus formation as compared with SES at 18 months after DES implantation.

Neointimal formation and late lumen loss

In the present study, PES showed higher late lumen loss as compared with SES. This has also been reported by large clinical trials.[4,5,7] Because late lumen loss is believed to represent the thickest portion of neointimal growth,[9,10] maximum neointimal coverage grade may have a relationship with late lumen loss in theory. However, there was no statistically significant difference in maximum grade between SES and PES. We speculated that this is because of qualitative aspects of angioscopic evaluation. For example, neointimal coverage grade remained 3 even if neointimal coverage became thicker when it showed grade 3 neointimal coverage before. There is also a possibility that thrombi contribute to higher late lumen loss, although it is unclear whether angioscopic red mural thrombi are intramural or supramural thrombi.[8]

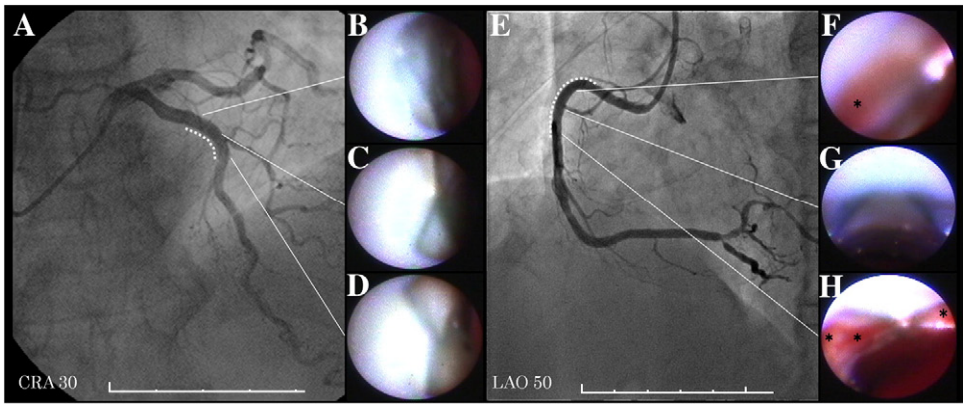
Arterial healing and thrombus formation

Although the pathogenesis is still not fully understood, the mural thrombus is believed to be initially built up adjacent to stent struts and to be gradually invaded by cellular components that result in neointimal proliferation.[6] Thus, lower minimum neointimal coverage grade and higher incidence of thrombus formation of PES as compared with SES might be due to more delayed arterial healing of PES, although PES showed similar maximum neointimal coverage grade and higher late lumen loss compared with SES. There is also a possibility that more heterogeneous neointimal formational property of PES leads to higher incidence of uncovered stent struts, resulting in higher incidence of thrombus formation.[8]

Multiple logistic regression analysis showed that stent type is the independent predictor of the presence of red mural thrombus. Thus, this difference of arterial healing process and incidence of thrombus formation may be derived from the components of DES (stent platform, polymer coating, and antirestenotic drugs) rather than clinical backgrounds. For example, sirolimus and paclitaxel increase tissue factor expression in a different mechanism on a subcellular level[6]; and this difference might contribute to the difference of the incidence of thrombus formation after DES implantation.

In the present study, PES had significantly lower maximum balloon inflation pressure than SES. However, IVUS parameters showed similar expansion results with complete stent apposition between SES and PES as shown in Table I. We speculated that the closed-cell design of SES may need higher pressures for satisfactory deployment compared with open-cell–type PES. Therefore, we do not think that worse stent apposition of PES leads to the

Figure 2



Representative coronary angioscopic images at 18 months after SES (**A**, **D**) and PES (**E**, **H**) implantations. On the left side of the panel, coronary angiography (**A**) shows a SES (3.5 × 18 mm) -implanted case in left anterior descending artery. Coronary angioscopy demonstrated grade 2 at proximal part (**B**) and grade 1 at middle and distal part of the stent (**C** and **D**). On the other hand, right side of the panel shows a coronary angiography (**E**) of a PES (3.5 × 24 mm) -implanted case in right coronary artery. Coronary angioscopy demonstrated grade 0 to 2 neointimal coverage with red mural thrombus at proximal part (**F**), grade 1 coverage at middle part (**G**), and grade 0 to 1 coverage with multiple thrombi at the distal part of the stent (**H**). Asterisk indicates red mural thrombus.

difference of neointimal formational pattern or incidence of thrombus formation between SES and PES.

Angioscopic thrombus and clinical stent thrombosis

Stent thrombosis is an uncommon but serious complication of coronary artery stents that may present as death or myocardial infarction.[4,5,7] Many factors, such as stent malapposition, stent length, slow coronary blood flow, diabetes, premature cessation of antiplatelet drugs, and so on, have been recognized to be associated with an increased risk for DES thrombosis.[6] Angioscopic thrombus formation and lower neointimal coverage are also believed to be risk factors for DES thrombosis.[8,11]

Although we showed higher incidence of angioscopic thrombus formation and lower minimum neointimal coverage grade of PES at 18 months, the risk of clinical stent thrombosis may be similar between SES and PES.[4,5,7] Thus, we believe that the clinical impact of these differences in neointimal formational pattern and incidence of thrombus formation is low at least during 18 months after stent implantation; and many of these angioscopic thrombi are subclinical. Longer-term assessment of these differences in arterial healing process and clinical outcomes is needed to further clarify the clinical impacts.

Study limitations

There are several limitations in the present study. First, this study is a nonrandomized retrospective observational study and has a small number of patients. Second, baseline characteristics were not identical between SES and PES groups. Third, only surrogate outcomes were assessed in this study. Fourth, simply evaluating minimum and maximum grade has the possibility to overestimate the difference in neointimal coverage between SES and PES in theory, although neointimal coverage has sequentiality and consecutiveness. Finally, although the inter-rater reliability showed almost perfect agreement, the evaluation of coronary angioscopy is subjective and has limited viewing field.[8]

Conclusions

The present study revealed that PES shows more heterogeneous neointimal coverage and higher incidence of thrombus formation as compared with SES at 18 months after stent implantation. These findings apply to patients who remain event-free at 18 months after DES implantation.

Disclosures

All authors disclose no relationship with industry and financial associations that might pose a conflict of interest in connection with the submitted article.

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