Lack of Association Between Large Angiographic Late Loss and Low Risk of In-Stent Thrombus

Angioscopic Comparison Between Paclitaxel- and Sirolimus-Eluting Stents

Masamichi Takano, MD; Masanori Yamamoto, MD; Daisuke Murakami, MD; Shigenobu Inami, MD; Kentaro Okamatsu, MD; Koji Seimiya, MD; Takayoshi Ohba, MD; Yoshihiko Seino, MD; Kyoichi Mizuno, MD

Background—It recently has been hypothesized that a larger late loss may have a protective role against stent thrombosis. The relationship between angiographic late loss and the presence of thrombus based on angioscopic findings within paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) was investigated in this study.

Methods and Results—Prospective 6-month follow-up angiographic and angioscopic examinations were performed on 18 patients for PES and on 20 patients for SES. Late loss was measured by quantitative coronary angiography. Angioscopic neointimal stent coverage (NSC) grade was classified as follows: 0=uncovered struts without neointima, 1=visible struts through thin neointima, and 2=no visible struts. In each patient, maximum NSC, minimum NSC, and the existence of thrombus were evaluated. Late loss and maximum NSC were greater in PES than in SES (0.38±0.43 versus 0.10±0.23 mm; \( P=0.02 \) and \( P=0.0004 \), respectively). Late loss was correlated with maximum NSC (grade 0, 0.06±0.01 mm; grade 1, 0.10±0.05 mm; and grade 2, 0.48±0.46 mm), whereas there was no correlation between late loss and minimum NSC. The prevalence of patients with uncovered struts did not differ (44% of PES, 40% of SES; \( P=0.78 \)). In-stent thrombus was found more frequently in PES than in SES (72% versus 40%, \( P=0.046 \)) despite no occurrence of stent thrombosis. Only within PES were thrombi found in the segments of NSC grade 2 associated with large late loss.

Conclusion—The present study suggests that angiographic large late loss was not associated with a low risk of in-stent thrombus. (Circ Cardiovasc Intervent. 2008;1:20-27.)

Key Words: drugs ■ stents ■ thrombus

Two kinds of drug-eluting stents (DES), paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES), are commercially available and most widely used in percutaneous coronary intervention to reduce angiographic and clinical restenosis rates compared with bare metal stents.1–3 A recent meta-analysis of 16 randomized trials showed some differences between the 2 types of DES.4 First, SES had more favorable effects on the inhibition of neointimal hyperplasia, identified as less late loss on angiogram, than did PES. Second, SES was superior to PES in reducing the risk of late stent thrombosis (LST), an infrequent but serious cardiovascular event. These phenomena do not support the recently reported hypothesis that a larger late loss may have a protective role against LST.5 Nevertheless, the precise mechanism is unclear, and a new question of why a larger late loss is potentially linked to a higher incidence of LST is raised. Previous pathological investigations have revealed that delayed arterial healing, incomplete endothelialization, and persistent uncovered stent struts are powerful predictors of LST after DES implantation.6,7 We therefore hypothesized that some differences in neointimal growth, the presence of persistent uncovered struts, and/or latent thrombus between PES and SES may contribute to the above phenomena.

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Coronary angioscopy provides direct visualization of the lumen and detailed information on the condition of neointimal stent coverage (NSC) and the presence of an intracoronary thrombus, beyond the information provided by angiography.8–11 Angioscopy has the advantage of allowing the identification of an intracoronary thrombus.12 Although several angioscopic follow-up examinations after SES implantation have been reported,8–10 no angioscopic investigation comparing PES with SES is currently available. The present study was performed to compare PES and SES, focusing on...
NSC and the presence of in-stent thrombus, and to examine
the relationship between late loss and angioscopic findings
after DES implantation.

Methods

Patient Population
This study consisted of 51 DES (PES [Taxus; Boston Scientific,
Natick, Mass] or SES [Cypher; Cordis Corp, Miami Lakes, Fla])
prospectively implanted in 38 lesions of 38 patients (34 men; age, 50
to 79 years) with ischemic heart disease who agreed to receive
follow-up angioscopic examinations. All procedures were performed
at the Chiba-Hokusoh Hospital. The patients were treated with SES
between March 2005 and May 2005 and with PES between May
2007 and July 2007 for their de novo and native coronary lesions
with >50% diameter stenosis. Beforehand, all patients received
dual-antiplatelet therapy with aspirin 100 or 200 mg/d and ticlopi-
dine 200 mg/d for >48 hours before DES implantation for preven-
tion against acute or subacute stent thrombosis. Exclusion criteria
included acute myocardial infarction within 48 hours from onset, a
contraindication to aggressive antiplatelet therapy, chronic renal
failure (serum creatinine ≥2.5 mg/dL) without regular hemodialysis,
restenotic lesions, lesions of coronary bypass grafts, low ejection
fraction of the left ventricle (<30%), and left main coronary disease or
ostial lesions. The last criterion was instituted because of the
expected difficulty in acquiring angioscopic images for entire stent
segments. The Medical Ethics Committee at our facilities approved
this study, and written informed consent was obtained from all
patients before each catheterization procedure.

Clinical Demographics
Patient demographics were obtained by a hospital chart review.
Acute coronary syndrome was defined as the group of clinical
symptoms, ECG changes, and elevation of cardiac biomarkers that
are compatible with acute myocardial infarction and unstable angi-

Clinical Follow-Up and Antiplatelet Regimen
Regular clinical follow-up visits occurred every month or every other
month for up to 6 months after DES implantation. Dual-antiplatelet
therapy, ticlopidine added to aspirin, was continued for the follow-up
period if there were no major side effects. During this study period,
neither clopidogrel nor glycoprotein IIb/IIIa was approved for
clinical use in Japan. Major adverse cardiac events were defined as
acute coronary syndrome, LST, cardiac sudden death, and target
lesion revascularization by coronary artery bypass graft or percuta-
neous coronary intervention.

Statistical Analysis
Data are presented as mean±SD. Categorical variables are presented
as frequencies and were analyzed by either the Fisher exact test or the
χ² test. Continuous data were tested by the Student t test to
calculate the differences by having an observer repeat the assessment of 50 images (presented
in random order) after 1 week. Interobserver agreement was mea-
sured by comparing the assessment of 50 images by 2 observers
blinded to clinical information, including the kind of DES. Intraob-
server agreement for evaluated angioscopic items (NSC grade and
thrombus) was 92% and 98%, respectively. Interobserver agreement
for those items was 90% and 94%, respectively. If there was no
consensus about the angioscopic items, then a third observer as-
sessed them.

Clinical Follow-Up and Antiplatelet Regimen

Follow-up angioscopic examinations were scheduled 6 months after
DES implantation. Entire stent segments were observed with an
angioscopic catheter (Vecmova Neo, FiberTech Corp, Chiba, Japan)
according to a previously described procedure. Angioscopic im-
ages and the exact position of the angioscopic catheter on fluoros-
copy during angioscopic observations were recorded on digital
videotape for later analysis.

Coronary Angioscopic Imaging

Definition and Analysis of Angioscopic Findings
The degree of neointimal growth as NSC on angioscopic images
and presence of an intracoronary thrombus within stent segments were
evaluated. NSC grade was classified according to our previous
report. In brief, the classifications were as follows: grade 0=un-

Figure 1. Angioscopic images of NSC grade and thrombus. A, Grade 0. No neointima is found on stent struts in an overlapping
segment. A red thrombus (arrow) is attached to uncovered
struts. B, Grade 1. Struts are visible under thin neointima. C, Grade 2. Struts are fully covered by white neointima and are

covered struts without neointima by macroscopic detection, grade
1=visible struts through thin neointima, and grade 2=no visible
struts under neointima (complete coverage) (Figure 1). In each
patient, the grade of the best-covered segment was defined as
maximum NSC and that of the worst-covered segment was defined
as minimum NSC. Heterogeneity of NSC was calculated as
maximum NSC minus minimum NSC. A thrombus was defined as
a coalescent red, pinkish-white, or white mass that clearly was a
separate structure and remained despite complete removal of blood
with a flush (Figure 1).

Intraobserver agreement on the angioscopic images was measured
by having an observer repeat the assessment of 50 images (presented
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The study population consisted of 18 patients (18 segments)
treated with PES (n=22) and 20 patients (20 segments)
treated with SES (n=29). The results of 16 patients in the

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Table 1. Baseline Clinical Characteristics

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<thead>
<tr>
<th></th>
<th>PES (n=18)</th>
<th>SES (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±7</td>
<td>65±8</td>
<td>0.69</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>15 (83)</td>
<td>19 (95)</td>
<td>0.24</td>
</tr>
<tr>
<td>Coronary risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (28)</td>
<td>8 (40)</td>
<td>0.43</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (67)</td>
<td>14 (70)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (56)</td>
<td>9 (45)</td>
<td>0.52</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (28)</td>
<td>8 (40)</td>
<td>0.43</td>
</tr>
<tr>
<td>Obesity</td>
<td>5 (28)</td>
<td>6 (30)</td>
<td>0.88</td>
</tr>
<tr>
<td>Family history</td>
<td>8 (44)</td>
<td>8 (40)</td>
<td>0.78</td>
</tr>
<tr>
<td>Reason for stent implantation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>5 (28)</td>
<td>5 (25)</td>
<td>0.85</td>
</tr>
<tr>
<td>Stable angina pectoris</td>
<td>13 (72)</td>
<td>15 (75)</td>
<td></td>
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<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>4 (22)</td>
<td>4 (20)</td>
<td>0.87</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention, n (%)</td>
<td>4 (22)</td>
<td>3 (15)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prior coronary bypass surgery, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>5 (28)</td>
<td>4 (20)</td>
<td>0.57</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>54±9</td>
<td>55±11</td>
<td>0.76</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>2 (11)</td>
<td>2 (10)</td>
<td>0.91</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual antiplatelet therapy</td>
<td>18 (100)</td>
<td>20 (100)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Insulin</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>5 (28)</td>
<td>6 (30)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate.

SES group have been reported previously.8,10 Multiple stent deployment completely overlapped without a gap. Two overlapping stents were deployed in 4 patients in the PES group and 5 patients in the SES group; 3 overlapping stents were deployed in 2 patients in the SES group. In terms of clinical characteristics, the proportion of diabetes mellitus, acute coronary syndrome, and chronic renal failure did not differ between the PES and SES groups (Table 1). Ejection fractions and prescribed medications also were similar between the 2 groups. There were no major side effects of dual-antiplatelet therapy, and all patients received continuous dual-antiplatelet therapy. No significant differences were noted between the 2 groups with regard to their lesion and procedural characteristics (Table 2). Maximum inflation pressure tended to be higher in the SES group than in the PES group.

Angiographic Findings and Major Adverse Cardiac Events

QCA and qualitative angiographic data are summarized in Table 3. Before the procedure, lesion length tended to be shorter in the PES group than in the SES group. At the 6-month follow-up, diameter stenosis tended to be smaller in the PES group than in the SES group. Late loss was significantly greater in the PES group. In-stent restenosis was found in 2 patients (11%) in the PES group and 1 patient (5%) in the SES group. One patient (6%) in the PES group received a target lesion revascularization (SES implantation) as a result of restenosis accompanied by symptoms of effort angina. No other major adverse cardiac events occurred during the follow-up period. Consequently, the frequency of major adverse cardiac events was not different between the 2 groups (6% versus 0% for the PES and SES groups, respectively; P=0.29). In qualitative angiographic analysis, abnormalities were recognized in the culprit lesions of acute coronary syndrome. Immediately after DES implantation, wall irregularity remained in 11% of the PES group and in 10% of the SES group. Wall irregularities disappeared at the 6-month follow-up except for in 1 patient (6%) in the PES group.

NSC on Angioscopic Findings

There were no angiographic procedure-related complications. Angioscopic NSC grade at follow-up is shown in Table 4. Maximum NSC was significantly higher in the PES group than in the SES group (P=0.0004). In contrast, minimum NSC was not different between the 2 groups (P=0.83). Heterogeneity of NSC in PES group was greater than in SES group (P=0.0053).

Late Loss and NSC

The relationship between maximum NSC and late loss in QCA analysis is shown in Figure 2. The numbers of patients in grades 0, 1, and 2 of maximum NSC were 7 (7 SES), 15 (3 PES, 12 SES), and 16 (15 PES, 1 SES), respectively. Although late loss of grades 1 and 2 differed significantly (P=0.001), there was no difference between grades 0 and 1 (P=0.75). There was no correlation between minimum NSC and late loss (Figure 3). Uncovered stent struts, NSC grade 0, were found in 8 patients (44%) in the PES group and 8
patients (40%) in the SES group (P=0.78; Figure 4). Among these patients, 3 of 8 segments with uncovered struts (38%) in the PES group and 6 of 8 segments with uncovered struts (75%) in the SES group were located in stent overlapping segments. Uncovered struts were found in 46% (6 of 13) of diabetes mellitus cases, 40% (4 of 10) of acute coronary syndrome cases, 50% (3 of 6) of low ejection fraction (40%) cases, 75% (3 of 4) of chronic renal failure cases, 33% (1 of 3) of chronic total occlusion cases, 100% (9 of 9) of multiple overlapping stents cases, and 50% (1 of 2) of bifurcating stent cases.

**Thrombus on Angioscopic Findings**

In-stent thrombi were identified by angioscopy in 13 patients (72%) in the PES group and 8 patients (40%) in the SES group. The frequency of in-stent thrombus was significantly higher in the PES group than SES group (P=0.046; Figure 4). Red, pinkish-white, and white thrombi were found in 7 patients (4 PES, 3 SES), 12 patients (8 PES, 4 SES), and 2 patients (1 PES, 1 SES), respectively. In the SES group, 7 thrombi (88%) were located in segments of NSC grade 0 and were attached to persistent uncovered struts (Figure 5). Another thrombus (12%) was found in a segment of NSC grade 1. Similar to SES, 4 thrombi (31%) and 2 thrombi (15%) in the PES group were found in segments of NSC grades 0 and 1, respectively. The other 7 thrombi (54%) were located in segments of NSC grade 2. No uncovered struts were identified around these thrombi, and surrounding areas were well covered by white neointima (Figure 5). The relationship between a thrombus and NSC grade in the area surrounding the thrombus is shown in Figure 6. In 1 case in the PES group, a thrombus was observed even at a restenotic lesion despite the fact that restenosis was infrequent (Figure 7).

**Discussion**

This angioscopic investigation demonstrated that maximum NSC was higher in PES than in SES. In contrast, minimum NSC and the prevalence of patients with uncovered struts

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**Table 3. Coronary Angiographic Findings**

<table>
<thead>
<tr>
<th></th>
<th>PES (n=18)</th>
<th>SES (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>2.84±0.41</td>
<td>2.80±0.26</td>
<td>0.72</td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>0.89±0.34</td>
<td>0.82±0.30</td>
<td>0.50</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>68.8±12.8</td>
<td>70.8±10.8</td>
<td>0.60</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>17.2±6.3</td>
<td>22.8±10.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Qualitative abnormalities, n (%)</td>
<td>3 (17)</td>
<td>4 (20)</td>
<td>0.79</td>
</tr>
<tr>
<td>Immediately after procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.72±0.36</td>
<td>2.64±0.28</td>
<td>0.44</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>4.3±12.7</td>
<td>5.7±9.8</td>
<td>0.70</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>1.83±0.36</td>
<td>1.82±0.29</td>
<td>0.93</td>
</tr>
<tr>
<td>Qualitative abnormalities, n (%)</td>
<td>2 (11)</td>
<td>2 (10)</td>
<td>0.91</td>
</tr>
<tr>
<td>Follow-up at 6 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.34±0.41</td>
<td>2.54±0.30</td>
<td>0.09</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>17.6±14.5</td>
<td>9.3±10.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.38±0.43</td>
<td>0.10±0.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Qualitative abnormalities, n (%)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Restenosis, n (%)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Focal pattern</td>
<td>1 (6)</td>
<td>1 (5)</td>
<td>0.94</td>
</tr>
<tr>
<td>Diffuse pattern</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Target lesion revascularization, n (%)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate.

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**Table 4. NSC on Angioscopy**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Minimum NSC, n</th>
<th>Maximum NSC, n</th>
<th>Heterogenicity of NSC, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PES (n=18)</td>
<td>8</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>SES (n=20)</td>
<td>7</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Categorical data between PES and SES were analyzed by the Mantel-Haenszel χ² test with 1 df. For minimum NSC, maximum NSC, and heterogenicity of NSC, P=0.83, P=0.0004, and P=0.0053, respectively.
(NSC grade 0) were similar between PES and SES. Most of the in-stent thrombi of SES were attached to uncovered struts (grade 0 segments associated with minimal late loss on angiogram). Within PES, thrombi were found not only in grade 0 segments but also in segments with complete coverage (grade 2 segments associated with larger late loss). In-stent thrombus was more frequent in PES than SES (72% versus 40%).

In our QCA analysis, late loss was greater in PES than in SES, similar to previous studies. Angioscopic findings showed that maximum NSC was significantly greater in PES than in SES. Moreover, maximum NSC was correlated with late loss on QCA. Angioscopic examination is not able to measure the absolute neointimal thickness because its images are not cross-sectional but only of the surface of coronary lumen. In an atherosclerotic plaque, the underlying lipid contents can be seen as a yellow plaque through a thinner fibrous cap (≤110 μm) by angioscopy, whereas a lipid plaque with a thicker fibrous cap (>110 μm) is observed as a white plaque. Therefore, it is understood that the thickness of the overlaying membrane is a determinant factor in angioscopic visualization of the underlying structures. Actually, the late loss in grade 2 of maximum NSC (invisible stent struts) was 0.48±0.46 mm and was significantly greater than that in grade 1 (visible stent struts). Therefore, patients with a larger late loss potentially had a segment better covered by neointima than did those with a smaller late loss. However, there were several limitations to determining the precise condition of NSC inside the whole stent segment on the basis of angiographic late loss. First, late loss between a grade 0 segment (without neointima) and grade 1 segment (with thin neointima) showed a slight difference (0.06±0.01 and 0.10±0.05 mm, respectively). These results suggested that the range of neointimal thickness between NSC grade 0 and 1 might be quite narrow. Second, late loss is usually measured at the point of maximum lumen narrowing and might reflect the best-covered segment within the stent (maximum NSC). It has been known that NSC within the DES is not uniform. Therefore, this angiographic parameter never reflects the segment least covered by neointima. In fact, no correlation between late loss and minimum NSC was found in this study. Third, some tissues inside the DES regarded as late loss may not be complete neointima and may contain other kinds of tissues such as thrombus, fibrin, and fibrinoid according to previous pathological reports.

In contrast to maximum NSC, minimum NSC was not different between PES and SES. Consequently, heterogeneity of NSC within PES was greater than that of SES at 6
months after implantation. These angioscopic findings suggested that neointimal growth in PES advanced partially but more heterogeneously than in SES. In addition, our study indicated that the prevalence of patients with uncovered struts was similar between the 2 kinds of DES. The presence of persistent uncovered stent struts is the most powerful predictor of LST after DES implantation.\textsuperscript{6,7} In this respect, therefore, PES may be equal to SES in developing LST.

With regard to in-stent thrombus, most of the thrombi within SES were attached to uncovered struts (NSC grade 0). These findings support the fact that uncovered struts with delayed healing contribute to the presence of thrombus.\textsuperscript{6,7} Notably, thrombi within PES were found not only in the segments of NSC grade 0 but also in the segments with complete coverage (NSC grade 2). Furthermore, 1 thrombus was observed even at a restenotic lesion of PES. These thrombotic segments of NSC grade 2 were probably regarded as segments with large angiographic late loss, and most of them had no qualitative angiographic abnormalities. These results indicated that the tissue inside PES regarded as late loss possibly contained thrombus. Moreover, patients treated by PES with relatively large late loss had a rate of uncovered struts similar to that of SES with a small late loss. Hence, our findings did not support the hypothesis that a larger late loss may have a protective role against thrombus formation.

The frequency of in-stent thrombus identified by angioscopy was significantly high (72% of PES versus 40% of SES). In an experimental report in which rabbits underwent PES and SES deployment in their iliac arteries, no mention of thrombus formation was found.\textsuperscript{17} Thrombogenicity may be quite different between a balloon injury model of rabbit iliac artery and advanced atherosclerotic plaque of human coronary artery. With regard to thrombogenicity, both of the drugs released from the DES, paclitaxel and sirolimus, enhance endothelial expression of tissue factors that exert prothrombogenic effects.\textsuperscript{18} A previous experimental study showed that relative to SES, reestablishment of a functional endothelium...
is delayed after PES implantation. Another pathological investigation using atherectomy specimens showed that delayed (or incomplete) healing and the appearance of fibrinoid were more pronounced in PES than in SES, even though the study was limited to restenotic lesions. As these studies have implied, the delayed endothelialization in PES may contribute to its high risk of thrombus formation compared with SES. Here, a question as to why part of the thrombus within the PES is located in the segment of complete coverage (NSC grade 2) is raised. As the above pathological study revealed, incomplete endothelialization was found even at the restenotic lesion of PES. Conventionally, white membranous structure covering stent struts was regarded as neointima by angioscopic evaluation. However, white neointima on angioscopy may not be accompanied by complete endothelialization. A thrombus may be formed in the area lacking endothelialization but covered by white tissue, especially in PES. It remains unclear whether fibrin and fibrinoid are recognized by angioscopic observation. In addition, it was unclear whether differences in drug-release kinetics, drug distribution within vessel wall, design of stent platform, or stent polymer between PES and SES affect the incidence of thrombus.

Previous 6-month angioscopic investigation for bare metal stents showed that frequencies of segments with uncovered struts and patients with in-stent thrombi were 6% and 8%, respectively. These ratios in both the PES and SES in this study were undoubtedly higher than with bare metal stents. Frequent incomplete neointimal coverage and in-stent thrombus probably are mutual features in first-generation DES.

Although all trials did not discover clinical differences between PES and SES, a recent meta-analysis showed that SES significantly reduced the risk of LST compared with PES. Moreover, a large-scale cohort study also indicated that LST occurred more frequently in patients treated with PES than in those treated with SES. A higher frequency of latent thrombus in PES likely results in a higher incidence of LST compared with SES. Nevertheless, there was a discrepancy between the prevalence of angiographic in-stent thrombus and the incidence of LST. When in-stent thrombi are present, additional special conditions such as increasing thrombogenicity of the blood and coronary flow disturbance may trigger the development of subclinical thrombus into clinical LST. A 2-year angioscopic follow-up study of patients treated with SES revealed that new thrombus appeared around uncovered struts despite continuous dual-antiplatelet therapy. Long-term follow-up study for PES also is required. Although in-stent thrombus and uncovered struts identified by angioscopy do not directly link to LST, prolonged dual-antiplatelet therapy in patients treated with DES is required to prevent LST regardless of large late loss.

Study Limitations
This study has several limitations. Although our study population was relatively small and select, our angioscopic observation demonstrated detailed features inside DES. The present data were not based on serial observation. It was unclear whether the thrombi were residual thrombi or newly formed thrombi. Baseline characteristics, including the proportion of acute coronary syndrome, were similar between SES and PES. Therefore, comparing the frequency of thrombus was meaningful. It is impracticable to quantitatively evaluate angioscopic data. Alternatively, a semiquantitative analysis for NSC was performed. Serial measurements by intravascular ultrasound were not performed; therefore, measures such as incomplete stent deployment and malapposition could not be assessed. Finally, the macroscopic NSC assessed by angioscopy probably did not completely reflect the pathological endothelialization.

Conclusions
This study suggests that angiographic large late loss within the DES segment is not associated with a low risk of thrombus as determined by angioscopy. Prolonged dual-antiplatelet therapy for patients treated with DES might be required regardless of large late loss.

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Disclosures
None.

References
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Angioscopic Comparison Between PES and SES


The present investigation was performed to compare angiographic and angioscopic findings at 6-month follow-up between 2 kinds of first-generation drug-eluting stents (DES): paclitaxel-eluting stents and sirolimus-eluting stents. Late loss, an angiographic index of neointimal coverage, was greater in paclitaxel- than in sirolimus-eluting stents (0.38 ± 0.43 versus 0.10 ± 0.23 mm, respectively). Direct visualization by angioscopy showed that uncovered stent struts, histologically a predictor of late stent thrombosis, were commonly and equally observed in both paclitaxel- and sirolimus-eluting stents (44% versus 40%, respectively). The proportion of uncovered stent struts and thrombi to total struts examined within the DES were higher than those seen with bare metal stents in previous angiographic reports. Although both uncovered stent struts and thrombi within the DES did not directly link to the occurrence of late stent thrombosis during the follow-up period, our results suggested that greater angiographic late loss was not associated with a lower risk of angiographically detected thrombus formation in current DES. Our findings also imply that prolonged dual-antiplatelet therapy may be required for patients treated with first-generation DES to prevent the occurrence of late stent thrombosis, regardless of the extent of late loss. Angioscopy may provide important information for the clinical management of patients treated with DES, beyond the information provided by angiography.
Lack of Association Between Large Angiographic Late Loss and Low Risk of In-Stent Thrombus: Angioscopic Comparison Between Paclitaxel- and Sirolimus-Eluting Stents
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