Serial Angioscopic Evidence of Incomplete Neointimal Coverage After Sirolimus-Eluting Stent Implantation Comparison With Bare-Metal Stents

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**Background**—The time course of neointimal formation after stent implantation has not been studied extensively by angioscopy in the drug-eluting stent era.

**Methods and Results**—Serial angioscopic findings at first follow-up (3.6±1.1 months), second follow-up (10.5±1.6 months), and third follow-up (21.2±2.2 months) after stent implantation were compared between sirolimus-eluting stents (SES, n=17) and bare-metal stents (BMS, n=11). Neointimal coverage, thrombus, and presence of yellow plaques underneath the stents were assessed. Neointimal coverage was graded as follows: grade 0, stent struts were fully visible; grade 1, struts bulged into the lumen, although they were covered; grade 2, struts were embedded by the neointima but were seen translucently; or grade 3, struts were fully embedded and invisible. Neointimal coverage was remarkably different between SES and BMS at each follow-up point. Neointimal coverage grade was 1.1±0.5 in SES versus 2.9±0.3 in BMS at the first follow-up (P<0.0001), 1.1±0.5 in SES versus 3.0±0.0 in BMS (P<0.0001) at the second follow-up, and 1.3±0.5 in SES versus 3.0±0.0 in BMS at the third follow-up (P=0.0009). No significant serial changes in coverage grade were noted in the BMS group, whereas coverage grade slightly but significantly increased at the third follow-up in the SES group (P<0.05). Thrombi were detected in 4 SES: a red thrombus was seen from the first to the third follow-up in 2; another was detected only at the third follow-up; and the fourth was seen at the first follow-up but disappeared at the second follow-up, associated with a new white thrombus despite dual antiplatelet therapy. Yellow plaques had disappeared by the time of the second follow-up in BMS. In contrast, yellow plaques were exposed in 71% of SES at the first follow-up and remained exposed until the third follow-up. Neointimal coverage grades correlated with thrombi (P=0.002) and with yellow plaques (P<0.0001).

**Conclusions**—Serial angioscopic findings up to 2 years after SES implantation were markedly different from those after BMS. Neointimal coverage was completed by 3 to 6 months in BMS. In contrast, SES demonstrated the presence of thrombi and yellow plaques even as much as 2 years after implantation. (Circulation. 2007;116:910-916.)

**Key Words:** coronary disease ■ imaging techniques ■ stents ■ thrombus

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Angioscopy, by using light instead of ultrasound, is a suitable tool for the visualization of lumen/stent surfaces. Angioscopy, we have previously reported incomplete

Sirolimus-eluting stents (SES) have demonstrated a major breakthrough in the reduction of restenosis compared with bare-metal stents (BMS) by inhibiting neointimal hyperplasia. Vascular brachytherapy also inhibits neointimal hyperplasia and thereby reduces restenosis; however, lesions that received vascular brachytherapy showed delayed neointimal hyperplasia, which was related to late stent thrombosis. Hence, similar to brachytherapy, insufficient neointimal coverage may be prolonged after SES implantation. In fact, several intravascular ultrasound (IVUS) studies demonstrated the sustained suppression of neointimal hyperplasia more than 1 year after SES implantation. The suppressed neointimal hyperplasia after SES implantation necessitated in situ evaluation of the extremely thin neointima. Although IVUS is a robust tool for the quantification of neointima, the resolution of IVUS may not be sufficient for measuring the suppressed neointima after SES.

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neointimal coverage and associated subclinical thrombosis 3 to 6 months after SES implantation, but the condition of intravascular surfaces more than 6 months after SES implantation remains unclear. Accordingly, in the present study, we investigated the time course of neointimal morphology using angioscopy as much as 2 years after SES implanted for de novo lesions of the native coronary arteries and compared the findings with BMS.

Methods

Patients

The study cohort consisted of 17 patients in whom 28 stents had been implanted in de novo native coronary lesions (14 men [82%]; age range 35 to 78 years old). Ten patients were treated with 17 SES (Cypher, Cordis, Miami, FL), and 8 patients were treated with 11 BMS (5 Bx Velocity, Cordis; 2 Zeta, Guidant Corp, St. Paul, Minn; 2 Express2, Boston Scientific, Natick, MA; 1 Driver, Medtronic, Minneapolis, Minn; and 1 Tsunami, Terumo, Tokyo, Japan). One patient was treated with both SES and BMS and was included in both groups. Patients who underwent percutaneous coronary intervention before August 2004 were treated with BMS alone because SES have only been available since August 2004 in Japan. SES were used after this date unless patients had not tolerated dual antiplatelet therapy (ticlopidine in addition to aspirin). Acute coronary syndrome patients were treated with BMS alone.

Between October 2004 and December 2006, all patients underwent serial coronary angioscopy at the first follow-up (3.6±1.1 months, median 3.1 months) and the second follow-up (10.5±1.6 months, median 10.3 months). In addition, 10 patients (14 SES and 4 BMS) underwent the third follow-up angioscopy (21.2±2.2 months, median 21.5 months). The medical ethics committee at Kansai Rosai Hospital approved the study, and all patients gave written informed consent.

Fourteen patients (82%) had hypertension, 16 (94%) had hyperlipidemia, 11 (65%) had diabetes mellitus, and 7 (41%) were current smokers. Hypertension included 1 or more of the following: antihypertensive medication use, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Hyperlipidemia included 1 or more of the following: treatment with medication, total cholesterol ≥220 mg/dL, LDL cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, or triglycerides ≥150 mg/dL. Diabetes mellitus included 1 or more of the following: oral agent or insulin treatment or hemoglobin A1C ≥6.5%.

Antiplatelet Regimen

All patients were taking aspirin 100 mg/d. Ticlopidine 200 mg/d was additionally given for at least 3 months after SES and for at least 1 month after BMS implantation. Neither glycoprotein Ib/IIa inhibitors nor clopidogrel was used because they have not been approved for clinical use in Japan.

Angiographic and Angioscopic Follow-Up

Heparin (5000 IU) was administered into the femoral artery via the inserted sheath, and isosorbide dinitrate (2.5 mg) was administered into the coronary artery before the procedure. Angioscopy was performed after coronary angiography with Vecmova (Clinical Supply, Gifu, Japan). Details about the procedure and specifications for these devices have been described elsewhere. Briefly, the optical fiber was placed at the distal segment of the coronary artery and was manually pulled back from the distal edge of the stent to the proximal edge under careful angioscopic and angiographic guidance. Angioscopic images consisted of 3000 pixels with full color and were stored on digital videotapes for subsequent analysis. The resolution of the angioscope used in the present study was 70 μm at a distance of 5 mm (manufacturer’s specifications), which was far better than the lateral resolution of IVUS (430 to 830 μm).

Quantitative Coronary Angiography

We routinely performed coronary angiography in at least 10 projections, and quantitative coronary angiography was performed with the Cardiovascular Angiography Analysis System (Pie Medical BV; Maastricht, The Netherlands) with the “worst view” used to assess the severity of the stenosis. Serial changes of quantitative coronary angiography were evaluated with the same angle of projection.

Angioscopic Analysis

Angioscopic images were analyzed with a focus on the following: (1) degree of neointimal coverage over the stent; (2) existence of thrombus; and (3) plaque characteristics underneath the stent struts. Neointimal coverage over the stent was classified into 4 grades as described previously. In brief, grade 0=stent struts were fully visible, similar to immediately after implantation; grade 1=stent struts bulged into the lumen and, although covered, were still transparently visible; grade 2=stent struts were embedded by the neointima but were seen translucently; and grade 3=stent struts were fully embedded and were invisible by angioscopy. Neointimal coverage was evaluated in the entire stented segments, and if neointimal coverage was heterogeneous, the dominant pattern was adopted. Any grade 0 coverage independent of length and dominance was marked separately from the dominant patterns. Overlapped stent segments were also evaluated separately. Thrombus was defined on the basis of the criteria adopted by the European Working Group on Coronary Angiography. The angioscopic definition of yellow plaques was adopted from previous reports, and the existence of yellow plaques underneath the stent was evaluated.

Statistical Analysis

Statistical analysis was performed with JMP 5.1 (SAS Institute, Cary, NC). All results are expressed as mean±SD unless otherwise stated. Wilcoxon rank sum test was used to compare the patient groups. Wilcoxon signed rank test was used for comparison between pairs. Friedman test was used for serial follow-up that included the third follow-up. Categorical variables were analyzed with Fisher exact test or χ² test. Statistical significance was defined as P<0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Comparison Between SES and BMS

Coronary risk factors were equally distributed in the SES and BMS groups (data not shown). The first follow-up was performed 3.6±0.8 months after SES and 4.2±1.5 months after BMS implantation (P=0.2). The second follow-up was done 10.2±1.3 months after SES and 11.0±1.4 months after BMS implantation (P=0.4). The third follow-up was done 20.5±2.2 months after SES (n=14) and 19.0±1.1 months after BMS (n=4) implantation (P=0.2). Dual antiplatelet therapy was continued until the third follow-up in all SES and in 4 (36%) of the BMS. The other BMS-implanted patients received dual antiplatelet regimen for ~1 month after stent implantation.

Lesion and Procedural Characteristics

No significant differences were noted between the SES and BMS groups with regard to lesion and procedural characteristics except for stent length (Table 1).

Quantitative Coronary Angiography

No significant differences existed in quantitative coronary angiography findings between the SES and BMS groups immediately after stent implantation with regard to minimal...
Angioscopic Findings

Mean neointimal coverage grade at the first follow-up was 2.9±0.3 in BMS versus 1.1±0.5 in SES (P<0.0001); at the second follow-up, it was 3.0±0.0 in BMS versus 1.1±0.5 in SES (P<0.0001), and at the third follow-up, it was 3.0±0.0 in BMS versus 1.3±0.5 in SES (P=0.0009; Figure 1). Hence, neointimal coverage grades were markedly different between SES and BMS throughout the study period. Although the stent length was longer in SES than in BMS, the stent length of each grade did not differ significantly when compared at the second follow-up: grade 0=23.0±0.0 mm, grade 1=25.7±1.2 mm, grade 2=23.0±2.5 mm, and grade 3=21.0±1.3 mm (P=0.2) in both the SES and BMS groups. A white thrombus was observed in an SES implanted segment, and mural red thrombi were observed in 4 patients in the SES group. Yellow plaques were detected in 12 SES (71%) and 1 BMS (9%) at the first follow-up (P=0.002). At the second and third follow-ups, no yellow plaques were evident in BMS, although all the yellow plaques remained in the SES implanted segments. The relationship between neointimal coverage, presence of thrombi, and existence of yellow plaques is shown in Tables 3 and 4. In the entire cohort of 74 angioscopic observations, a relationship existed between neointimal coverage grades and the presence of thrombi (P=0.002). In addition, low neointimal coverage grades were associated with yellow plaques (P<0.0001). Detailed characteristics of individual patients and stents in the SES group are described in Tables 5 and 6.

### Table 2. Serial Changes in Quantitative Coronary Angiography Data

<table>
<thead>
<tr>
<th></th>
<th>After Stent Implantation</th>
<th>First Follow-Up</th>
<th>Second Follow-Up</th>
<th>Third Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.84±0.41</td>
<td>2.06±0.33*</td>
<td>1.79±0.50*</td>
<td>...</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>14.3±6.00</td>
<td>30.0±11.2*</td>
<td>34.0±18.1*</td>
<td>...</td>
</tr>
<tr>
<td>In-stent late loss, mm (since stent implantation)</td>
<td>...</td>
<td>0.79±0.60</td>
<td>1.05±0.65</td>
<td>...</td>
</tr>
<tr>
<td><strong>SES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.74±0.40</td>
<td>2.66±0.38†</td>
<td>2.55±0.52†</td>
<td>2.46±0.52</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>12.1±6.11</td>
<td>15.3±9.08†</td>
<td>17.7±13.4†</td>
<td>16.0±18.1</td>
</tr>
<tr>
<td>In-stent late loss, mm (since stent implantation)</td>
<td>...</td>
<td>0.08±0.11†</td>
<td>0.19±0.43†</td>
<td>0.20±0.57</td>
</tr>
</tbody>
</table>

*Data are mean±SD. The third follow-up in the BMS arm included only 4 stents, for which the data are not shown.

*Statistical differences were observed vs after stent implantation.

†P<0.01 vs BMS.
TABLE 3. Relationship Between Neointimal Coverage and Thrombus

<table>
<thead>
<tr>
<th></th>
<th>Grade 0/1</th>
<th>Grade 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus present</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Thrombus absent</td>
<td>29</td>
<td>36</td>
</tr>
</tbody>
</table>

*P = 0.002 by Fisher exact test.*

Figure 1. Changes in neointimal coverage grades from the first to the third follow-up in 28 stents. Seventy-six percent of the SES showed grade 1 coverage, whereas 91% of BMS showed grade 3 coverage at the first follow-up. Grade 3 coverage was noted in the BMS group throughout the follow-up term except for 1 stent that showed grade 2 coverage. In contrast, lower-grade neointimal coverage (grades 0 to 2) was recognized in the SES group. Although neointimal coverage grade remained unchanged from the first to the second follow-up in the SES group, it became slightly greater at the third follow-up in 3 SES stents. Open circles represent SES group (n = 17); solid circles, BMS group (n = 11).

Serial Changes After Stent Implantation

Although MLD, percent diameter stenosis, and in-stent late loss significantly worsened from immediately after stenting to the first follow-up in the BMS group, no significant differences existed between the first and second follow-ups in either the SES or the BMS group, although a trend could be observed in the BMS group to a late loss increase compared with the SES group (Table 2). Thirteen SES (76%) showed grade 1 coverage at the first follow-up, whereas 91% of BMS revealed grade 3 coverage (Figure 1). The other BMS, which showed grade 2 coverage at first follow-up, changed to grade 3 at the second follow-up. All BMS unanimously showed grade 3 coverage at the third follow-up. All SES remained unchanged from the first to the second follow-up, but by the time of the third follow-up, an SES of grade 0 had changed to grade 1, and 2 SES of grade 1 had become grade 2. Hence, neointimal coverage grade was unchanged from the first to the second follow-up both in BMS and in SES, but it became slightly greater afterward in SES (*P* < 0.05). Neointimal proliferation was completely different between SES and BMS throughout the follow-up period (Figures 2 and 3). We also analyzed grade 0 coverage independent of length and dominance. One of the SES showed grade 0 throughout the stent. Additionally, localized grade 0 coverage was detected in 4 stents: 3 were localized at the ostium of a side branch, and the other was localized at the stent-overlapped segment of SES covering SES. All segments showing grade 0 were detected from the first follow-up; no new grade 0 appeared during the follow-up term. Two of the 5 segments classified as grade 0 became grade 1 at the third follow-up; the others remained grade 0 during the follow-up term. Thus, grade 0 coverage in SES remained grades 0 to 1 even 2 years after implantation (Table 6).

A mural red thrombus was detected in 4 SES. A red thrombus was seen from the first to the third follow-ups in 2 SES; another was detected only at the third follow-up; and the other was seen at the first follow-up, but it was replaced with a new white thrombus at the second follow-up, which disappeared at the third follow-up. It was difficult to determine whether thrombi observed by angioscopy were persistent in a particular location or newly formed.

Yellow plaques underneath the stent struts were decreased from 13 to 12 segments from the first to the second follow-ups. A BMS showing grade 2 coverage at the first follow-up presented yellow plaques underneath the stent, but the plaques disappeared at the second follow-up. In this case, the neointimal coverage over the stent struts changed to grade 3 (ie, neointimal proliferation sealed the yellow plaques underneath), although the yellow plaques were persistently seen at the reference segments (outside the stent). The remainder of the yellow plaques in SES were recognized serially until the third follow-up.

Angioscopic Findings of Neointimal Coverage at Stent-Overlapped Segments

Eight stented segments were overlapped (BMS covering BMS [n = 2], SES covering SES [n = 4], and BMS covering SES [n = 2]). BMS covering BMS segments presented grade 3 neointimal coverage throughout the follow-up term. In contrast, SES covering SES showed low-grade coverage. One of the SES overlapped segments demonstrated grade 0. Another remained as grade 1 throughout the follow-up period. Another remained as grade 1 until the second follow-up, then changed to grade 2 at the third follow-up. The remainder revealed in-stent restenosis, demonstrating grade 3 coverage.
TABLE 6. Details of Individual Stents in SES Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treated vessels</strong></td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
<td>LAD</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Prox</td>
<td>Mid</td>
<td>Mid</td>
<td>Prox</td>
<td>Mid</td>
<td>Dist</td>
<td>Mid</td>
<td>Prox</td>
<td>Mid</td>
<td>Prox</td>
</tr>
<tr>
<td><strong>Implanted stent</strong></td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.0</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Length, mm</strong></td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>28</td>
<td>23</td>
<td>28</td>
<td>18</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td><strong>Stent/artery at implantation</strong></td>
<td>1.3</td>
<td>1.1</td>
<td>1.3</td>
<td>1.1</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Infrastent restenosis</strong></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Dominant neointimal grade</strong></td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Existence of grade 0</strong></td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Thrombus</strong></td>
<td>Red</td>
<td>−</td>
<td>−</td>
<td>Red</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Red</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Yellow plaque</strong></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; Prox, proximal; dist, distal; DS, diameter stenosis; +, present; −, absent; and N/A, not available because third follow-up was not performed.

*Restenotic site (12 mm of lesion length) showed grade 3 neointimal coverage, whereas the other surfaces showed grade 1 coverage.

†At the ostium of a side branch.

‡At overlapping segments.

Discussion

The present study demonstrated that all BMS had grade 3 neointimal coverage by the first follow-up (4.2 ± 1.5 months after implantation) except for 1 that had grade 2 coverage. In contrast, the majority of SES had grade 1 neointimal coverage. An SES revealed totally exposed struts throughout the stent even at the second follow-up (10 months after implantation). The low-grade neointimal coverage observed in SES left the underlying plaques unsealed. Hence, 71% of SES demonstrated yellow plaques beneath the stent struts during the follow-up periods. Subclinical thrombi were also associated with low-grade (grade 0 or 1) coverage.

Several modalities have been used to evaluate the patterns of neo-intima after BMS, such as angiography, IVUS, and angioscope. Angiographic studies have shown that the peak of neointimal hyperplasia falls within 6 months after stenting. Afterward, MLD increases up to 3 years (regression). An IVUS study showed neointimal hyperplasia progressed uniformly throughout the stent. Earlier angioscopic studies showed the transparency of neo-intima gradually decreased for 3 to 6 months after stenting, where the transparency of neo-intima was associated with the thickness of the neo-intima. These results were in accordance with the present observations in the BMS arm.

Neointimal proliferation after SES implantation has been less well understood. The First In Man study reported long-term follow-up using both quantitative coronary angiography and IVUS for as long as 48 months and showed a virtual lack of neointimal hyperplasia after implantation of a slow-release SES, which has a similar release profile as the Cypher stent. Using angioscopy, we found incomplete neointimal coverage after SES within 6 months in our previous study. Such a prolonged tissue reaction as seen in SES implanted segments resembles that after vascular brachytherapy. Tissue proliferation after SES may be completed by 6 months after implantation. In contrast, the healing process after SES implantation may continue well beyond a year. Interestingly, neointimal coverage became slightly but significantly greater at the third follow-up in the SES group, although no significant differences were found between the first and second follow-ups in either the BMS or SES group. Angioscopy showed grade 1 to 2 coverage in 94% of SES as early as 4 months after implantation, and all SES showed grade 1 to 2 coverage after 2 years, whereas IVUS showed a virtual lack of neo-intima in these periods in the First In Man study. The incidence and timeline of incomplete coverage after implantation of emerging drug-eluting stents should be investigated in large-scale studies.

The present study showed a correlation between neointimal grade and the presence of thrombi (P = 0.002). No thrombus was detected in BMS throughout the follow-up period. In contrast, 4...
Stabilization of unstable plaques. These authors claimed that BMS demonstrated that stent implantation may aid in the slow healing process. A previous pathological study suggested thrombus attachment was the initial phase for vascular repair. One could speculate that the low-grade coverage over SES might be a consequence of the slow healing process.

Interestingly, low-grade (grade 0 to 1) neointimal coverage was associated with the presence of yellow plaques underneath the stent struts \((P<0.0001)\). The majority of stents with grade 0 to 1 coverage (76%) showed yellow plaques, whereas yellow plaques were reduced to 55% with grade 2 coverage. No stent presenting with grade 3 had yellow plaques. A previous angioscopic study that assessed serial morphological changes after BMS demonstrated that stent implantation may aid in the stabilization of unstable plaques. These authors claimed that stenting induced angioscopic plaque stabilization (smooth and white plaques without thrombi) by neointimal proliferation. Using angioscopy, Miyamoto et al demonstrated that in vitro intimal wall thickness and percent yellow saturation correlated inversely (ie, angioscopic color reflected the thickness of the fibrous cap), which indicates the high resolution of angioscopy. Sealing was completed \(\approx 6\) months after BMS and was associated with complete neointimal coverage. The majority of SES, however, demonstrated grade 1 neointimal coverage at 2 years after implantation in the present study.

Despite the fact that subclinical thrombus in 3 stents and yellow plaques in many stents were found with low-grade neointimal coverage even at 2 years after SES implantation, none of the patients experienced thrombotic clinical events during the follow-up period. These angioscopic findings had no direct link to thrombotic clinical events. The fact that all patients remained under dual antiplatelet therapy is a confounding factor. Large-scale controlled studies are warranted.

**Study Limitations**

The present study has several limitations. First, this study was a single-center, nonrandomized, historical control study with a small sample size. Nonetheless, the patient background was not statistically different between groups except for stent length, and serial changes in neointimal coverage were assessed in identical patients. Second, although the angioscope we used provides a wide-angle forward view, anatomic structures, such as tortuous vessels, may prohibit a complete circumferential view, which may lead to small regions without neointimal hyperplasia being missed in the examination. Third, we assessed neointimal coverage over the stent using angioscopy, which may include changes in the transparency of the neointima and neointimal thickness; however, those factors cannot be differentiated by angioscopy. Next, the present study only investigated neointimal morphology; local endothelial functional status remains unclear. Indeed, endothelial coverage rather than neointimal hyperplasia is the goal after stent implantation. Reendothelialization with a functional active endothelium has yet to be demonstrated in animals or humans even after BMS implantation. Unfortunately, detection of the endothelial monolayer at stented segments has not been established in living humans, even though optical coherence tomography has higher resolution than IVUS. Finally, only 4 patients underwent angioscopy at the third follow-up in the BMS group. Nonetheless, this should not affect the conclusions, because all of the BMS patients showed grade 3 coverage.

**Conclusions**

Serial angioscopic findings up to 2 years after SES implantation were markedly different from those after BMS implantation. Neointimal coverage was completed by 3 to 6 months after BMS implantation. In contrast, SES demonstrated the presence of thrombi and yellow plaques even 2 years after implantation.

**Acknowledgments**

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**Disclosure**

None.

**References**


**CLINICAL PERSPECTIVE**

Drug-eluting stents (DES) have demonstrated a major breakthrough in the reduction of restenosis compared with bare-metal stents by inhibiting neointimal hyperplasia. However, recent reports have indicated that there may be an increased risk of late and very late (≥1 year) stent thrombosis with the use of DES. This thrombosis may be due to incomplete neointimal coverage over the DES. Late stent thrombosis occurs most commonly after the discontinuation of dual antiplatelet therapy. A number of science advisory boards have recommended the continuation of dual antiplatelet therapy for 12 months after DES implantation if patients are not at high risk of bleeding. Nonetheless, sufficient evidence does not exist for the continuation or discontinuation of dual antiplatelet therapy beyond 12 months after DES implantation. Angioscopy is a robust tool for the visualization of lumen/stent surfaces. In the present study, we performed serial angiographic observations after sirolimus-eluting stent implantation at 4 months, 11 months, and 2 years and demonstrated that neointimal coverage after sirolimus-eluting stent implantation was not completed by 2 years, as demonstrated by the presence of yellow plaques and subclinical thrombi, whereas bare-metal stents showed complete neointimal coverage. Our angiographic findings may support the need for prolonged dual antiplatelet therapy beyond 1 year after sirolimus-eluting stent implantation, although the optimal duration of dual antiplatelet therapy has yet to be determined.

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