Angioscopic Assessment of Arterial Repair Following Biodegradable Polymer-Coated Biolimus A9-Eluting Stent Implantation – Comparison With Durable Polymer-Coated Sirolimus-Eluting Stent –

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**Background:** Second-generation drug-eluting stents (DES) are expected to show better arterial repair than older DES. We angioscopically compared the biodegradable polymer-coated biolimus A9-eluting stent (BES) and durable polymer-coated sirolimus-eluting stent (SES) to explore differences in arterial repair.

**Methods and Results:** Angioscopy was performed 9±1 months after 15 BES and 16 SES were implanted initially in the native coronary artery. Heterogeneity of neointimal coverage (NIC) as well as the dominant NIC grade was examined. NIC was defined as: grade 0 = fully visible struts; grade 1 = struts bulging into the lumen, but covered; grade 2 = embedded, but translucent struts; grade 3 = invisible struts. Heterogeneity was judged when the NIC grade varied ≥1. In-stent late loss (0.06±0.23 vs. 0.07±0.18 mm, P=0.80), and dominant NIC grade (1.5±0.8 vs. 1.3±0.7, P=0.45) were similar for BES and SES. Within the stents, NIC was more heterogeneous in SES than in BES (P=0.035). 80% of BES showed homogeneous NIC, while 56% of SES had heterogeneous NIC.

**Conclusions:** BES showed limited late loss similar to that for SES. Nonetheless, the NIC with BES was more homogeneous than that with SES. Biodegradable polymer-coated BES may have an advantage in homogeneous NIC.

**Key Words:** Angioscopy; Biodegradable polymer; Biolimus A9; Durable polymer; Neointima

**D**rug-eluting stents (DES) have drastically reduced in-stent late loss (LL) and target lesion revascularization (TLR) by inhibiting neointimal hyperplasia. However, poor reendothelialization, partly due to hypersensitivity reactions to polymer carriers, has gained attention as a cause for late stent thrombosis (LST) with first-generation DES.

With the second-generation DES, various attempts have been made to achieve both inhibitory effects on restenosis and sufficient arterial repair. The TRE-956 stent (Terumo Corporation, Tokyo, Japan) is a second-generation DES that elutes biolimus A9, an analog of sirolimus. Because biolimus A9 is more highly lipophilic than sirolimus, the transport and tissue retention of the drug should be better.

Biodegradable polymer (polylactic acid) is adopted only to the abluminal stent surface, ensuring that drug is distributed to the target vessel tissue side. Hence, adequate vascular healing as well as strong inhibitory effects on restenosis may be expected with the TRE-956 stent. Using angioscopy, we sought to investigate the intra-stent conditions following biolimus A9-eluting stent (BES) implantation, and to compare the results with the first-generation sirolimus-eluting stents (SES, Cypher, Cordis, Miami Lakes, FL, USA).

**Methods**

**Patients**
The study subjects consisted of 31 DES implanted in 24 patients (19 men, age range 50–80 years) who suffered from stable angina pectoris. Between July 2007 and July 2008, 18...
BES were implanted in 12 patients in a clinical trial of the TRE-956 stent in our facility and 10 of these patients (15 BES implanted for 12 lesions) agreed to undergo follow-up angiography as well as angioscopy. Follow-up angiography was performed approximately 8 months after stent implantation. Angioscopic findings were compared with the pooled data of 16 SES in consecutive 14 patients who also fulfilled the matching criteria. Patients all agreed to receive follow-up angioscopy 8 months after implantation. Matching criteria included: (1) de novo lesion >50% diameter stenosis that caused myocardial ischemia; (2) native coronary artery of 2.25–3.5 mm in diameter; (3) non-culprit lesion in acute coronary syndrome; (4) total stented length <47 mm. All stents were implanted using standard techniques. The Medical Ethics Committee at Kansai Rosai Hospital approved the study, and all patients gave written informed consent.

**Table 1. Patient and Lesion Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>BES</th>
<th>SES</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>65.1±9.87 [65.5]</td>
<td>65.6±7.06 [67.5]</td>
<td>0.77</td>
</tr>
<tr>
<td>Male</td>
<td>7 (70)</td>
<td>12 (86)</td>
<td>0.61</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (90)</td>
<td>11 (79)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (100)</td>
<td>12 (86)</td>
<td>0.49</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (60)</td>
<td>4 (29)</td>
<td>0.21</td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (60)</td>
<td>7 (50)</td>
<td>0.70</td>
</tr>
<tr>
<td>History of previous MI</td>
<td>3 (30)</td>
<td>3 (21)</td>
<td>0.67</td>
</tr>
<tr>
<td>No. of treated lesions</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>LAD/LCX/RCA</td>
<td>4 (33)/4 [33]/4 (33)</td>
<td>8 (57)/2 (14)/4 (29)</td>
<td>0.40</td>
</tr>
<tr>
<td>Type B2/C lesions*</td>
<td>7 (58)</td>
<td>10 (71)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD [median] or number (%). *Based on American College of Cardiology/American Heart Association Classification.

BES, biolimus A9-eluting stent; SES, sirolimus-eluting stent; MI, myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

**Table 2. Procedural Characteristics and Serial Changes in Quantitative Coronary Angiography Data**

<table>
<thead>
<tr>
<th></th>
<th>BES (15)</th>
<th>SES (16)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Number of stents</td>
<td>15</td>
<td>16</td>
<td></td>
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<tr>
<td>Stent diameter, mm</td>
<td>3.17±0.31 [3.00]</td>
<td>3.22±0.31 [3.25]</td>
<td>0.61</td>
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<tr>
<td>Stent length, mm</td>
<td>15.6±6.90 [18.0]</td>
<td>18.2±6.78 [23.0]</td>
<td>0.30</td>
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<tr>
<td>Stents for lesion, number</td>
<td>1.3±0.5 [1.10]</td>
<td>1.1±0.4 [1.09]</td>
<td>0.50</td>
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<tr>
<td>Stent-to-artery ratio</td>
<td>1.11±0.12 [1.10]</td>
<td>1.14±0.16 [1.09]</td>
<td>0.87</td>
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Quantitative coronary angiography

Pre-intervention

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<thead>
<tr>
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<th>BES (15)</th>
<th>SES (16)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Lesion length, mm</td>
<td>15.2±6.90 [15.3]</td>
<td>18.2±6.77 [18.9]</td>
<td>0.30</td>
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<tr>
<td>Reference diameter, mm</td>
<td>2.88±0.49 [2.77]</td>
<td>2.86±0.39 [2.92]</td>
<td>0.58</td>
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<tr>
<td>Minimal lumen diameter, mm</td>
<td>0.69±0.24 [0.64]</td>
<td>0.58±0.28 [0.68]</td>
<td>0.73</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>75.8±6.90 [76.0]</td>
<td>79.9±10.3 [77.6]</td>
<td>0.45</td>
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</tbody>
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Post-intervention

<table>
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<th>BES (15)</th>
<th>SES (16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.86±0.26 [2.79]</td>
<td>2.69±0.34 [2.78]</td>
<td>0.34</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>12.5±7.60 [13.0]</td>
<td>10.4±5.56 [11.0]</td>
<td>0.31</td>
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Follow-up

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<th>BES (15)</th>
<th>SES (16)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Minimal lumen diameter, mm</td>
<td>2.80±0.34 [2.81]</td>
<td>2.62±0.31 [2.61]</td>
<td>0.10</td>
</tr>
<tr>
<td>Diameter stenosis, %</td>
<td>12.7±7.58 [11.0]</td>
<td>15.3±7.37 [15.6]</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Follow-up duration, months

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<thead>
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<th></th>
<th>BES (15)</th>
<th>SES (16)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Follow-up duration, months</td>
<td>8.7±0.48 [8.67]</td>
<td>8.6±1.03 [8.40]</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD [median].

BES, biolimus A9-eluting stent; SES, sirolimus-eluting stent.

**Antiplatelet Regimen**

All patients were taking aspirin 100–200 mg/day. Ticlopidine 200 mg/day was additionally given at the end of follow-up angiography except for 2 patients. Neither glycoprotein IIb/IIIa inhibitors nor clopidogrel was used because they were not approved for clinical use in Japan at the time of this study.

**Angiographic and Angioscopic Follow-up**

After the administration of heparin (5,000 IU) into the femoral artery via the inserted sheath, and isosorbide dinitrate (2.5 mg) into the coronary artery, angiography was performed following coronary angiography using VecmovaNEO™ (FiberTech, Tokyo, Japan). The detailed specifications and the procedures have been described elsewhere. Briefly, the optical fiber was placed at the distal segment of the coronary artery and manually pulled back from the distal edge of the stent to the...
proximal edge under careful fluoroscopic and angioscopic guidance. Angioscopic images consisted of 3,000 pixels with full color, and were stored on digital videotapes for off-line analysis.

**Quantitative Coronary Angiography**
We routinely performed coronary angiography in at least 10 projections, and the view showing the most severe stenosis was selected for quantitative coronary angiography. Quantitative coronary angiography was performed using the CASS system (Pie Medical BV, Maastricht, The Netherlands) at pre-, post-intervention, and at follow-up with the same angle of projection.

**Angioscopic Analysis**
Angioscopic images were analyzed by focusing on the following: (1) the dominant degree of neointimal coverage (NIC) over the stent; (2) heterogeneity of NIC; (3) existence of thrombus; (4) existence of yellow plaques underneath the stent. NIC over the stent was classified into 4 grades as previously described. In brief, grade 0 = stent struts fully visible, similar to immediately after implantation; grade 1 = stent struts bulge into the lumen, and although covered, are still transparently visible; grade 2 = stent struts embedded in neointima, but translucent; and grade 3 = stent struts fully embedded and invisible on angioscopy. The definition of the heterogeneity of NIC was adopted from our previous study. If different NIC grades of more than or equal to 1 grade were present in the entire stented segment, then NIC was judged as heterogeneous. Struts crossing the side branches were excluded from grading because they all showed grade 0 regardless of the stent type. The stent edges and overlapping segments were also excluded from heterogeneity analysis in the same manner as in our previous analysis. Homogeneous NIC means that all stent struts had an identical grade, except for the side branch ostia, stent edges, and stent overlap segments. Thrombus was defined according to the criteria adopted by the European Working Group on Coronary Angioscopy. The angioscopic definition of yellow plaque was adopted from earlier reports, and the existence of yellow plaques underneath the stent was evaluated.

**Statistical Analysis**
All results are expressed as mean±SD [median] or number (%). Comparisons between 2 groups were done with the Wilcoxon rank sum test. Categorical variables were analyzed with chi-square test; if ≥1 cell had expected values less than 5 in 2×2 comparisons, Fisher’s exact test was used. The analyses for quantitative coronary angiography and angioscopic findings were performed per stent, but not per patient. Statistical significance was defined as P<0.05. All calculations were performed using JMP, version 7.0.1 (SAS Institute, Cary, NC, USA).

**Results**

**Patients**
Patients’, lesion, and procedural characteristics were equally distributed among the groups (Tables 1, 2). The periods from stent implantation to follow-up angiography and angioscopy were similar (Table 2). All patients were prescribed aspirin, and all continued taking ticlopidine for the duration of this study except for 1 SES-implanted patient, and 1 BES-implanted patient. Ticlopidine administration was ceased 3 months after stent implantation in these 2 patients.

**Quantitative Coronary Angiography Findings**
The quantitative coronary angiography findings in both groups are shown in Table 2. There were no significant differences in any pre- and post-angiographic lesion characteristics. Mean [median] in-stent LL from post-intervention to follow-up was similar in both groups at 0.06±0.23 [–0.02] mm with
BES and 0.07±0.18 [0.06] mm with SES (P=0.80), reaching similar minimal lumen diameters and % diameter stenosis at follow-up. None of the lesions showed in-stent restenosis (>50 of % diameter stenosis) on follow-up angiography.

**Angioscopic Findings**

The dominant degree of NIC grade showed a similar distribution between BES and SES (Figure 1). The average [median] grade was 1.5±0.8 [2] in BES vs. 1.3±0.7 [1] in SES (P=0.45). The majority of the SES group (n=10, 63%) was grade 1. Grade 2 predominated in the BES group (n=7, 47%). Dominant grade 0 was detected in 2 BES and in 1 SES (P=0.60). Within the stents, NIC was more heterogeneous in SES than in BES (P=0.035). 12 BES (80%) showed homogeneous NIC; the remaining 3 BES had heterogeneity of 1 grade. In the SES group, 56% (n=9) had heterogeneous NIC; heterogeneity of 1 grade was detected in 50% and heterogeneity of 2 grades was detected in 6% (Figure 2). Representative cases are shown in Figures 3 and 4.

Thrombi were detected in 3 BES and in 5 SES (P=0.69). All thrombi observed in this study were mural and subclinical, and were associated with the sites of grade 0 or 1 NIC. All thrombi were red except for a white thrombus that was detected in an SES showing grade 1 coverage. Yellow plaques were similarly observed between BES (n=12, 80%) and SES (n=11, 69%, P=0.69), and 83% of yellow plaques were observed underneath neointima of grade 0–2.

**Discussion**

A first-generation SES and a second-generation BES were angioscopically compared in this study of intra-stent conditions. Both SES and BES strongly and similarly attenuated LL, which in this study was similar to LL in earlier clinical studies. Although the distribution of the dominant NIC grade was similar between SES and BES, 56% of SES showed heterogeneous NIC, whereas the majority of BES (80%) showed homogeneous NIC. Thrombus adhesion was observed only in sections with grade 0 or grade 1 NIC. The frequency of thrombus was 31% for SES and 20% for BES (P=0.69). The frequency of yellow plaques was 69% in SES and 80% in BES (P=0.69).

SES was the first DES to successfully reduce LL and TLR by inhibiting neointimal hyperplasia. However, very LST occurs more often with first-generation DES (SES and paclitaxel-eluting stent [PES, TAXUS, Boston Scientific, Natick, MA, USA]), than with bare-metal stents. The risk of LST has been attributed to impaired vessel healing, as evidenced
Angioscopic Findings of Biolimus-Eluting Stent

by incomplete NIC\textsuperscript{24,25} and poor reendothelialization of the stent struts.\textsuperscript{5,26} In this study, dominant NIC grade of 0–1 accounted for 69\% of the SES group, which was the major difference from NIC following implantation of bare-metal stents and zotarolimus-eluting stents (Endeavor, Medtronic Minneapolis, MN, USA).\textsuperscript{10,12,13,27} Because the frequency of thrombus adhesion was higher with NIC of grades 0–1 than with NIC of grades 2–3, reendothelialization may be poor with NIC of grade 0–1.\textsuperscript{10,12} In the present study, BES showed no difference in the distribution of the dominant NIC grade when compared with SES. The dominant NIC grades were 0–1 in 47\% of BES. Thrombus adhesion was similarly observed in BES and SES. From the angioscopic findings of BES obtained in this study, sufficient reendothelialization may not be obtained with BES. Similar to SES, careful follow-up should be considered for the potential risk of LST with BES.

In the present study, yellow plaques were observed in the implanted part of the stent at a frequency of 69\% for SES and 80\% for BES (P=0.69). Poorly formed neointima over the DES that has failed to cover and stabilize underlying thrombogenic yellow plaque may be one of the causes of LST.\textsuperscript{28} Neointima covering the bare-metal stent has a plaque-sealing effect similar to a thick fibrous cap.\textsuperscript{8,29} In this study, however, the frequency of yellow plaques in BES was similar to that in SES and a plaque-sealing effect can not be expected in BES. Medications such as statins to achieve plaque stabilization are probably useful in the prevention of LST with stents such as the BES and SES that show little plaque-sealing effect.\textsuperscript{15,30–34}

NIC was more homogeneous with BES than with SES, and 80\% of SES showed homogeneity. In comparisons of the angioscopic findings after PES and SES implantations, PES showed greater NIC heterogeneity than SES.\textsuperscript{14,35} PES with the dominant NIC grades of 2–3 had NIC of grades 0–1 in parts. Some PES did not show good arterial repair throughout the stent. Consequently, NIC heterogeneity was inversely related to arterial repair. From these results, homogeneous NIC may be important for sufficient arterial repair after stent implantation. The reasons for the homogeneity with BES remain unclear. Since BES contains a biodegradable polymer, few adverse reactions to the polymer would occur during arterial repair. In addition, because the drug and polymer are coated only on the abluminal stent surface of BES, transfer of the drug to the injured tissue should be uniform and efficient. Arterial repair on the luminal surface may be less affected by biolimus A9. The lipophilic nature of biolimus A9 (~10-fold more lipophilic than sirolimus)\textsuperscript{6,7} may also play a role in the homogeneity of NIC. The high lipophilicity may contribute to homogeneous drug diffusion to the tissue cells.

**Clinical Implications**

With BES, the dominant NIC was grades 0–1 in 47\% of patients. Because subclinical thrombus adhesion with NIC of grades 0–1 has been observed by angioscopy, reendothelial-
ization may be incomplete with BES. Dual antiplatelet therapy should be continued for at least 8 months after stent implantation using BES.

Study Limitations
This study was a single-center, non-randomized, and historical control study with a small sample size. Although serial angioscopic observations are necessary to determine arterial repair, we only observed at 8 months after stent implantation. Nonetheless, determining the in-stent condition at 8 months is important for stratifying stent thrombosis risk and policies for antiplatelet therapy within the year after the procedure. The frequency of yellow plaques and thrombus at follow-up should be affected by conditions immediately after stent implantation, but angioscopy was not performed immediately after stent implantation, which remains as a limitation of this study. Presumably, however, the index frequency of yellow plaques and of thrombus was similar between BES and SES as judged from the similarity of the patients’ characteristics.

Conclusions
BES showed limited LL similar to SES. NIC was strongly inhibited; thrombus adhesion and yellow plaques were similarly observed as in SES. Nonetheless, the NIC with BES was more homogeneous than that with SES. Biodegradable polymer-coated BES may have an advantage in generating homogeneous NIC.

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Disclosures
Conflict of Interest: None.

References