Early-Phase Vascular Healing of Bioabsorbable vs. Durable Polymer-Coated Everolimus-Eluting Stents in Patients With ST-Elevation Myocardial Infarction — 2-Week and 4-Month Analyses With Optical Coherence Tomography —

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Background: Despite the revolution of coronary stents, there remain concerns about the risk of stent thrombosis, especially in patients with ST-elevation myocardial infarction (STEMI). The present study compared early vascular healing as a contributing factor to reducing stent thrombosis between Xience everolimus-eluting stents (X-EES) and Synergy everolimus-eluting stents (S-EES) in patients with STEMI.

Methods and Results: The present study included 47 patients with STEMI requiring primary percutaneous coronary intervention with X-EES (n=25) or S-EES (n=22). Optical coherence tomography (OCT) assessments of the stented lesions were performed 2 weeks and 4 months after stent implantation. Neointimal strut coverage, malapposition and the frequency of thrombus formation were evaluated. In the 2-week OCT analysis, the proportion of covered struts in S-EES (42.4±15.4%) was significantly higher than in X-EES (26.3±10.1%, P<0.001). In the 4-month OCT analysis, the proportion of covered struts in S-EES (72.2±17.9%) was still significantly higher than in X-EES (62.0±14.9%, P=0.04).

Conclusions: Compared with X-EES, S-EES showed a higher proportion of covered struts in the early phase after stent implantation for STEMI patients.

Key Words: Neointimal coverage; Stent thrombosis; Vascular healing

Although the use of drug-eluting stents (DES) has been shown to significantly reduce the rate of restenosis and target lesion revascularization,1-2 there remain concerns about the risk of stent thrombosis.3-5 Very late stent thrombosis seems to be uniquely associated with DES, whereas most cases of stent thrombosis are clustered in the early phase after stent implantation, as shown in recent clinical trials.6-7 Especially in patients with ST-elevation myocardial infarction (STEMI), the risk of early-phase stent thrombosis is even more pronounced.8 Of several factors related to stent thrombosis, delayed vascular healing within the stented segment is a major contributory factor for stent thrombosis.9-11 Therefore, earlier vascular healing with neointimal strut coverage is a crucial concept in developing new DES. In the present study, we used optical coherence tomography (OCT) to compare strut coverage between durable polymer-coated Xience everolimus-eluting stents (X-EES) and bioabsorbable polymer-coated Synergy everolimus-eluting stents (S-EES) at 2 weeks and 4 months after stent implantation for culprit lesions in STEMI patients.

Methods

Study Population
This study was designed as a single-center prospectively planned observational study to compare X-EES (Xience Expedition™, or Xience Alpine™; Abbott Vascular, Santa Clara, CA, USA) with S-EES (Synergy™; Boston Scientific Corporation, Marlborough, MA, USA) in terms of strut coverage.
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Netherlands) was used for automated contour-detection and quantification by a single individual blinded to the patient’s information. Using the guiding catheter for calibration, the reference vessel diameter, minimum lumen diameter, and percent stenosis were measured in the view that demonstrated lesions to be the most severe and not foreshortened. As pre- and post-procedural antegrade coronary flow assessments, the standard Thrombolysis in Myocardial Infarction (TIMI) flow grades were assessed as previously described.

OCT Protocol and Image Analysis
OCT assessments of target lesions were conducted at 2 weeks and 4 months after stent implantation. A frequency-domain ILUMIEN OPTIS system using a Dragonfly™ catheter (St. Jude Medical Inc., Saint Paul, MN, USA) was used. The Dragonfly™ catheter was advanced over a 0.014-inch guidewire, with the imaging core placed distal to the stent. Automated OCT pullback with a speed of 18–36 mm/s was performed with continuous injection of contrast medium from the guiding catheter, acquiring images at a rate of 180 frames/s. OCT images were analyzed using a dedicated offline review system with semi-automated contour-detection software (St. Jude Medical). To evaluate image quality, all cross-sectional frames were initially screened. If the image quality was poor because of residual blood or reverberation, or if there were any parts of the strut out of the screen, frames were excluded from analysis.

Intrastent thrombus was defined as a mass protruding beyond the stent strut into the lumen with signal-free shadowing behind the mass.

After calibration, the OCT images were quantitatively evaluated at longitudinal intervals of 1 mm within the stented lesions and 5 mm proximal and distal to the stent edges. Neointimal coverage was assessed for each individual strut. An uncovered strut was defined if any part of the strut was visibly exposed to the lumen. Intra- and interobserver variability for neointimal coverage was assessed in 60 randomly selected struts and showed excellent concordance (κ=0.760 and κ=0.812, respectively). Struts were classified as malapposed if they protruded into the lumen at a distance greater than the sum of the strut and polymer thickness plus the axial resolution limit of OCT (20 μm).

Procedures and Medical Management
Percutaneous coronary intervention (PCI) for culprit lesions was performed according to standard techniques. Thrombus aspiration, direct stenting, use of distal protection devices and post-dilatation were left to the operator’s discretion. Before intervention, all patients were pretreated with 200 mg of aspirin and a loading dose of P2Y12 inhibitor (300 mg of clopidogrel or 20 mg of prasugrel). After intervention, all patients received dual antiplatelet therapy (DAPT: aspirin 100 mg and a P2Y12 inhibitor [75 mg of clopidogrel or 3.75 mg of prasugrel]) daily for at least 12 months.

Coronary Angiography
A computerized quantitative analysis system using QCA software (CAAS 5.9, Pie Medical Imaging, Maastricht, The Netherlands) was used for automated contour-detection and quantification by a single individual blinded to the patient’s information. Using the guiding catheter for calibration, the reference vessel diameter, minimum lumen diameter, and percent stenosis were measured in the view that demonstrated lesions to be the most severe and not foreshortened. As pre- and post-procedural antegrade coronary flow assessments, the standard Thrombolysis in Myocardial Infarction (TIMI) flow grades were assessed as previously described.

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Figure 1. Study flow chart. CAG, coronary angiography; OCT, optical coherence tomography; S-EES, Synergy everolimus-eluting stent; X-EES, Xience everolimus-eluting stent.
Table 1. Baseline Patient Characteristics

|                      | X-EES (n=25) | S-EES (n=22) | P value |
|----------------------|--------------|--------------|---------|
| Age, years           | 65.9±12.1    | 65.4±13.1    | 0.61    |
| Male sex             | 17 (68.0)    | 17 (77.3)    | 0.53    |
| Coronary risk factors|              |              |         |
| Diabetes mellitus    | 7 (28.0)     | 2 (9.1)      | 0.10    |
| Hypertension         | 14 (56.0)    | 12 (54.5)    | 0.92    |
| Dyslipidemia         | 10 (40.0)    | 9 (40.9)     | 0.95    |
| Hemodialysis         | 0 (0)        | 0 (0)        | 1.00    |
| Current smoker       | 17 (68.0)    | 14 (63.6)    | 0.76    |
| Family history       | 6 (24.0)     | 5 (22.7)     | 0.92    |
| Prior myocardial infarction | 0 (0) | 0 (0) | 1.00    |
| Prior PCI            | 0 (0)        | 2 (9.1)      | 0.13    |
| PCI with thrombolysis| 0 (0)        | 0 (0)        | 1.00    |
| Clinical status on admission |            |              | 0.18    |
| Killip I             | 23 (92.0)    | 22 (100)     |         |
| Killip II            | 2 (8.0)      | 0 (0)        |         |
| Killip III           | 0 (0)        | 0 (0)        |         |
| Killip IV            | 0 (0)        | 0 (0)        |         |

Data are mean±SD or n (%) values. PCI, percutaneous coronary intervention; S-EES, Synergy everolimus-eluting stent; X-EES, Xience everolimus-eluting stent.

Table 2. Medications

|                      | X-EES (n=25) | S-EES (n=22) | P value |
|----------------------|--------------|--------------|---------|
| Aspirin              | 25 (100.0)   | 22 (100.0)   | 1.00    |
| Prasugrel            | 13 (52.0)    | 12 (54.5)    | 0.87    |
| Clopidogrel          | 12 (48.0)    | 10 (45.5)    | 0.87    |
| Statin               | 25 (100.0)   | 22 (100.0)   | 1.00    |
| ACEI                 | 20 (80.0)    | 18 (81.8)    | 0.88    |
| ARB                  | 2 (8.0)      | 2 (9.1)      | 0.90    |
| β-blocker            | 23 (92.0)    | 19 (86.4)    | 0.54    |
| Calcium-channel antagonist | 1 (4.0) | 1 (4.5) | 0.93    |
| DOAC                 | 1 (4.0)      | 0 (0)        | 0.35    |
| Oral antidiabetic agent | 6 (24.0) | 2 (9.1) | 0.18    |
| Insulin              | 0 (0)        | 0 (0)        | 1.00    |

Data are n (%). ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; DOAC, direct oral anticoagulant.

Statistical Analysis
Data are expressed as mean±standard deviations or as median and interquartile range with differences [95% confidence interval]. Categorical variables are expressed as frequencies (%). Normality of distribution was tested by the Kolmogorov-Smirnov test. Continuous variables were compared using the unpaired Student t-test, and categorical variables were compared using the chi-squared or Fisher’s exact test where appropriate. Mann-Whitney U tests were performed for nonparametric data. Serial changes in OCT parameters between the 2-week and 4-month assessments were analyzed by paired t-test. To measure intra- and interobserver variability for neointimal coverage, Cohen’s κ was calculated using the R statistical software package (version 3.2.3, with the use of ‘IRR’ package; The R Foundation, Vienna, Austria: www.r-project.org). Other statistical analyses were performed with SPSS (version 22.0, IBM, Armonk, New York). Statistical significance was assumed at P<0.05.

of bifurcation were excluded from the analysis of neointimal coverage and malapposition. Cross-sectional areas of the stent, lumen, and neointima (defined as stent minus intrastent lumen) were measured at every 1 mm along the stented segment. In the 4-month OCT analysis, neointimal tissue characteristics were evaluated in the cross-section of maximum neointima area. Homogeneous neointima was characterized by uniform optical properties without focal variations in backscattering pattern, heterogeneous neointima by focally changing optical properties with various backscattering patterns, and layered neointima by concentric layers with different optical properties.16
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Results

Patients’ Characteristics
A total of 66 patients with STEMI were enrolled in the present study (Figure 1). We excluded the following: 4 patients with X-EES and 4 with S-EES who withdrew their consent for the 2-week follow-up OCT; 2 patients with S-EES who died before the 2-week follow-up OCT (pneumonia and cardiac rupture, respectively); 1 patient with insufficient images; and 4 patients with X-EES and 2 with S-EES who withdrew their consent for the 4-month follow-up OCT. Consequently, there were 25 patients with X-EES and 22 patients with S-EES for serial OCT analysis. The patients’ clinical characteristics and medications are summarized in Table 1 and Table 2, respectively. There were no significant differences in age, sex, or known coronary risk factors between the 2 DES groups. The patients’ clinical conditions and clinical status on admission were also similar between groups. Aspirin and thienopyridines were continued for all patients throughout follow-up. In
terms of stent-related complications, there were no cases of stent thrombosis, or target vessel revascularizations in either group during the 4-month follow-up period.

**Procedural Characteristics and Angiographic Results**

Procedural characteristics and angiographic findings are summarized in Table 3. Preprocedural TIMI flow grade and procedural characteristics were similar between the groups. The minimum lumen diameter at the very end of the index procedure was comparable between the groups.

**OCT Findings**

There were no OCT procedural-related complications. The results of the OCT analyses at 2 weeks and 4 months are summarized in Table 4 and Table 5, respectively. The median follow-up periods were similar between the groups. In the 2-week OCT analysis, the proportion of covered struts in the stent strut-level analysis of X-EES and S-EES was 24.3% and 42.0%, respectively. In the stent-treated lesion-level analysis, the proportion of covered struts was significantly higher in the S-EES group than in the X-EES group (42.4±15.4% vs. 26.3±10.1%, P<0.001, Figure 2). In the 4-month OCT analysis, the proportion of covered struts in the stent strut-level analysis of X-EES and S-EES was 60.3% and 71.6%, respectively. In the stent-treated lesion-level analysis, the proportion of covered struts was significantly higher in the S-EES group than in the X-EES group (72.2±17.9% vs. 62.0±14.9%, P=0.04). As serial changes in the OCT parameters, the proportion of covered struts and neointimal volume were significantly increased from 2 weeks to 4 months in both groups (Table S1).

Representative cases of patients with X-EES and S-EES are shown in Figure 3, with serial changes in the OCT images between 2 weeks and 4 months after stent implantation.

**Discussion**

The present study demonstrated that S-EES provided better strut coverage than X-EES at both 2 weeks and 4 months after stent implantation for STEMI. Our results suggested that vascular healing in the early phase is different according to whether X-EES or S-EES is used.

To the best of our knowledge, the present study is the first to compare early-phase vascular healing between X-EES and S-EES in patients with STEMI. Although 2nd-generation DES are equipped with biocompatible polymers, late stent failure, including neoatherosclerosis, is still an unresolved issue. The presence of durable polymer in the coronary arterial wall may be most responsible for the late-phase inflammatory reaction resulting in late stent failure. To reduce the incidence of polymer-derived inflammation, bioabsorbable polymers have been introduced in new-generation DES and the potential advantage might be expected to emerge once the polymer has dissolved in the late phase after implantation. However, even in the early phase, S-EES have some clinical advantages in terms of vascular healing, as shown by the results of the present study.

**Vascular Healing After S-EES Implantation**

The S-EES was designed to promote vascular healing by the use of thinner struts (74µm) on a platinum-chromium platform with an ultrathin (4µm) abluminal polymer, which is reabsorbed within 4 months. Strut thickness is a critical factor in modulating stent thrombogenicity and
demonstrated that most of the cases of stent thrombosis are clustered in the early phase after stent implantation.\textsuperscript{6,7} Uncovered struts after DES implantation are closely associated with stent thrombosis,\textsuperscript{10,11} because exposure of the strut surface to the bloodstream may promote thrombus formation.\textsuperscript{28} A recent prospective, multicenter study using OCT demonstrated that uncovered struts are a common dominant finding adjudicated for stent thrombosis in every phase after DES implantation.\textsuperscript{29} More strut coverage in S-EES, as shown in the present study, might reduce the risk of early-phase stent thrombosis and might enable safe minimization of the duration of DAPT. Strong evidence to support our hypothesis was reported in a recent large trial. In the SENIOR trial, S-EES with a short duration of DAPT (1 month for stable patients and 6 months for acute endothelialization. A thicker strut will promote flow separation and the development of recirculation zones, resulting in low shear stress. In contrast, a thinner strut will minimize or avoid the generation of a low flow velocity environment distal and proximal to the strut, resulting in less thrombogenicity and faster endothelialization.\textsuperscript{22–24} Although both the polymers and antiproliferative drugs used on DES have been implicated as factors contributing to poor endothelialization,\textsuperscript{25} uncoated stents promote more rapid endothelialization and higher vascular endothelial-cadherin expression.\textsuperscript{26} In fact, in an animal experiment using rabbits, S-EES showed the fastest neointimal coverage of stent struts as compared with other DES.\textsuperscript{27} These study results are consistent with our findings in terms of more rapid neointimal coverage in S-EES. Recent clinical trials have
coronary syndrome patients) was superior to bare-metal stents with respect to the occurrence of major adverse cardiac events without increasing the risk of stent thrombosis.

From a practical point of view, the safety of short DAPT for patients with S-EES should be confirmed by further trials.

Study Limitations

Some limitations need to be acknowledged. First, this study was a non-randomized single-center study with a relatively small population and might therefore have a risk of selection bias. The number of patients was not evenly distributed in each group, because the stent type was selected according to a predetermined enrollment period. Moreover, a rigorous study design requiring OCT evaluation at 2 weeks and 4 months after stenting limits patient enrollment and leads to a high drop-out rate. Nevertheless, the present study still makes an enormous contribution to understanding vascular healing in the early phase after DES implantation. Second, current OCT systems cannot identify tissue coverage <10 μm on the stent struts. Endothelial cell dimensions are generally below the lower limit of resolution capacity of OCT, and it is possible that some struts appearing bare were covered by endothelium, resulting in misclassification.

Finally, to differentiate soft tissue such as fibrin from neointimal coverage in the early phase after stenting is quite difficult. This issue is very important because coverage with neointima and that by fibrin has quite different effects on the clinical outcome. To minimize such misreading, we classified strut as uncovered if any part of the strut was visibly exposed to the lumen. At 4-month follow-up, which is the phase in which fibrin has less effect, results consistent with those from the 2-week follow-up were observed. Future developments in OCT technology are necessary to allow improved tissue characterization.

Conclusions

Compared with X-EES, S-EES showed a higher proportion of covered struts in the early phase after stent implantation for STEMI patients.

Conflict of Interest

H.A. has received research grants for this study from Chukyo Geriatric Research Promotion Financial Group. All other authors report that they have no relationships relevant to the content of this paper to disclose.

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Supplementary Files

Table S1. Serial changes in OCT findings between 2-week and 4-month assessments
Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-18-0230