Comparison of Optical Coherence Tomographic Assessment between First- and Second-Generation Drug-Eluting Stents

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Purpose: There is a lack of sufficient data in comparison of optical coherence tomographic (OCT) findings between first- and second-generation drug-eluting stents (DES). Compared to first-generation (i.e., sirolimus- or paclitaxel-eluting stents), second-generation DESs (i.e., everolimus- or biolinx-based zotarolimus-eluting stents) might have more favorable neointimal coverage.

Materials and Methods: Follow-up OCT findings of 103 patients (119 lesions) treated with second-generation DESs were compared with those of 139 patients (149 lesions) treated with first-generation DESs. The percentage of uncovered or malapposed struts, calculated as the ratio of uncovered or malapposed struts to total struts in all OCT cross-sections, respectively, was compared between the two groups.

Results: Both DES groups showed similar suppression of neointimal hyperplasia (NIH) on OCT (mean NIH cross-sectional area; second- vs. first-generation=1.1±0.5 versus 1.2±1.0 mm², respectively, \( p=0.547 \)). However, the percentage of uncovered struts of second-generation DESs was significantly smaller than that of first-generation DESs (3.8±4.8% vs. 7.5±11.1%, respectively, \( p<0.001 \)). The percentage of malapposed struts was also significantly smaller in second-generation DESs than in first-generation DESs (0.4±1.6% vs. 1.4±3.7%, respectively, \( p=0.005 \)). In addition, intra-stent thrombi were less frequently detected in second-generation DESs than in first-generation DESs (8% vs. 20%, respectively, \( p=0.004 \)).

Conclusion: This follow-up OCT study showed that second-generation DESs characteristically had greater neointimal coverage than first-generation DESs.

Key Words: Optical coherence tomography, stent

INTRODUCTION

With the introduction of first-generation drug-eluting stents (DES), a significant reduction in restenosis rates and an improvement in short-term clinical outcomes were reported.1,2 However, the use of first-generation DESs, e.g., sirolimus- and paclitaxel-eluting stents, has been shown to be strongly related with the occurrence of late or very late stent thrombosis, raising safety concerns.3,4 Several attempts to develop newer DESs have set out to prevent the occurrence of stent thrombosis by...
modifying the eluted drugs, drug carrying systems, and stent design. Of these, second-generation DESs, e.g., everolimus-eluting stents (EES) and Biolinx-based zotarolimus-eluting stents (Bx-ZES), have been reported to suppress neointima hyperplasia (NIH) effectively and simultaneously demonstrate favorable long-term outcomes.²⁹ Optical coherence tomography (OCT) has enabled researchers to evaluate neointimal coverage of DESs in detail, even at the strut level.¹⁰,¹¹ However, no sufficient OCT data has been reported comparing neointimal coverage between first- and second-generation DESs. Therefore, using OCT, we sought to compare healing responses, including neointimal coverage, between the two groups.

**MATERIALS AND METHODS**

**Study population**

We used data submitted to the Yonsei OCT registry, evaluating neointimal coverage in patients who underwent coronary stent implantation for de novo lesions.¹²,¹³ General exclusion criteria for the follow-up OCT study were as follows: 1) untreated significant left main coronary artery disease, 2) apparent congestive heart failure, 3) renal insufficiency (baseline creatinine ≥2.0 mg/dL), and 4) lesions unsuitable for OCT imaging (vessel size ≥3.5 mm or lesions within 10 mm of the ostium of a major epicardial artery). Between September 2007 and October 2010, a total of 242 patients with 268 lesions were selected from the OCT registry database. Inclusion criteria of the current study comprised lesions treated with EES, Bx-ZES, sirolimus- or paclitaxel-eluting stents, as well as those followed with a follow-up OCT examination at 12±4 months after stent implantation. Exclusion criteria were 1) bifurcation treated with 2-stent techniques, 2) angiographic evidence of restenosis, 3) lesions with repeated revascularization, 4) bare-metal stent implantation, and 5) poor OCT image quality. Second-generation DESs were deployed in 103 patients for 119 lesions including EES (Xience V®, Abbott Vascular, Santa Clara, CA, USA) and Bx-ZES (Endeavor Resolute®, Medtronic, Santa Rosa, CA, USA), while first-generation DESs were implanted in 139 patients for 149 lesions including sirolimus-eluting stents (Cypher®, Cordis, Miami, FL, USA) and paclitaxel-eluting stents (Taxus®, Boston scientific, Natick, MA, USA). DES implantation was performed using current, conventional techniques, and the choice of DES was made according to the operators’ discretion. After DES implantation, all patients received dual antiplatelet therapy with aspirin and clopidogrel until the follow-up OCT was conducted. This study was approved by the Institutional Review Board of our institute, and written informed consent was obtained from each patient.

**OCT imaging and analysis**

Detailed explanations regarding the OCT system and methods for imaging have been described in our previous studies.¹²,¹³ OCT examination was performed using a conventional OCT system (Model M2 Cardiology Imaging System, LightLab Imaging, Westford, MA, USA) with a motorized pull-back system at 1.0 mm/s. The occlusion catheter was positioned proximal to the stent, and a 0.014-inch wire-type imaging catheter (ImageWire, LightLab Imaging) was positioned distal to the stent. During image acquisition, the occlusion balloon (Helios, Avantec Vascular, Sunnyvale, CA, USA) was inflated to 0.4-0.6 atm, and lactated Ringer’s solution was infused at a rate of 1.0 mL/s. The imaging wire was pulled from distal to proximal, and continuous images were acquired and stored digitally for subsequent analysis.¹²,¹³ OCT analysis was performed by an independent investigator blinded to patient and procedural information.

Cross-sectional OCT images were analyzed at 1-mm intervals (every 15 frames). Stent and luminal cross-sectional areas (CSAs) were measured at 1-mm intervals, and NIH CSA was calculated as the stent CSA minus the luminal CSA. Percent NIH CSA was calculated as NIH CSA×100/stent CSA. Mean values are reported in this study. The thickness of NIH, defined as the distance between the endoluminal surface of neointima and the strut, was measured inside the struts at a line as perpendicular as possible to the neointima and strut.¹⁰ An uncovered strut was defined as having a NIH thickness of 0 μm.¹⁰,¹⁴ A malapposed strut was defined as a strut that had detached from the vessel wall (Cypher®, ≥160 μm; Taxus®, ≥130 μm; Endeavor Resolute®, ≥110 μm; Xience®, ≥100 μm).¹⁵,¹⁶ The percentage of uncovered or malapposed struts was investigated for evaluation of the healing responses of DESs as shown on OCT. The percentage of malapposed or uncovered struts in each stented lesion was calculated as the (number of malapposed or uncovered struts/total number of struts in all cross-sections of the lesion)×100, respectively. Cross sections with major side branches (diameter ≥2 mm) were excluded from this analysis. The neointimal coverage of stent struts in each cross-section was evaluated, and then the percentage of uncovered struts was analyzed and compared between the two groups.
groups. Intra-stent thrombi were defined as a signal-rich, low-backscattering protrusions or high-backscattering protrusions inside the lumen of the artery with signal-free shadowing on OCT images (dimension ≥250 μm).13

RESULTS

Baseline clinical characteristics are shown in Table 1. There were no significant differences in baseline clinical characteristics between the two groups. Baseline angiographic and procedural characteristics are listed in Table 2. There were also no significant differences in baseline angiographic and procedural characteristics between the two groups.

Table 3 summarizes the OCT findings of both groups. There were no significant differences in mean lumen and stent CSA, as well as time to follow-up OCT (days) between the two groups. Although both groups showed a nearly similar suppression of NIH, the percentage of uncovered struts of second-generation DESs was significantly smaller than that of first-generation DESs (3.8±4.8% vs. 7.5±11.1%, respectively, p<0.001). The percentage of malapposed struts was also significantly smaller in second-generation DESs than in first-generation DESs (0.4±1.6% vs. 1.4±3.7%, respectively, p=0.005). In addition, intrastent thrombi were less frequently detected in second-generation DESs than in first-generation DESs (8% vs. 20%, respectively, p=0.004).
Table 2. Baseline Angiographic and Procedural Characteristics

| Variables                        | First-generation DESs (n=149) | Second-generation DESs (n=119) | p value |
|----------------------------------|-------------------------------|-------------------------------|---------|
| Lesion morphology, type C, n (%)| 101 (68)                      | 81 (68)                       | 1.000   |
| Lesion length (mm)               | 23.1±6.3                      | 22.8±6.2                      | 0.123   |
| Stent diameter (mm)              | 2.95±0.30                     | 2.91±0.29                     | 0.306   |
| Stent length (mm)                | 25.1±7.2                      | 24.8±4.9                      | 0.211   |
| Types of implanted DES           |                               |                               |         |
| Sirolimus-eluting stent, n (%)   | 89 (60)                       | -                             |         |
| Paclitaxel-eluting stents, n (%) | 60 (40)                       | -                             |         |
| Everolimus-eluting stents, n (%) | -                             | 67 (56)                       |         |
| Biolinx-based zotarolimus-eluting stents, n (%) | -                             | 52 (44)                       |         |
| Quantitative coronary angiography analysis |                               |                               |         |
| Reference vessel diameter (mm)   | 2.78±0.44                     | 2.80±0.50                     | 0.515   |
| Pre-intervention MLD (mm)        | 0.74±0.49                     | 0.80±0.48                     | 0.232   |
| Post-intervention MLD (mm)       | 2.63±0.32                     | 2.59±0.37                     | 0.103   |
| Follow-up MLD (mm)               | 2.19±0.56                     | 2.17±0.47                     | 0.662   |

Table 3. Follow-Up Optical Coherence Tomography Measurements

| Variables                        | First-generation DESs (n=149) | Second-generation DESs (n=119) | p value |
|----------------------------------|-------------------------------|-------------------------------|---------|
| Number of cross sections         | 3709                          | 2665                          |         |
| Total number of analyzable struts| 32972                         | 23750                         |         |
| Time to follow-up OCT (days)     | 296±60                        | 290±43                        | 0.273   |
| Mean stent CSA (mm^2)            | 7.1±1.7                       | 7.0±1.6                       | 0.925   |
| Mean lumen CSA (mm^2)            | 5.9±1.6                       | 5.9±1.7                       | 0.923   |
| Mean NIH CSA (mm^2)              | 1.2±1.0                       | 1.1±0.5                       | 0.547   |
| Mean percent NIH CSA (%)         | 16.9±12.4                     | 17.1±8.3                      | 0.884   |
| Mean NIH thickness (µm)          | 148±111                       | 142±63                        | 0.666   |
| Percentage of uncovered struts, %| 7.5±11.1                      | 3.8±4.8                       | <0.001  |
| Percentage of malapposed struts, %| 1.4±3.7                      | 0.4±1.6                       | 0.005   |
| Presence of intra-stent thrombi, n (%) | 30 (20)                      | 9 (8)                         | 0.004   |

Comparisons among the DES

| Sirolimus-eluting stents (n=89) | Paclitaxel-eluting stents (n=60) | Everolimus-eluting stents (n=67) | Biolinx-based zotarolimus-eluting stents (n=52) | p value |
|----------------------------------|-------------------------------|-------------------------------|-------------------------------|---------|
| Percentage of uncovered struts, %| 10.2±12.9                     | 3.5±6.0*                      | 3.6±4.1*                      | 3.9±5.6* | <0.001 |
| Percentage of malapposed struts, %| 1.7±4.1                       | 0.8±3.1                       | 0.3±0.6†                      | 0.6±2.3  | 0.014  |
| Presence of intra-stent thrombi, n (%) | 25 (28)                      | 5 (8)*                        | 8 (12)|                       | 1 (2)*  | <0.001 |

CSA, cross-sectional area; DES, drug-eluting stent; NIH, neointimal hyperplasia; OCT, optical coherence tomography; SD, standard deviation.
Values are expressed as means±SD for quantitative variables or as n (%) for qualitative variables.
*<0.01 and †<0.05 when compared to sirolimus-eluting stents.

DISCUSSION

This follow-up OCT study demonstrated that second-generation DESs lead to a lower percentage of uncovered and malapposed struts, as well as a lower incidence of intra-stent thrombi, compared with first-generation DESs. In spite of superior healing responses of second-generation DESs, the efficacy of second-generation DESs in the suppression of NIH growth was not different from that of first-generation DESs. As concerns regarding the safety issues of first-generation DESs have increased, newly developing DESs have focused more on safety with a similar efficacy to that of first-generation DESs through the long-term follow-up studies.3,4 Among many newly developed DESs, EES and Bx-ZES have been shown to have both excellent efficacy and safety.5-9 Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients
with de novo Native Coronary Artery Lesions (SPIRIT) III randomized study showed that EES implantation resulted in a statistically significant reduction of angiographic late loss at 8-month follow-up and showed significantly improved event-free survival, compared with implantation of paclitaxel-eluting stents at 2-year follow-up. In addition, compared with patients treated with paclitaxel-eluting stents, those treated with EES tended to have fewer episodes of late stent thrombosis at 1 and 2 years (0.2% versus 1.0%; \( p=0.10 \)) thereafter. Recently, Bx-ZES, which comprises a low-profile, thin-strut platform, and a Biolinx tri-polymer, also showed favorable short-term angiographic outcomes with a comparable low late loss. Many potential mechanisms or factors are expected to be related with the favorable outcomes demonstrated in second-generation DESs. Of these, the degree of reendothelialization, regarded as the most powerful predictor of stent thrombosis, might be strongly related with better outcomes in DESs. Although some studies have evaluated neointimal coverage for various types of DES, they were conducted as an autopsy or animal study. A new imaging tool, OCT, has enabled researchers to evaluate the reendothelialization of DES in live patients with a superior resolution capacity. Therefore, using OCT, healing responses, including neointimal coverage of stent struts, was evaluated between second-generation and first-generation DESs in this study.

In the current OCT study, the rate of uncovered struts as shown on OCT was significantly different between the two groups; second-generation DESs showed a higher % of uncovered struts, meaning more complete neointimal coverage. However, the amount of NIH was similar between the first- and second-generation DESs. The superior nature of second-generation DESs, showing better endothelialization and healing responses compared with first-generation DESs, while maintaining similar efficacy represented by the suppression of NIH on OCT or a low late loss on follow-up angiogram, might be caused by the unique components comprising DESs, including the use of novel drugs, superior biocompatibility and morphology of polymers, reduced polymer layers, and thin-strut design. As a result, newer DESs are both safe and have equal efficacy to first-generation DESs, and this study, in comparison of the OCT findings thereof, suggests that second-generation DESs are close to the ideal DES.

The degree of stent malapposition, evaluated by OCT, was also significantly different between the two groups; the percentage of malapposed struts of second-generation DESs was significantly lower than that of first-generation DESs. Stent malapposition has been also regarded as an important predictor of DES thrombosis in intravascular ultrasound studies. DES type has been suggested as one of the most determining factors of stent malapposition. A difference in the incidence of stent malapposition dependent upon the type of DES might be associated with differences in long-term outcomes. Namely, a lower rate of malapposition in second-generation DESs may translate to more favorable clinical outcomes after DES implantation thereof.

**Study limitations**

This study has several limitations. First, selection bias might affect the results because this was a non-randomized registry study. Second, because this study was not a controlled comparative one, direct comparisons among four different DESs could not be performed. However, there were no significant differences in the baseline clinical and angiographic parameters between the two groups. Third, because the study population of the current study was free of major adverse events after DES implantation until follow-up OCT, the lesions of this study might not represent those seen in real world practice. Fourth, in this study, the first-generation DES group, which consisted of sirolimus-eluting stents and paclitaxel-eluting stents, was compared with second-generation DESs. However, because sirolimus-eluting stents and paclitaxel-eluting stents showed different outcomes in some pathologic and imaging studies, careful attention must be given when interpreting the results. Finally, no clinical follow-up data was provided due to the short duration of clinical follow-up after OCT evaluation.

In conclusion, this follow-up OCT study showed that second-generation DESs characteristically had greater neointimal coverage than first-generation DESs. For more definite conclusions, long term clinical and serial OCT follow-up with a larger population will be needed in the future.

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