Comparison by Optical Coherence Tomography of Paclitaxel-Eluting Stents With Sirolimus-Eluting Stents Implanted in One Coronary Artery in One Procedure – 6-Month Follow-up –

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Background: Differences between paclitaxel-eluting stents (PES) and sirolimus-eluting stent (SES) in neointimal proliferation under strictly matched conditions remain to be clarified by optical coherence tomography (OCT).

Methods and Results: Between May and December 2007, 27 patients were implanted with a PES and a SES, randomized to either the proximal or distal site in a single coronary artery, and underwent follow-up angiography and OCT examination at 6 months. The frequency of vessel wall apposition with neointima was greater for PES than for SES (92.6% vs 85.8%, $P<0.01$). The median (25th, 75th percentiles) neointimal thickness (NIT) in PES was significantly greater than that in SES ($90\ \mu\text{m}$ [25th: $40\ \mu\text{m}$; 75th: $200\ \mu\text{m}$] vs $50\ \mu\text{m}$ [25th: $20\ \mu\text{m}$; 75th: $140\ \mu\text{m}$]; $P<0.01$). Both the average difference between the maximum and minimum NIT in each cross-section and the average difference between the maximum and minimum NIT in the longitudinal axis were larger in PES than in SES (206 ± 88 vs $131\pm 57\ \mu\text{m}$; $P<0.001$, 607 ± 243 vs $400\pm 185\ \mu\text{m}$; $P<0.001$). Low-density spots were significantly more frequently observed in PES than in SES (30.9% vs 17.0%, $P=0.001$).

Conclusions: Compared with SES, PES had a non-uniform and larger neointimal thickness with fewer uncovered struts, and more peri-strut low-density areas. (*Circ J* 2010; **74**: 903–908)

Key Words: Neointima; Optical coherence tomography; Paclitaxel-eluting stent; Peri-strut low intensity; Sirolimus-eluting stent

Paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES) more effectively decrease angiographic restenosis and target lesion revascularization than bare-metal stents.^{1–9} The safety of these drug-eluting stents (DES), however, is currently under debate with regard to their potential for late stent thrombosis (LST), a life-threatening complication, especially after discontinuation of dual antiplatelet therapy. Hypersensitivity reactions to the polymer used in DES, delayed endothelialization of the stents, and discontinuation of dual antiplatelet therapy are thought to be potential risk factors for DES stent thrombosis.^{10–14} Thus, discrimination of DES in terms of efficacy and safety has emerged as an important issue in the DES era.

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Although clinical outcomes, such as target lesion revascularization, adverse cardiac events, stent thrombosis, and mortality, are similar between SES and PES,¹⁵ several reports suggest that the extent and pattern of neointimal proliferation differ between them.^{16–20} In those studies, however, intravascular ultrasound (IVUS) or quantitative angiography was used without a pure matched comparison to evaluate neointimal growth after DES implantation. The axial resolution of optical coherence tomography (OCT: $10\text{--}20\ \mu\text{m}$) is superior to that of IVUS ($100\text{--}150\ \mu\text{m}$). The distribution of neointimal coverage and neointimal thickness (NIT) can be evaluated by OCT in the order of micrometers.²¹

In the present study, using OCT in the chronic stage, we

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Figure 1. Optical coherence tomography images. (A) Non-uniform neointimal proliferation in paclitaxel-eluting stents. (B) Uniform thin neointima in sirolimus-eluting stents. (C) Arrows show struts at side-branch orifice without neointimal coverage. (D) Arrowhead shows a strut that is malapposed to the vessel wall. (E) Measurement of neointimal thickness. (F) Struts are surrounded by an area of low intensity. (G) Stent with mural thrombus.

compared a single SES and PES implanted in a single coronary artery with a long diffuse lesion and with stent placement randomized to a proximal or distal location.

Methods

Patients and Procedures

Between May and December 2007, 27 patients who had a long diffuse obstruction in a single coronary artery were each implanted with a PES (Taxus Express™ stent, Boston Scientific Corp, Natick, MA, USA) and a SES (Cypher™ stent, Cordis/Johnson & Johnson, Miami Lakes, FL, USA). The site of each stent implantation, proximal or distal, was randomly assigned. Prior to DES implantation, IVUS was performed using a 2.9Fr 20-MHz IVUS catheter (Eagle-Eye™; Volcano Therapeutics, Inc, Rancho Cordova, CA, USA) with an automatic pullback device at 0.5 mm/s to measure the vessel size and identify the location of the plaque. After stent implantation, IVUS was again performed to ensure that the DES was fully expanded. If not, additional high-pressure balloon expansion was repeated until IVUS indicated that the DES was well-expanded. In 12 cases, the PES was deployed at the proximal site and the SES at the distal site (P-S group), and in 15 cases, the SES was deployed at the proximal site and the PES at the distal site (S-P group). After 6 months, all patients underwent follow-up angiography and OCT examination. Oral aspirin 100 mg/day and oral ticlopidine 200 mg/day or clopidogrel 75 mg/day were prescribed to all patients at least 3 days prior to percutaneous coronary intervention and continued for 6 months. This study was approved by the Ethical Committee of Kobe University and all the patients enrolled in this study provided written informed consent.

OCT Examination

OCT images were obtained as previously described.^{21,22} Briefly, an OCT imaging probe (ImageWire™, LightLab Imaging, Westford, MA, USA) was inserted through the over-the-wire lumen of the occlusion balloon (Helios™, LightLab Imaging). To clear blood from the imaging site, the proximal occlusion balloon was inflated to 0.5 atm and lactated Ringer's solution was infused into the coronary artery from the distal tip of the occlusion balloon at 0.5 ml/s. The entire length of the stent was imaged with an automatic pullback device moving at 1 mm/s and OCT imaging clearly visualized the stent's cross-section.

OCT Analysis

The OCT images were analyzed by 2 independent observers using a proprietary off-line review system (LightLab Imaging). All OCT cross-sectional image frames were evaluated to detect thrombi and to inspect whether stent struts were covered with neointima and apposed to the vessel wall. In every 15th frame (1 mm), we evaluated each stent strut condition for classification into 1 of 6 categories: (1) well-apposed to the vessel wall with neointimal coverage overlaying the strut, (2) well-apposed to the vessel wall without neointimal coverage, (3) malapposed to the vessel wall with neointimal coverage, (4) malapposed to the vessel wall without neointimal coverage, (5) orifice branch site with neointima, (6) orifice branch site without neointima. A malapposed strut was defined as a distance of more than 170 μm between the center reflection of the strut to the vessel wall. This criterion was determined by adding the actual strut thickness and polymer thickness to the OCT resolution limit (130 μm + 14 μm + 20 μm in PES; 140 μm + 10 μm + 20 μm in SES). If neointimal coverage of the strut was observed, its thickness was measured from the neointimal surface to the center

reflection of the strut.²³ To evaluate the radial unevenness of NIT (RUNIT), the difference between the maximum and minimum NIT was calculated for each cross-section and to evaluate the longitudinal axis unevenness of NIT (LUNIT), the difference between the maximum NIT and minimum NIT in the longitudinal axis was calculated for each stent. In addition, frequency of thrombus formation and low-density spots surrounding the strut were recorded. A thrombus was defined as a mass protruding beyond the stent strut into the lumen with significant attenuation behind the mass.^{24–26} A low-density spot was defined as a contrasting area of lower intensity than the adjacent surrounding neointimal tissue. Representative images of neointimal coverage in PES and SES, struts with a side-branch orifice, malapposed struts, NIT measurement, and a peri-strut low-intensity mural thrombus are shown in **Figure 1**.

Statistical Analysis

Qualitative data are presented as frequencies and quantitative data are shown as medians (25th, 75th percentiles) or mean values $\pm$ SD, as indicated. Classification data of 2 groups were compared using the chi-square test. A statistical difference in NIT was determined by Mann-Whitney U test. Other quantitative data were analyzed using an unpaired t-test. A 2-sided P-value of less than 0.05 was considered statistically significant. Statistical evaluation was performed with dedicated software (MedCalc version 10.3.1.0; MedCalc Software, Mariakerke, Belgium).

Results

Table shows the baseline characteristics of the study subjects, comprising 15 with angina pectoris and 12 with old myocardial infarction; among them, 8 had chronic total occlusion. The average interval to follow-up angiography was 199 ± 63 days. Mean length of the PES ($n=27$) and SES ($n=27$) was 21.37 ± 7.80 mm vs 24.30 ± 6.88 mm ($P=0.14$), and the mean diameter was 2.99 ± 0.39 mm vs 3.09 ± 0.39 mm ($P=0.34$), respectively. We evaluated 3,769 struts of PES and 4,377 struts of SES. The frequency of well apposed to the vessel wall with neointima was greater in the PES group than in the SES group (92.6% vs 85.8%, $P<0.01$). The frequencies of well apposed to the vessel wall without neointimal coverage, malapposition to the vessel wall with neointimal

Table. Patients' Characteristics

	P-S group	S-P group	P value
n (M/F)	12 (11/1)	15 (12/3)	NA
Age (years)	68 ± 12	69 ± 7	0.80
Follow up (days)	197 ± 74	201 ± 56	0.87
Disease (%)			
AP	7 (58)	8 (53)	0.90
Old MI	5 (42)	7 (47)	0.90
Risk factor (%)			
Hypertension	10 (83)	15 (100)	0.37
Hyperlipidemia	7 (58)	11 (73)	0.68
Diabetes mellitus	11 (92)	10 (67)	0.27
Smoking	4 (33)	5 (33)	0.68
Vessel			
LAD/LCX/RCA	4/1/7	3/2/10	NA
Lesion type (%)			
Chronic total occlusion	4 (33)	4 (27)	0.96

P-S group, paclitaxel-eluting stent (PES) implanted proximal and sirolimus-eluting stent (SES) implanted distal; S-P group, SES implanted proximal and PES implanted distal; NA, not applicable; AP, angina pectoris; MI, myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

coverage, and malapposition without neointimal coverage were significantly less frequent for PES than for SES (6.6% vs 12.3%, $P<0.01$; 0.5% vs 1.0%, $P=0.012$; 0% vs 0.4%, $P<0.01$; **Figure 2**). In the struts at the orifice branch site, 8 of 15 were uncovered in the PES, and 19 of 25 were uncovered in the SES. Three PES and 4 SES were fully covered with neointima (11% vs 17%, $P=1.00$). The NIT was significantly greater in PES than in SES: P-S group, $100 \mu\text{m}$ (25th: $40 \mu\text{m}$; 75th: $220 \mu\text{m}$) vs $60 \mu\text{m}$ (25th: $20 \mu\text{m}$; 75th: $130 \mu\text{m}$) ($P<0.001$); S-P group, $90 \mu\text{m}$ (25th: $40 \mu\text{m}$; 75th: $180 \mu\text{m}$) vs $50 \mu\text{m}$ (25th: $20 \mu\text{m}$; 75th: $150 \mu\text{m}$) ($P<0.001$); Total, $90 \mu\text{m}$ (25th: $40 \mu\text{m}$; 75th: $200 \mu\text{m}$) vs $50 \mu\text{m}$ (25th: $20 \mu\text{m}$; 75th: $140 \mu\text{m}$) ($P<0.001$). The average NIT of PES was $149 \pm 163 \mu\text{m}$ and that of SES was $83 \pm 100 \mu\text{m}$ (**Figure 3**). RUNIT was larger in the PES group than in the SES group: 206 ± 88 vs $131 \pm 57 \mu\text{m}$ ($P<0.001$), and LUNIT was also larger in the PES group than in the SES group: 607 ± 243 vs $400 \pm 185 \mu\text{m}$ ($P<0.001$). The distribution of NIT on the struts is shown in

Figure 2. Classification of chronic strut conditions. Of the 3,769 stent struts in 27 PES and 4,377 struts in 27 SES, 3,490 struts and 3,755 struts (92.6% vs 85.8%, $P<0.01$) were classified as well-apposed with neointima, 249 struts and 538 struts (6.6% vs 12.3%, $P<0.01$) as well-apposed without neointima, 18 struts and 43 struts (0.5% vs 1.0%, $P=0.012$) as malapposed with neointima, and 0 struts and 17 struts (0% vs 0.4%, $P<0.01$) as malapposed without neointima, respectively. PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents.

Figure 3. Comparison of neointimal thickness (NIT) between PES and SES. In this basic box-and-whisker plot, the central box represents the values from the lower to upper quartile (25–75th percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding “outside” and “far out” values, which are displayed as separate points. Statistical difference was analyzed by Mann-Whitney U test. The P-S group of PES, 100 μm (25th: 40 μm ; 75th: 220 μm), was significantly larger than that of SES 60 μm (25th: 20 μm ; 75th: 130 μm). The S-P group of PES, 90 μm (25th: 40 μm ; 75th: 180 μm) was significantly larger than that of SES, 50 μm (25th: 20 μm ; 75th: 150 μm). The total of the P-S group and S-P group of PES, 90 μm (25th: 40 μm ; 75th: 200 μm) was significantly larger than that of SES, 50 μm (25th: 20 μm ; 75th: 140 μm). PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents; P-S group, PES implanted proximal and SES implanted distal; S-P group, SES implanted proximal and PES implanted distal.

Figure 4. Neointimal thickness (NIT) distribution in PES and SES. The peak frequency of the NIT distribution was 40–60 μm for both PES and SES. Frequency at 0–60 μm was greater for SES than PES, and at 60–80 μm , the frequency was similar between SES and PES. PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents.

Figure 4. Struts with low-intensity spots were significantly more frequent in the PES group than in the SES group (30.9% vs 17.0%, $P=0.001$). We detected a mural thrombus in 9 stents of PES and 7 stents of SES (33% vs 26%, $P=0.77$).

Discussion

This is the first report of using OCT examination to compare PES and SES implanted under strictly matched conditions. Neointimal non-coverage and malapposition were significantly less frequently observed with PES than with SES. NIT was significantly greater in PES than in SES, regardless

of the stent's location, proximal or distal. Compared with SES, the larger RUNIT and LUNIT of PES suggest non-uniformity of neointimal proliferation with PES.

The median NIT of SES (50 μ m [25th: 20 μ m; 75th: 140 μ m]) in this study was close to that observed in our previous study (52.5 μ m [25th: 28.0 μ m; 75th: 147.6 μ m]),²¹ suggesting good reproducibility of the OCT findings for DES follow-up. The NIT of 90 μ m in PES was larger than that in SES. For uniform neointimal suppression, distribution of an effective dose concentration to the vessel is crucial. Optimization of drug distribution requires symmetric expansion of the stent for homogeneous distribution.²⁷ The closed cell of the SES maintains a relatively regular strut distribution despite expansion in various anatomic situations and appears to provide more regular and predictable drug delivery. The PES, however, has an open cell design and a more uneven strut distribution, especially when implanted into a tortuous lesion.²⁸ This uneven strut distribution may result in uneven drug delivery. In addition, the narrow therapeutic window of paclitaxel may contribute to heterogeneous neointimal growth after PES implantation.²⁹ Farb et al found a paclitaxel dose-dependent neointimal suppression and subsequent increase in vessel wall toxicity in a porcine coronary model.³⁰ Sirolimus, on the other hand, uniformly suppresses neointimal proliferation after vascular injury at a relatively wide range of therapeutic doses.³¹ These mechanisms explain the non-uniform neointimal proliferation in PES, which may contribute to the clinically different pattern and frequency of restenosis with PES compared with SES.¹⁸

In this study, we found mural thrombi in approximately 30% of both PES and SES (PES: 33%, SES: 26%). We previously reported that a mural thrombus in SES is not rare and that the presence of a mural thrombus is related to a longer stent, asymmetric stent expansion, increased number of uncovered struts, and unevenness of the NIT.²⁶ On the other hand, Murakami et al reported that the presence of thrombus in first-generation DES was not related to advanced neointimal growth.³² Although it could be hypothesized that the higher frequency of uncovered SES, and the NIT unevenness in PES relate to the formation of mural thrombus, further investigation is necessary to understand thrombus formation. Also, whether the next generation of DES will reduce the incidence of mural thrombus remains to be clarified.

Based on pathologic studies, incomplete neointimal stent coverage is the most important morphometric predictor of LST because it is the most powerful surrogate indicator of endothelialization.^{33,34} None of the cases of mural thrombus in our study subjects, however, resulted in LST. We speculate that thrombosis with complete vessel obstruction requires specific factors, such as blood flow stasis or increased coagulability, in addition to the thrombogenicity of uncovered struts.

According to our results, PES had a higher frequency of peri-strut low-intensity areas than SES. Gonzalo et al³⁵ showed the OCT pattern of restenotic tissue after DES implantation. In their report, restenotic tissue backscatter was divided into high or low (high: the majority of the tissue showed high backscatter and appeared bright; low: the majority of the tissue showed low backscatter and appeared dark or black). Also, they categorized the tissue structure as homogeneous, heterogeneous, or layered. Low backscatter was observed even in non-restenotic, thin neointimal tissue surrounding stent struts, hence in both restenotic and non-restenotic tissue, low backscatter tissue surrounding stent struts was determined as a low-density spot in that study.

Upon histological analysis, fibrin was mainly observed at the "black spot site" (we call it a "low-density spot") on the corresponding OCT image. Hyaluronic acid and proteoglycan were also observed, and, in small amounts, neutrophil and macrophage infiltration. The "black spots" seem to represent the process of fibrin resolution.³⁶ Lüscher et al³⁷ reported that PES showed early fibrin deposition around stent struts, which persisted for up to 8 months as a sign of delayed healing. In contrast, SES showed a predominance of inflammatory cells, including giant cell formation, at early time points (1 and 3 months), and fibrin deposition was stronger at 8 months. Both circumferential and radial drug concentration gradients are greatest near the struts and decay rapidly before increasing again near the perivascular space.²⁷ This high drug concentration may result in peri-strut inflammation. Structures with delayed healing might be imaged as peri-strut low-intensity areas by OCT. The difference in the frequency of peri-strut low-intensity areas suggests a different time course of vascular healing, which may be caused by the pharmacologic differences between paclitaxel and sirolimus.³⁸ This mechanism may also underlie the difference between PES and SES in NIT.

Struts at the side-branch orifice site were evaluated separately, because they were not apposed to the vessel wall permanently and the flow at the side-branch orifice should be different from that at the vessel wall site. Indeed, more than 50% of both types of struts at the side-branch orifice site were not covered with neointima.

Although this is a simple observational study, we set up a strictly matched condition between PES and SES. This study using OCT demonstrated clear morphological differences between PES and SES, such as the frequency of uncovered struts, median value and evenness of NIT, and frequency of peri-strut low-intensity areas or mural thrombus. This knowledge could be helpful in understanding the differences in neointimal proliferation among DES. These OCT data will be the basic data when comparing the next generation DES.

Study Limitations

First, even though we evaluated the stents in a strictly matched manner, our findings were based on a relatively small number of subjects. Second, because OCT cannot diagnose tissue character, we could not discriminate between neointima and the smooth surface of a white thrombus. A higher frequency of mural thrombus is therefore possible. Third, the only PES evaluated was the Taxus ExpressTM stent. The next-generation PES, Taxus LibertéTM stent, which has a denser stent distribution, may produce a better outcome with suppressed and uniform neointimal proliferation.

Conclusion

Our OCT findings indicate that PES (Taxus ExpressTM) have a non-uniform and larger NIT with fewer uncovered struts, and more frequent peri-strut low-intensity areas than SES.

Disclosure

Conflict of Interest: none declared.

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