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Difference of vascular response between everolimus- and paclitaxel-eluting stents for small coronary artery disease: Optical coherence tomography analysis☆,☆☆,★

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ABSTRACT

Background: Previous clinical trials have demonstrated the clinical and angiographic superiority of everolimus-eluting stents (EES) compared with paclitaxel-eluting stents (PES) in the small coronary vessel. However, the differences of vascular response including assessment of morphological neointimal tissue (NIT) characteristics using optical coherence tomography (OCT) have not been fully evaluated. The aim of this study is to evaluate the differences of chronic vascular response following small coronary stenting between EES and PES using OCT.
Methods and results: A prospective OCT examination at 9 month follow-up was performed for 50 small coronary artery diseases (50 patients) treated by a single 2.5 mm stent for each stent group. Cross-sectional area within stent segments were analyzed at an interval of 1 mm. NIT structure (homogeneous or heterogeneous) was evaluated for qualitative assessment. Homogeneous NIT was observed significantly higher and heterogeneous NIT was lower in EES compared with PES (93% vs. 89%; $p = 0.003$, 6.5% vs. 10.3%; $p = 0.002$, respectively). The frequencies of exposed and malapposed struts were lower in EES compared with PES (0.2% vs. 1.7%; $p = 0.0001$, 0.1% vs. 0.3%; $p = 0.001$, respectively). NIT eccentricity index and NIT area were lower in EES compared with PES (0.69 ± 0.08 vs. 0.76 ± 0.10; $p = 0.001$, 0.97 ± 0.42 mm^2 vs. 1.27 ± 0.67 mm^2; $p = 0.01$, respectively).
Conclusions: A favorable vascular response was observed after EES implantation compared with PES for small coronary artery disease. In addition, the characteristics of NIT after EES implantation were more stable than PES at 9 month follow-up.

1. Introduction

Lesions in small coronary vessels comprise a challenging disease subset in contemporary interventional practice. Although drug-eluting stents (DES) have been able to strikingly reduce the rate of in-stent restenosis, vessel size is still one of the strong independent predictors of angiographic and clinical restenosis [1]. Previous studies have been shown that an everolimus-eluting stent (EES), a second generation DES, was superior to a paclitaxel-eluting stent (PES) in terms of a significant reduction of in-stent late loss and target lesion revascularization rate in small coronary vessels [2–4]. However, morphological differences of neointimal tissue (NIT) have not been evaluated between these two stents. Optical coherence tomography (OCT) is a novel intravascular imaging modality that can produce in vivo high-resolution images of the coronary artery, providing new insights into the characteristics of atherosclerotic plaques [5–8] and NIT structure in stents [9]. The aim of this study is to evaluate the differences of chronic vascular response following small coronary stenting between EES and PES evaluated by OCT.

2. Material and methods

2.1. Study design and population

This study was designed as the OCT sub-analysis of SACRA (SmAll CoronaRy Artery treated by TAXUS Liberté) and PLUM (PROMUS/Xience V Everolimus-ELUting Coronary Stent for sMall coronary artery disease) registries. These registries were performed consecutively. SACRA was a prospective multi-center registry performed at 26 sites in Japan in which 245 patients with 258 lesions were enrolled from April, 2009, to February, 2010. PLUM was also a prospective multi-center registry performed at the same 26 sites in which 252 patients with 266 lesions were enrolled from March, 2010, to June, 2011. The objective of both

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registries was to evaluate the efficacies of EES (PROMUS [Boston Scientific, Natick, MA]/XIENCE V [Abbott Vascular, Santa Clara, CA]) and PES (TAXUS Liberte [Boston Scientific, Natick, MA]) for small coronary artery disease. Both registries included males and non-pregnant females, aged 20 years or older, with evidence of myocardial ischemia. The de novo target lesion(s) in native coronary artery had to have a reference vessel diameter <2.5 mm by visual estimation, a target lesion length <28 mm for single stenting, and a visually estimated stenosis of the luminal diameter between 75 and 99%. Exclusion criteria were: 1) primary angioplasty for ST-elevation myocardial infarction; 2) left ventricular ejection fraction <30%; 3) other concomitant disease or medical condition that could impact patient/procedural outcomes, such as history of bleeding diathesis, stroke, or transient ischemic neurological attacks within the past year; or hypersensitivity to stainless steel, everolimus, paclitaxel, heparin, aspirin, ticlopidine, clopidogrel or X-ray contrast media; 4) chronic total occlusion; 5) in-stent restenosis; and 6) severe vessel tortuosity or calcification which would hinder successful stent delivery; 7) serum creatinine level >2 mg/dl. The primary endpoint of both registries was a one year target lesion revascularization rate. In each registry, 50 consecutive patients were enrolled at two centers (Toyohashi Heart Center, Aichi, Japan and The Cardiovascular Institute Hospital, Tokyo, Japan) for a formal prospective sub-analysis using OCT at 9 month follow-up angiography. The inclusion criteria of the OCT sub-analysis were: 1) stent at the target lesion without in-stent restenosis; 2) non-ostial lesion; 3) absence of extreme vessel tortuosity or calcification which would hinder successful occlusion balloon catheter delivery. The study protocol for OCT sub-analysis was approved by ethics committees in both institutions, and all eligible patients gave written informed consent.

2.2. Quantitative coronary angiography

An independent core laboratory (CVIC: CardioVascular Image Center, Toyohashi, Japan) analyzed baseline, post-procedural and 9-month follow-up angiographic images using a validated automated edge-detection system (QCA-CMS version 5.1, CMS-MEDIS, the Netherlands). The core laboratory was blinded to the treatment assignment. Off-line quantitative coronary analysis was performed on the view that clearly showed the highest degree of stenosis. Quantitative measurements were performed at baseline and post-procedure. At follow-up angiography, quantitative parameters included the area 5 mm distal and proximal to the stent as well as inside the stent. Binary restenosis was defined as >50% luminal diameter stenosis. In-stent late lumen loss was defined as the difference between minimum luminal diameter post-procedure and that at 9-month follow-up angiography.

2.3. OCT imaging

After completion of coronary angiography, patients were evaluated with OCT. OCT imaging was performed using the M2 OCT system (LightLab Imaging; Westford, MA) and Helios occlusion balloon catheter (LightLab Imaging) method. The occlusion balloon catheter was advanced proximal to the implanted stent under the guidance of a 0.014-in angioplasty wire, and the guide wire was then exchanged with the OCT imaging wire, which was then positioned distal to the stent. During image acquisition, lactated Ringer solution was continuously flushed through the inner lumen of the occlusion catheter at a rate of 0.5 to 1.0 ml/s by power injector, and the balloon was inflated to 0.4 to 0.8 atm until blood flow was fully occluded. Motorized pullback OCT imaging was performed at a rate of 1.0 mm/s throughout the stent. Images were acquired at 15.6 frames/s and digitally archived.

2.4. OCT quantitative and qualitative analysis

OCT analysis was performed using LightLab Imaging proprietary software. Both qualitative and quantitative analyses of OCT images were performed by independent core laboratories (CICL: Cardiovascular Imaging Core Laboratory, Tokyo, Japan). The analyses, including lumen and stent areas or morphological appearance, were performed at 1-mm longitudinal steps throughout the pullback from distal stent edge to proximal stent edge. The thickness of NIT on each stent strut was measured. An uncovered strut was defined as a strut with a measured NIT thickness equal to 0 μm. A malapposed strut was a strut with a distance from its surface to the adjacent vessel surface more than 108 μm in EES and more than 134 μm in PES (a total of the thickness of stent strut and polymer layer) [10–12]. At every frame, maximum and minimum thicknesses of NIT were recorded and NIT eccentricity index ([maximum − minimum thickness of NIT] / maximum thickness of NIT) was calculated. The lumen and stent were manually traced, and NIT area (stent area − lumen area) was calculated. Percent NIT area was also calculated [(NIT area / stent area) × 100]. To evaluate the morphological appearance of NIT, the pattern of tissue structure in cross-sectional images at every 1-mm interval was categorized as follows: (1) homogeneous intima where tissue has uniform optical properties and does not show focal variations in backscattering pattern (Fig. 1A) [13]; (2) heterogeneous intima where tissue has focally changing optical properties with various backscattering patterns (Fig. 1B) or tissue consists of signal poor area with or without adluminal high scattering layer (Fig. 1C) [14,15]; (3) peri-stent ulcer-like appearance (Fig. 1D) [15]; (4) visible intraluminal materials (Fig. 1E) [14]. When the reading of the qualitative analysis by 2 observers differed, a consensus was reached and used in the final decision. To test the interobserver variability of the qualitative OCT analysis, a total of 100 cross-sections within the stent from 10 patients with 10 cross-sections each were selected and analyzed independently by 2 observers not involved in the primary data analysis. One of the observers repeated the analysis 2 weeks later to assess the intraobserver variability.

2.5. Statistical analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean ± SD or median and interquartile ranges. Comparisons between groups were performed with a 2-tailed Student *t* test for normally distributed variables, Mann–Whitney *U* test for non-normally distributed variables, or with the chi-squared test or Fisher exact test for categorical variables. The reproducibility of qualitative variables was assessed with [kappa] test. SPSS 15.0 (SPSS, Inc., Chicago, Illinois) was used for data analysis. A probability value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Clinical characteristics

A total of 50 patients were enrolled from each stent group. Clinical characteristics, laboratory data, and medication therapies of the study population are listed in Table 1. Dual anti-platelet therapy continued during the follow-up period in both groups.

3.2. Lesion characteristics and procedural results

Baseline lesion characteristics and procedural results are summarized in Table 2. Lesion location was similar between the two groups. Maximum stent dilatation pressure was significantly lower and post dilatation was performed more frequently in the EES group.

3.3. QCA analysis

QCA findings revealed no significant differences in any parameters at pre-procedure, post-procedure, and 9 month follow-up between the 2 groups (Table 3). Late loss was similar between the two group (EES group vs. PES group; 0.38 ± 0.41 mm vs. 0.42 ± 0.36, p = 0.61).

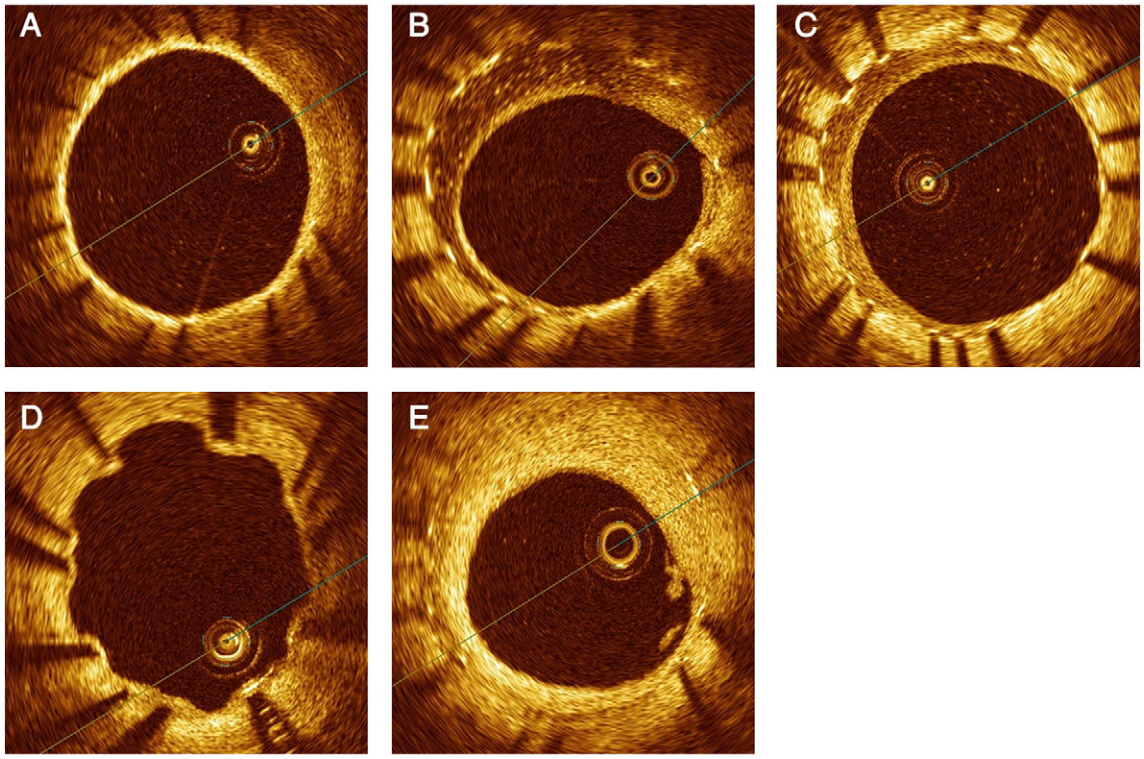

Fig. 1. The morphological appearance of neointimal tissue. A. Homogeneous intima where tissue has uniform optical properties and does not show focal variations in backscattering pattern. B. Heterogeneous intima where tissue has focally changing optical properties with various backscattering patterns. C. Tissue consists of signal poor area with or without adluminal high scattering layer. D. Peri-stent ulcer-like appearance. E. Visible intraluminal materials.

3.4. OCT analysis

Representative examples of EES and PES groups are shown in Figs. 2 and 3, respectively. The results of OCT quantitative and qualitative analysis are shown in Table 4. At strut level, EES presented a lower percentage with exposed and malapposed struts than PES (exposed strut: 0.2% vs. 1.7%; p = 0.0001, malapposed strut: 0.1% vs. 0.3%; p = 0.001). In addition, although there were no significant differences in thickness of averaged NIT and minimal NIT between the two groups, the significantly higher thickness of maximum NIT in PES group resulted in the lower NIT eccentricity index.

At cross-sectional level, NIT area in the EES group was significantly lower compared with the PES group (0.97 ± 0.42 mm^2 vs. 1.27 ± 0.67 mm^2; p = 0.01). In qualitative analysis, there was a significantly higher rate of homogeneous pattern of NIT with EES than with PES, however, the rates of heterogenous pattern of NIT and peri-stent ulcer-like appearance with EES were significantly lower than with PES. Intraluminal materials were rarely observed in the overall study population.

Table 1
Baseline clinical characteristics and laboratory data.

Variable	EES (n = 50)	PES (n = 50)	p
Age, yrs	70.5 ± 7.4	70.4 ± 8.0	0.94
Male	30 (60%)	38 (76%)	0.6
Coronary risk factors			
Diabetes	18 (36%)	18 (36%)	0.13
Hypertension	27 (54%)	28 (74%)	>0.99
Hyperlipidemia	20 (40%)	15 (39%)	0.4
Smoking	3 (6%)	7 (18%)	0.2
Family history			
Prior MI	13 (26%)	9 (224%)	0.47
Prior PCI	22 (44%)	10 (224%)	0.02
Left ventricular EF, %	57.5 ± 10.3	54.2 ± 8.7	0.16
Total cholesterol, mg/dl	182.7 ± 29.5	185.2 ± 40.5	0.75
LDL cholesterol, mg/dl	102.5 ± 26.6	104.7 ± 31.5	0.73
HDL cholesterol, mg/dl	50.9 ± 12.8	48.0 ± 11.5	0.25
Medication			
DAPT	50 (100%)	50 (100%)	>0.99
ACE-I	5 (10%)	7 (14%)	0.48
Statins	28 (56%)	30 (60%)	0.84
Insulin	2 (4%)	1 (2%)	>0.99
Oral hypoglycemics	16 (32%)	17 (34%)	>0.99

Values are the numbers (%) or mean ± SD.
ACE-I = angiotensin converting enzyme inhibitors. EES = everolimus-eluting stent. PES = paclitaxel-eluting stent. MI = myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary artery bypass graft. EF = ejection fraction. DAPT = dual antiplatelet therapy.

Table 2
Lesion characteristics and procedural results.

Variable	EES (n = 50)	PES (n = 50)	p
Location of stent			
LAD	19 (38%)	15 (30%)	0.53
LCX	16 (32%)	20 (40%)	
RCA	15 (30%)	15 (30%)	
Calcification	10 (20%)	7 (14%)	0.6
Bending	4 (8%)	4 (8%)	>0.99
De novo lesion	47 (94%)	47 (94%)	>0.99
Length of stent, mm	18 (12–23)	16 (12–20)	0.42
>20 mm stenting	14 (28%)	18 (36%)	0.52
Direct stenting	8 (16%)	9 (18%)	>0.99
Maximum stent dilatation pressure, atm	8 (8–12)	12 (10–15)	<0.0001
Post dilatation	45 (90%)	29 (58%)	0.0005
Post dilatation balloon size, mm	2.75 (2.5–3.0)	2.75 (2.5–3.0)	0.95

Values are the numbers (%), mean ± SD, or median and interquartile ranges.
EES = everolimus-eluting stent. PES = paclitaxel-eluting stent. LAD = left anterior descending artery. LCX = left circumflex artery. RCA = right coronary artery.

Table 3
Quantitative coronary angiography analysis.

Variable	EES (n = 50)	PES (n = 50)	p
Pre-procedure			
Lesion length, mm	14.6 ± 7.6	12.6 ± 6.6	0.16
Reference diameter, mm	2.28 ± 0.25	2.30 ± 0.26	0.73
Minimal luminal diameter, mm	0.87 ± 0.19	0.87 ± 0.24	0.96
Diameter stenosis, %	62.1 ± 8.7	62.2 ± 9.8	0.98
Post-procedure			
Reference diameter, mm	2.52 ± 0.21	2.50 ± 0.23	0.61
Minimal luminal diameter, mm	2.32 ± 0.25	2.32 ± 0.21	0.98
Acute gain, mm	1.47 ± 0.37	1.45 ± 0.29	0.83
Diameter stenosis, %	8.2 ± 7.0	7.1 ± 7.1	0.47
Follow-up			
Reference diameter, mm	2.44 ± 0.23	2.39 ± 0.22	0.28
Minimal luminal diameter, mm	1.94 ± 0.42	1.90 ± 0.41	0.65
Late loss, mm	0.38 ± 0.41	0.42 ± 0.36	0.61
Diameter stenosis, %	20.7 ± 14.7	20.8 ± 14.7	0.98

Values are the numbers (%) or mean ± SD.
EES = everolimus-eluting stent. PES = paclitaxel-eluting stent.

At stent level, there was a significantly higher rate of stent with all homogeneous NIT frames in the EES group. Additionally, the rate of stents with complete stent coverage and all homogeneous frames was also significantly higher in the EES group. On the other hand, the rate of stents with any heterogenous NIT frame was significantly lower than the PES group.

3.5. Reproducibility of qualitative OCT analysis

Interobserver/intraobserver variability (kappa values) for the qualitative OCT analysis was as follows: 0.87/0.88 for NIT structure (homogeneous versus heterogeneous intima), 0.84/0.88 for peri-stent ulcer-like appearance, 0.89/0.92 for thrombi.

4. Discussion

This study was a comparison of the vascular response evaluated by OCT at 9 months between EES and PES for small coronary artery disease. The main findings of this study were that (1) the OCT heterogeneous pattern of NIT was more frequently observed in the PES group and the OCT homogeneous pattern of NIT was more frequently observed in EES, (2) the more concentric NIT was observed in EES, and (3) the rates of exposed strut and malapposed strut after EES implantation were lower than those after PES.

Percutaneous coronary intervention (PCI) in small coronary arteries poses a greater procedural challenge compared to PCI in large vessels, and higher rates of adverse cardiovascular events have been observed in patients with small coronary artery disease even in the DES era [16–18]. Large scale studies showed the clinical and angiographic superiorities of EES over PES [19] and definite or probable stent thrombosis increased after PES implantation for compared with EES [19]. It is well known that delayed healing and incomplete endothelial cell coverage

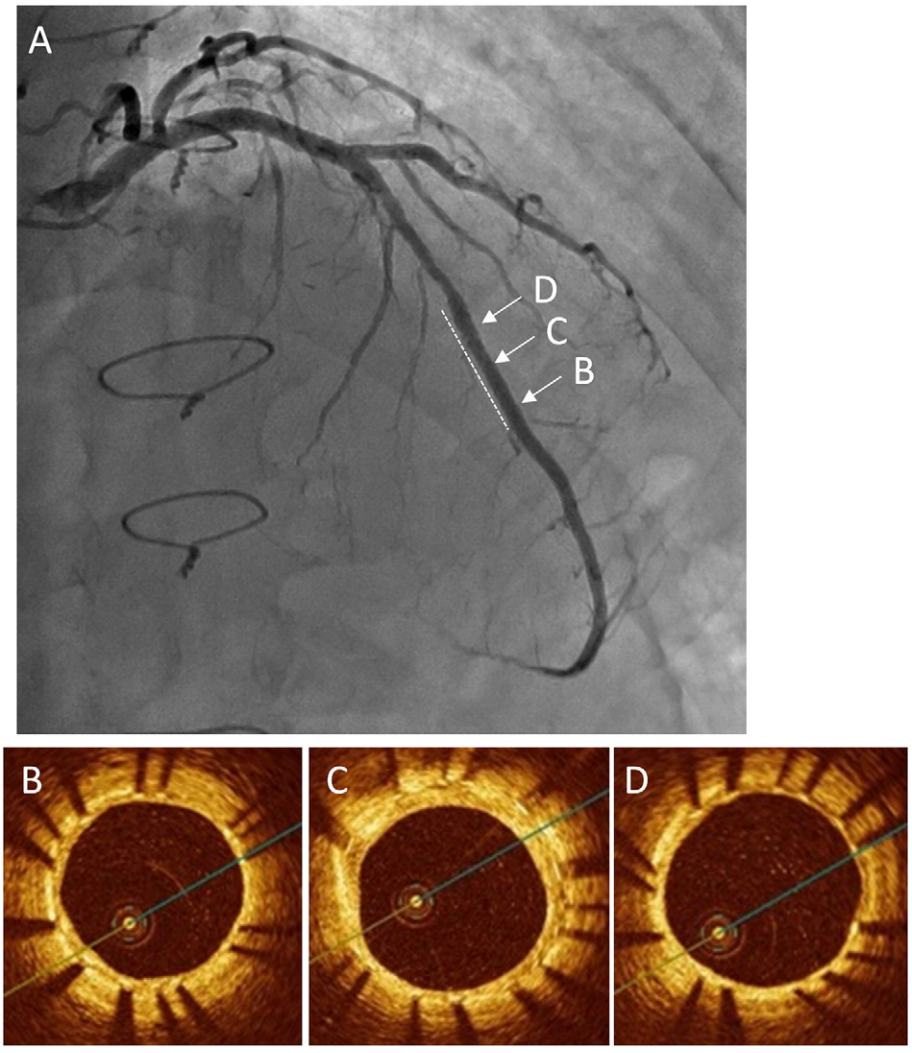

Fig. 2. Optical coherence tomography (OCT) findings of everolimus-eluting stent at 9 month follow-up. There was no angiographic restenosis. In OCT findings, the morphology of neointimal tissue was homogeneous and concentric.

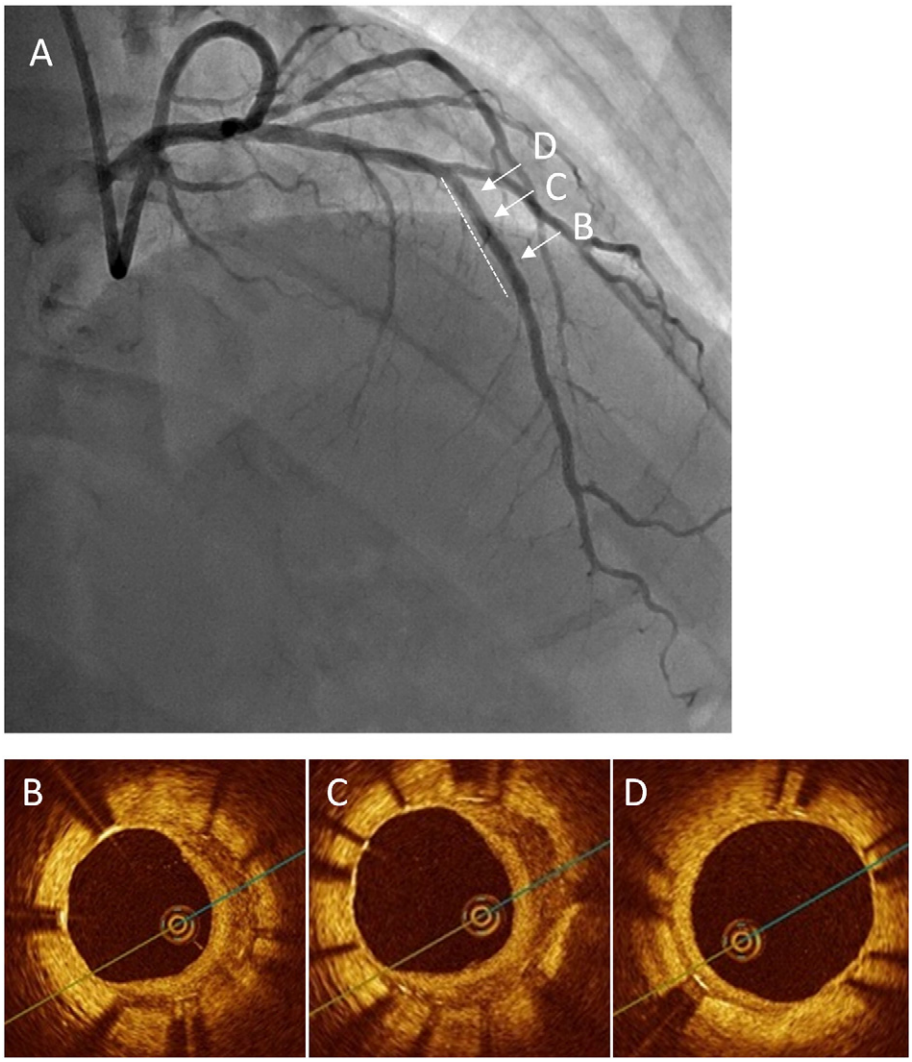

Fig. 3. Optical coherence tomography (OCT) findings of paclitaxel-eluting stent at 9 month follow-up. There was no angiographic restenosis. In OCT findings, the morphology of neointimal tissue was heterogeneous and eccentric.

is significantly associated with late stent thrombosis after DES implantation [20]. In a previous study, the percentage of exposed strut at 9 months follow-up was significantly smaller in EES than sirolimus-eluting stent, however, the percentage of malapposed strut was similar between the two stent groups [21]. On the other hand, in this study, lower exposed and malapposed stent strut rates with EES suggest the clinical superiority to those of PES and several factors might be attributable as follows. First, the difference in the polymer might have an impact on the vascular response. The nonthrombogenic fluoropolymer is relatively thin (8 μm) on the surface of the EES, on the other hand, PES is covered with the thicker (17.8 μm) 3-layer styrene-isobutylene-styrene polymer. Second, the difference in the drug may be associated with various NIT growth. Although both everolimus and paclitaxel inhibit proliferation of smooth muscle cells and endothelial cells, only paclitaxel disrupts migration of endothelial cells. In consequence, paclitaxel showed a higher cytotoxicity than everolimus.

On the other hand, there was no significant difference in angiographic late loss and averaged thickness of NIT between the two stent groups. In addition, a relatively higher NIT thickness in both stent groups were observed compared with previous studies [10,11] including larger coronary artery disease. However, maximum thickness of NIT in the PES group was significantly higher than that in the EES group. This difference was associated with the differences of NIT eccentricity index (EES 0.69 ± 0.08 vs. PES 0.76 ± 0.10, $p = 0.001$) and NIT area (EES 19.1 ± 8.3 mm^2 vs. PES 24.6 ± 13.6 mm^2, $p = 0.02$) between the two stent groups. The clinical significance of NIT eccentricity has not been well established, however, it may be associated with neo-atherosclerosis in NIT after DES implantation as eccentric lipid rich plaque in the native coronary artery which can increase risk for instability [22]. From previous autopsy studies [23,24], in-stent neoatherosclerosis after drug-eluting stent implantation occurred at an earlier time point as compared with bare metal stents. Previous OCT studies showed that the duration after stent implantation was associated with the progression of in-stent atherosclerotic change [25] and a part of the heterogeneous pattern of NIT at 9 month follow-up might change to the lipid-laden neointima at 2 year follow-up [26]. In this study, heterogeneous NIT was observed more frequently in the PES group at cross-sectional level analysis and half of the PES group included at least one frame with heterogeneous NIT at stent level analysis. Thus, NIT after EES implantation for small coronary artery disease showed a more stable morphology at 9 month follow-up compared with PES. These results also might be associated with the lower incidence of major adverse cardiac events including definite or probable stent thrombosis after EES implantation compared with PES [19].

4.1. Limitations

This study was not randomized study and performed consecutively. Therefore, some procedural characteristics were not matched between

Table 4
Quantitative and qualitative optical coherence tomography results.

Variable	EES	PES	p
Strut level analysis			
Number of stent strut	9705	7605	
Exposed struts	23 (0.2%)	130 (1.7%)	0.0001
Malapposed struts	9 (0.1%)	60 (0.3%)	0.001
Averaged thickness of NIT, mm	0.13 ± 0.06	0.17 ± 00.09	0.05
Maximum thickness of NIT, mm	0.21 ± 0.08	0.30 ± 0.14	0.001
Minimal thickness of NIT, mm	0.07 ± 0.04	0.08 ± 0.06	0.5
NIT eccentricity index	0.69 ± 0.08	0.76 ± 0.10	0.001
Cross-sectional level analysis			
Number of cross-sectional frame	859	825	
Stent area, mm^2	5.16 ± 1.05	5.29 ± 0.74	0.46
Lumen area, mm^2	4.18 ± 1.03	4.03 ± 1.04	0.48
NIT area, mm^2	0.97 ± 0.42	1.27 ± 0.67	0.01
% NIT area, %	19.1 ± 8.3	24.6 ± 13.6	0.02
Frame with homogeneous NIT	803 (93%)	737 (89%)	0.003
Frame with heterogeneous NIT	56 (6.5%)	88 (10.7%)	0.003
Frame with peri-stent ulcer-like appearance	36 (4.1%)	65 (7.9%)	0.002
Frame with thrombi	0	4 (0.5%)	–
Stent level analysis			
Number of stent	50	50	
Stent with all homogeneous NIT frames	22 (44%)	8 (16%)	0.004
Stent with complete stent coverage and all homogeneous frames	20 (40%)	4 (8%)	0.0003
Stent with any heterogeneous NIT frame	12 (24%)	25 (50%)	0.01
Stent with the presence of thrombus	0	1 (2%)	–

Values are the numbers (%) or mean ± SD.
EES = everolimus-eluting stent. NIT = neointimal tissue. PES = paclitaxel-eluting stent.

the two groups and the operator's experience in stent implantation technique for small coronary artery diseases might be different between the two stent groups. The present study includes a small number of patients without in-stent restenosis. The association of long-term clinical results including very late thrombosis and late catch-up in-stent restenosis with OCT findings in this study could not be evaluated, due to a single-point observation. Although the incidence of angiotensin converting enzyme inhibitors (ACE-I) was not different between the two stent groups and drug types of ACE-I were not evaluated in this study, ACE-I might have some effect of NIH formation after implantation of PES and EES [27,28]. OCT analysis immediately after stent implantation was not performed in this study. Histological data is required to validate the sensitivity and specificity of OCT findings of NIT.

5. Conclusions

A more favorable vascular response was observed after EES implantation compared with PES for small coronary artery disease. In addition, the characteristics of NIT after EES implantation were more stable than PES at 9 month follow-up examination.

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