Temporal Course of Vascular Response After Fluoropolymer Paclitaxel-Eluting Stent Implantation for Femoropopliteal Artery Lesions

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Background: Limited data are available regarding the vascular response after fluoropolymer paclitaxel-eluting stent (FP-PES) implantation. This study sought to assess the vascular response at 6 and 12 months after FP-PES implantation for femoropopliteal artery lesions using serial optical coherence tomography (OCT) examination.

Methods and Results: From the IMPERIAL trial, this study evaluated 10 de novo femoropopliteal lesions treated with FP-PES. The primary study endpoint was neointimal tissue coverage at a 6- and 12-month follow up, as assessed by serial OCT examination. The incidence of peri-strut low-intensity area (PLIA) and extra-stent lumen (ESL) was also assessed. A total of 203 matched cross-sectional images were evaluated at 6 and 12 months (5,615 and 5,763 struts, respectively). From 6 to 12 months, the mean neointimal thickness tended to increase from 198 μ m to 233 μ m, with a significant reduction in the incidence of malapposed struts (0.59% vs. 0.28%, $P=0.039$). Conversely, uncovered struts and PLIA were more frequently observed at 12 months (4.4% vs. 7.8%, $P=0.01$; 12.7% vs. 21.0%, $P<0.001$, respectively). The ESL area significantly increased over time without any difference in its incidence (0.24 ± 0.32 mm² vs. 0.38 ± 0.36 mm², $P=0.009$).

Conclusions: Neointimal proliferation was markedly inhibited from 6 to 12 months after FP-PES implantation, whereas the incidence of uncovered struts and PLIA significantly increased over time with the enlargement of ESL.

Key Words: Endovascular therapy; Optical coherence tomography; Paclitaxel-eluting stent

The fluoropolymer paclitaxel-eluting stent (FP-PES) (Eluvia, Boston Scientific, Marlborough, MA, USA) is a newer-generation drug-eluting stent (DES), allowing the controlled and sustained release of paclitaxel over 12 months after stent implantation.¹ Histopathological studies in porcine models demonstrated that FP-PES resulted in a lower level of neointimal proliferation with sustained biological effects vs. those obtained with a paclitaxel-coated stent (PCS) (Zilver PTX, Cook Medical, Bloomington, IN, USA) within 6 months,^{2,3} suggesting that FP-PES might lead to better outcomes compared with PCS. Indeed, the randomized controlled IMPERIAL trial recently demonstrated superiority of FP-PES vs. PCS in terms of 1-year primary patency for femoropopliteal artery lesions.⁴ To date, however, limited data are available regarding the vascular response to FP-PES beyond 6 months, particularly in human femoropopliteal artery lesions. In the present study, we sought to assess the vascular response at 6 and 12 months after FP-PES implantation for femoropop-

liteal artery lesions using serial optical coherence tomography (OCT) examination.

Methods

Study Population

From December 2015 to December 2016, a total of 20 patients from Kokura Memorial Hospital were enrolled in the IMPERIAL trial,⁴ and randomly assigned in a 2:1 fashion to either the FP-PES ($n=13$) or PCS ($n=7$) group. At the initial procedure, acute technical and procedural success based on the Peripheral Academic Research Consortium (PARC) criteria were obtained in all patients.⁵ For the purpose of the present study, 6- and 12-month follow-up OCT studies were performed only in the FP-PES group. This study was approved by the ethics committees of our institution, and written informed consent was provided by all patients in accordance with the tenets of the Declaration of Helsinki.

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Figure 1. Representative optical coherence tomography images. (A) Homogeneous neointima. (B) Heterogeneous neointima (red arrows). (C) Layered neointima. (D) Extra-stent lumen (blue arrows). (E) Peri-strut low-intensity area (yellow arrows). (F) intra-stent thrombus (yellow arrowheads).

Endovascular Procedure

A 6-Fr sheath was inserted into the common femoral artery via a contralateral approach. After infusion of 5,000 units of heparin, the activated clotting time was maintained at >200s. The procedural strategy was primary stenting. A 0.014-, 0.018-, or 0.035-inch guidewire was successfully crossed, followed by predilatation using an appropriately sized angioplasty balloon with a diameter equal to the reference vessel diameter, according to visual estimation. After predilatation, a FP-PES was implanted. The stenting strategy was full-coverage stenting. After stenting, routine post-balloon angioplasty was performed to achieve better stent expansion and apposition. Dual antiplatelet therapy (DAPT) was continued based on the package insert instructions.

OCT Imaging Protocol and Analysis

The OCT examination was performed using the frequency-domain OCT system (C8 OCT-system; St Jude Medical, St. Paul, MN, USA). After the insertion of a 6-Fr guiding catheter via the contralateral femoral artery, a 0.014-inch guidewire was passed through the entire stent. The OCT catheter (Dragonfly JP™; Abbott Vascular Inc., Santa Clara, CA, USA) was advanced to the distal end of the stent. To flush the blood within the vessel, we continuously infused low-molecular weight dextran using an injector pump (Mark V Provis; Medrad Inc., Warrendale, PA, USA) from the guiding catheter. The stent was imaged with an automatic pull-back device moving at 36mm/s. To obtain clear OCT images, we continued to manually compress the ipsilateral common femoral artery throughout the procedure. The corresponding images obtained from the serial OCT examination were identified by the following landmarks: (1) side branch loca-

tion; (2) stent edges; or (3) calcification within the vessel.

Cross-sectional OCT images were analyzed at 5.0-mm intervals for quantitative and qualitative evaluations.⁶ Quantitative and qualitative assessments were performed with the OCT off-line analysis software (LightLab Imaging Inc, Westford, MA, USA). The stent and lumen areas were manually traced, and the neointimal thickness (NIT) was semiautomatically measured. The NIT was determined based on automated measurements performed from the center of each strut blooming and its distance to the luminal contour.⁷ The difference between the maximum and minimum NIT was defined as the dNIT.⁸ A strut with a NIT of 0 μm was defined as uncovered. A strut with a distance between the center reflection of the strut and vessel wall >238.5 μm was defined as malapposed. This criterion was determined by adding the actual strut thickness to the OCT resolution limit (223.5+15 μm). Lumen and stent areas were drawn in each analyzed cross-section, and the neointimal area, extra-stent lumen (ESL) area, and peri-strut low-intensity area (PLIA) were calculated as appropriate.^{9,10} The appearance of neointima was classified as follows: homogeneous; layered; and heterogeneous pattern.¹¹ Intra-stent thrombus was defined as an irregular mass protruding beyond the stent strut into the lumen, with significant underlying attenuation (Figure 1).¹² All OCT images were analyzed by 2 investigators (Y.T. and S.K.) who were blinded to the patients' information. In case of discordance between the investigators, a consensus reading was obtained from a third independent investigator (Y.S.).

Statistical Analysis

Data are presented as values (percentages) or the mean $\pm$ standard deviation. Intra- and inter-observer variability for

uncovered strut, malapposed strut, PLIA, and in-stent thrombus were estimated by means of the kappa coefficient (κ). In the strut-level analysis, apposition was estimated through the categorical variable (well apposed or malapposed). Tissue coverage was estimated through the percentage of uncovered struts (dichotomous variable) and through the mean thickness of coverage (continuous variable). We compared the proportions or means of the strut-level and cross-sectional-level variables between 6- and 12-month OCT findings. Odds ratios for dichotomous variables were estimated using multilevel logistic models with random intercepts at the cross-section (nested by lesion) and lesion levels. Similarly, mean differences in continuous variables were estimated using multilevel linear models with random intercepts at the same levels. All models were fitted with normally distributed random effects through the Laplace approximation of likelihood marginalized over the random effects.

All statistical analyses were performed by 2 physicians (Y.T. and S.K.) and a statistician (T.S.) with the use of the JMP version 13.0 (SAS Institute Inc., Cary, NC, USA) software for data description and baseline comparisons. The GLIMMIX procedure in the SAS version 9.4 (SAS Institute Inc.) software was performed for multilevel modeling. A 2-sided P value <0.05 denoted a statistically significant difference.

Results

Study Population

Among the 13 patients assigned to the FP-PES group, 3 patients were excluded due to refusal to participate in this study. Finally, 10 patients who received FP-PES were analyzed in the present study.

Baseline Patient and Lesion Characteristics

The baseline clinical characteristics are summarized in **Table 1**. All patients exhibited intermittent claudication (Rutherford category II/III) and continued to receive DAPT for 12 months following stent implantation. The mean lesion length was 9.9 ± 3.8 cm. All procedures were performed with intravascular ultrasound guidance.

OCT Findings

Table 2 summarizes the OCT findings at 6 and 12 months. Among 260 matched cross-sectional images, 57 were excluded due to poor image quality. Between 6 and 12 months, the mean NIT tended to increase from $198 \mu\text{m}$ to $233 \mu\text{m}$ ($P=0.051$ from the multilevel-modeling analysis), whereas the percentage of malapposed struts was significantly decreased (0.59% vs. 0.28% , $P=0.039$). The distribution of the NIT is shown in **Figure 2**. However, dNIT, and the percentages of uncovered struts and PLIA significantly increased during follow up ($414 \pm 227 \mu\text{m}$ vs. $516 \pm 269 \mu\text{m}$, $P<0.001$; 4.4% vs. 7.8% , $P=0.01$; and 12.7% vs. 21.0% , $P<0.001$, respectively) (**Figure 3**). The stent and neointimal areas were not statistically different between 6 and 12 months, whereas the lumen area significantly decreased. The qualitative analysis demonstrated that, between 6 and 12 months, the frequency of homogeneous neointima significantly decreased (67.0% vs. 48.8% , $P=0.003$), whereas layered neointima increased (6.9% vs. 17.2% , $P=0.024$) (**Figure 4**). The ESL area was enlarged during follow up, despite the absence of difference in its incidence ($0.24 \pm 0.32 \text{ mm}^2$ vs. $0.38 \pm 0.36 \text{ mm}^2$, $P=0.009$; 67.0% vs. 67.0% , $P=1.00$, respectively) (**Figure 5**). The frequency of intra-stent thrombus did not change over time

Table 1. Baseline Clinical Characteristics

Number of patients	10
Age (years)	76.4 ± 7.5
Males	7 (70)
Body mass index (kg/m^2)	21.4 ± 3.5
Hypertension	10 (100)
Hyperlipidemia	9 (90)
Diabetes mellitus	6 (60)
Current smoking	3 (30)
Cerebrovascular disease	3 (30)
Coronary artery disease	6 (60)
Atrial fibrillation	3 (30)
Rutherford classification II/III	6/4
Pre-procedure ABI	0.70 ± 0.14
Medication at discharge	
Aspirin	10 (100)
Thienopyridine	10 (100)
Cilostazol	1 (10)
Statin	6 (60)
Oral anticoagulant	2 (20)
Lesion characteristic	
Lesion length (cm)	9.9 ± 3.8
Reference vessel diameter (mm)	5.2 ± 1.2
Stenosis (%)	89.8 ± 8.9
Chronic total occlusion	1 (10)
TASC classification A/B/C/D	3/4/3/0
PACSS classification 0/1/2/3/4	2/5/0/1/2
Stent length (cm)	12.5 ± 2.8
Stent diameter (mm)	6.3 ± 4.8

Data are expressed as the mean $\pm$ standard deviation or n (%). Lesion length (cm), reference vessel diameter (mm), and stenosis (%) were calculated by Quantitative Vascular Analysis (QVA). ABI, ankle-brachial index; PACSS, Peripheral Arterial Calcium Scoring System; TASC, Trans-Atlantic Inter-Society Consensus.

($P=0.99$). Intra- and inter-observer variabilities were $\kappa=0.99$ and 0.88 for uncovered strut, $\kappa=1.0$ and 1.0 for malapposed strut, $\kappa=0.84$ and $\kappa=0.90$ for PLIA, and $\kappa=0.80$ and $\kappa=0.80$ for intra-stent thrombus.

Follow-up Clinical Data

Clinical symptoms and ankle-brachial index (ABI) values at 6- and 12-month follow up are summarized in **Supplementary Table**. After the procedure, all patients had improved symptoms with normal ABI values.

Discussion

The main findings of this study are as follows: (1) the mean NIT tended to increase between 6 and 12 months after FP-PES implantation for femoropopliteal lesions; (2) uncovered struts and PLIA were more frequently observed at 12 months, despite a significant reduction in the incidence of malapposed struts; and (3) the frequency of ESL did not change from 6 to 12 months, whereas it was significantly enlarged.

FP-PES is a newer-generation DES that consists of a self-expanding nitinol stent with a low dose of paclitaxel and fluoropolymer. This stent enables controlled and sustained release of paclitaxel over the first 12 months after

Table 2. Optical Coherence Tomography Findings

	6 months	12 months	Difference (95% CI)*	Odds ratio (95% CI)*	P value*
Strut level analysis					
Number of stent struts	5,615	5,763			
Neointimal thickness (μm)	198 $\pm$ 189	233 $\pm$ 245	37.5 (−0.07, 75.08)		0.051
Uncovered strut	247 (4.4)	450 (7.8)		1.88 (1.16, 3.04)	0.01
Malapposed strut	33 (0.59)	16 (0.28)		0.48 (0.24, 0.96)	0.039
Presence of PLIA	711 (12.7)	1,209 (21.0)		1.94 (1.55, 2.43)	<0.0001
Cross-sectional level analysis					
Total number of cross sections	203	203			
Stent area (mm^2)	26.1 $\pm$ 4.7	25.3 $\pm$ 3.9	−0.86 (−2.10, 0.38)		0.17
Lumen area (mm^2)	22.8 $\pm$ 4.1	21.5 $\pm$ 3.6	−1.34 (−2.61, −0.08)		0.039
Neointimal area (mm^2)	3.5 $\pm$ 2.3	4.0 $\pm$ 3.0	0.57 (−0.18, 1.32)		0.14
Percent neointimal area	13.0 $\pm$ 7.7	15.5 $\pm$ 10.7	2.56 (−0.32, 5.44)		0.08
dNIT (μm)	414 $\pm$ 227	516 $\pm$ 269	101.97 (61.81, 142.13)		<0.0001
Stent eccentricity index	0.92 $\pm$ 0.05	0.92 $\pm$ 0.05	0.00 (−0.01, 0.00)		0.85
Total ESL area (mm^2)	0.24 $\pm$ 0.32	0.38 $\pm$ 0.36	0.13 (0.04, 0.23)		0.009
Cross-sections with ESL	136 (67.0)	136 (67.0)		1.00 (0.41, 2.42)	1.00
Frequency of homogeneous neointima	136 (67.0)	99 (48.8)		0.44 (0.25, 0.76)	0.003
Frequency of heterogeneous neointima	53 (26.1)	69 (34.0)		1.51 (0.87, 2.63)	0.15
Frequency of layered neointima	14 (6.9)	35 (17.2)		3.17 (1.17, 8.56)	0.024
Intra-stent thrombus	13 (6.7)	13 (6.4)		0.98 (0.07, 13.65)	0.99

Data are presented as the mean $\pm$ standard deviation, or n (%). Difference or odds ratio (95% CI) was estimated by multilevel models. *Estimates of the fixed-effect coefficients of 12-month (vs. 6-month) in the multilevel linear models (difference) or the multilevel logistic models (odds ratio), adjusting for cases (level 3), cross-sections (level 2), and evaluation timing of 6 months/12 months (level 1) as nested, normally distributed, random intercepts. CI, confidence interval; dNIT, difference of maximum and minimum neointimal thickness; ESL, extra-stent lumen; PLIA, peri-strut low intensity area.

Figure 2. Distribution of neointimal thickness between 6 and 12 months.

Figure 3. Serial optical coherence tomography images of stent coverage. (A,B) At 6 months. (C,D) At 12 months. During follow up, some covered struts changed to uncovered ones (yellow and blue arrows in B and D).

Figure 4. Changes in neointimal tissue between 6 and 12 months.

implantation. Histopathological studies demonstrated that FP-PES significantly suppressed neointimal proliferation compared with PCS within the initial 180 days.^{3,4} To date, however, limited data exists on the vascular response to FP-PES beyond 180 days after implantation. The present study demonstrated that the mean NIT tended to increase from 6 to 12 months after FP-PES implantation for femoropopliteal lesions, whereas the neointimal area did not. These findings suggested that FP-PES could sustain the inhibition of proliferative response up to 12 months. Of note, uncovered struts were more frequently observed at 12 months than 6 months, despite a significant reduction in the incidence of malapposed struts. A possible explanation

for this observation is that the microthrombi on both struts and under struts might be dissolved during follow up, resulting in an increased frequency of uncovered struts. Also, the dNIT was significantly increased over time in the present study, which was in line with a previous study.⁹ Compared with PCS, FP-PES exhibits numerous differences in terms of stent platform, paclitaxel dose, and polymer use (fluoropolymer vs. polymer-free). However, both DESs elute the same drug to suppress neointimal proliferation, potentially contributing to the heterogeneous process of vascular healing.

The ESL is recognized as a dilatation of the external elastic membrane area over time, which is histopathologically

Figure 5. Serial optical coherence tomography images of the extra-stent lumen (ESL). (A,B) At 6 months. (C,D) At 12 months. The ESL area was enlarged from 6 to 12 months (yellow and blue arrows in B and D).

attributed to localized inflammation or excessive fibrin deposition.¹³ Recently, we reported a serial OCT study demonstrating that the ESL was enlarged from 6 to 12 months after PCS implantation.⁹ FP-PES adopts a biocompatible fluoropolymer coating, which has shown less platelet aggregation and inflammatory cell attachment, as well as earlier endothelialization in animal studies.¹⁴ In coronary arteries, previous OCT studies demonstrated better vascular response after implantation of a fluoropolymer-coated DES.^{15,16} However, little evidence exists on the vascular response after FP-PES implantation for femoropopliteal artery lesions. The present study demonstrated that the ESL was significantly enlarged during follow up, suggesting that the abnormal vascular response continues to occur for as long as 12 months, irrespective of fluoropolymer use. Indeed, Bisdas et al reported that formation of an aneurysm was observed in 8% of patients at 1 year after FP-PES implantation for femoropopliteal artery lesions.¹⁷ Our OCT findings might support this phenomenon. Furthermore, dissolved microthrombi surrounding the struts might contribute to the enlargement of ESL. Although the underlying mechanism of the ESL remains partially understood, the effects of paclitaxel itself may be mainly attributed to the enlargement of the ESL.

The PLIA indicates the presence of fibrinoid and proteoglycans in porcine models, which is associated with neointimal proliferation and peri-strut inflammation.^{18,19} The present study demonstrated that the incidence of PLIA significantly increased from 6 to 12 months. Similarly, the layered neointima increased during follow up. Recently, Kim et al reported that peri-strut inflammation was more frequently observed in the layered neointima than homogeneous and heterogeneous neointima.²⁰ These findings suggest that peri-strut inflammation accelerates from 6 to 12 months after FP-PES implantation. However, it is noteworthy that the incidence of PLIA was numerically lower in the

FP-PES vs. the PCS group.⁹ A histological study reported that FP-PES showed a lower level of peri-strut inflammation at 90 days than PCS.⁸ Taken together, FP-PES might enable the reduction of peri-strut inflammation compared with PCS, although it could not be completely inhibited.

The current OCT study suggested heterogeneity of neointimal proliferation with peri-strut inflammation from 6 to 12 months after FP-PES implantation. This indicated an unfavorable vascular response to FP-PES. Recently, the 2-year outcomes of the IMPERIAL trial showed that the primary patency was higher in the FP-PES than the PCS group; however, the difference did not reach statistical significance (83.1% vs. 77.1%, $P=0.10$). Notably, the clinical benefits of FP-PES over PCS were reduced between 1 and 2 years.⁴ The underlying mechanism of this phenomenon remains poorly understood, whereas our OCT results suggested that peri-strut inflammation persists or accelerates beyond 12 months after FP-PES implantation, resulting in a late catch-up phenomenon of FP-PES. To obtain better outcomes in femoropopliteal artery lesions, we might have to reconsider the optimal DES components in terms of the type (e.g., everolimus, sirolimus, or paclitaxel), dose, and duration of eluting drug, polymer use, and stent platform. Nevertheless, the present study results are hypothesis-generating. Further long-term follow-up studies are warranted to validate the safety and efficacy of FP-PES.

Study Limitations

There are several limitations in the present study. First, the study population was very small and selected from patients enrolled in the IMPERIAL trial. Given that the potential of bias is inevitable in the present study, our results should be interpreted with caution. To our knowledge, however, this is the first study to assess the vascular response beyond 6 months after FP-PES implantation, as assessed by serial OCT examination. Further large-scale studies are required

to confirm our results. Second, the present study did not have a control group. Third, because the axial penetration of the current OCT system is relatively limited, we excluded 22% of the cross-sectional images from the present analysis. Fourth, it might be impossible to compare OCT findings in the same segment at 6 and 12 months, although the current OCT system is highly accurate in terms of length measurement. These shortcomings might have affected the conclusions of this investigation. Finally, OCT evaluations immediately after stent implantation were not available in the present study. Therefore, we could not distinguish between persistent and late-acquired ESL in the current study.

Conclusions

Neointimal proliferation was markedly inhibited from 6 to 12 months after FP-PES implantation for femoropopliteal artery lesions, whereas the incidence of uncovered struts and PLIA significantly increased over time with the enlargement of the ESL.

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Disclosures

The authors have no conflicts of interest to declare.

IRB Information

The study protocol was approved by the institutional review boards of the Kokura Memorial Hospital (Reference number: 19112901).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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