Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Cardiovascular Intervention

Edge Vascular Response After Polymer-Free vs. Polymer-Based Paclitaxel-Eluting Stent Implantation

– Serial Intravascular Ultrasound Study From the Late Incomplete Stent Apposition Evaluation (LISA) Trial –

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Background: It is unknown if lack of polymer can provoke a different edge response in drug-eluting stents. The aim of this study was to compare edge vascular response between polymer-free paclitaxel-eluting stent (PF-PES) and polymer-based paclitaxel-eluting stents (PB-PES).

Methods and Results: A total of 165 eligible patients undergoing percutaneous coronary intervention were prospectively randomized 1:1 to receive either PF-PES or PB-PES. Those patients with paired intravascular ultrasound (IVUS) after procedure and at 9-month follow-up were included in this analysis. Seventy-six patients with 84 lesions, divided into PB-PES (38 patients, 41 lesions) and PF-PES groups (38 patients, 43 lesions) had paired post-procedure and 9-month follow-up IVUS and were therefore included in this substudy. There was a significant lumen decrease at the proximal edge of PF-PES (from 9.02±3.06 mm^2 to 8.47±3.05 mm^2; P=0.040), and a significant plaque increase at the distal edges of PF-PES (from 4.39±2.73 mm^2 to 4.78±2.63 mm^2; P=0.004). At the distal edge there was a significant plaque increase in the PF-PES compared to PB-PES (+8.0% vs. –0.6%, respectively; P=0.015) with subsequent lumen reduction (–5.2% vs. +6.0%, respectively; P=0.024).

Conclusions: PF-PES had significant plaque increase and lumen reduction at the distal edge as compared to PB-PES, probably due to difference in polymer-based drug-release kinetics between the 2 platforms. (*Circ J* 2014; **78:** 2657–2664)

Key Words: Drug-eluting stent; Edge vascular response; Intravascular ultrasound; Polymer-based paclitaxel-eluting stent; Polymer-free paclitaxel-eluting stent

Compared with bare metal stents (BMS), polymer-based drug-eluting stents (DES) reduce in-stent restenosis and target vessel revascularization.[1–4] The permanent polymer coating, however, has been variously associated with impaired vascular healing and incomplete stent malapposition, which may eventually provoke stent thrombosis.[5,6] Therefore, many attempts have been done to reduce this phenomenon by introducing polymer-free or biodegradable-polymer DES.[7–11]

Edge vascular response (EVR) is another cautionary problem after DES implantation, because it is considered 1 of the causes of edge restenosis because of a potential toxic effect of drug on arterial tissue.[12] Restenosis of polymer-based paclitaxel=eluting stent (PB-PES) has been shown, for example, to be more frequent at the proximal than the distal edge, exhibiting positive vascular remodeling at the distal edge, probably due to higher downstream concentration of the drug at this level.[13–18] The AXXION™ stent is a polymer-free paclitaxel-eluting stent (PF-PES), the drug dose of which is approximately 3-fold higher than in PB-PES, and which allows faster release of paclitaxel as compared to PB-PES. The combination of paclitaxel with a polymer-free platform on EVR has not been investigated.

The purpose of this study was to evaluate EVR between

Received March 26, 2014; revised manuscript received July 15, 2014; accepted August 6, 2014; released online September 22, 2014 Time for primary review: 75 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0345

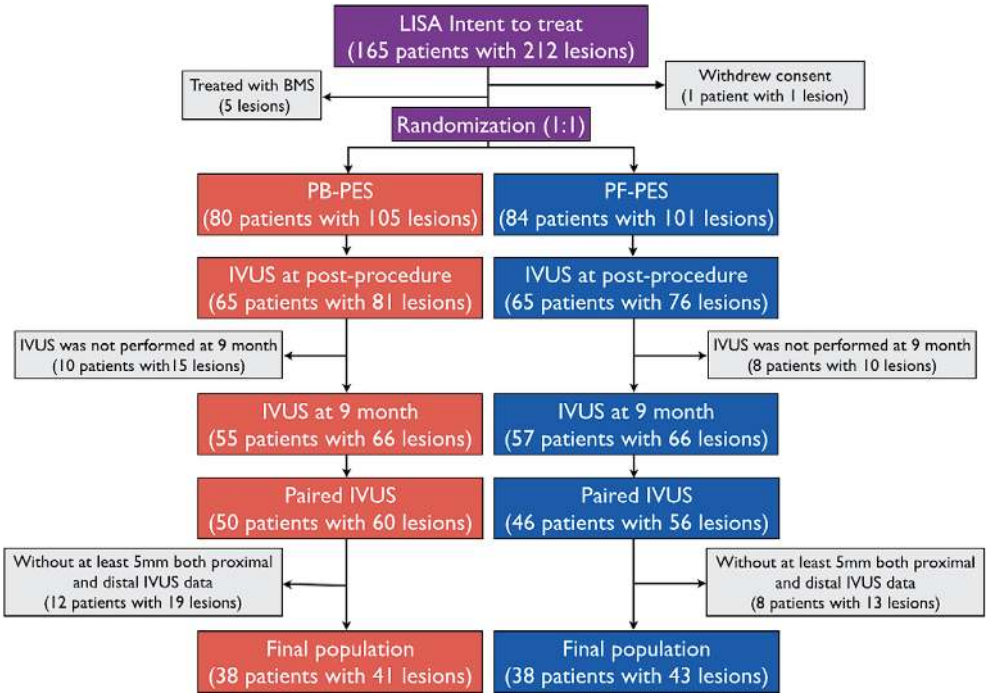

Figure 1. Study flow diagram. From October 2007 to April 2009, a total of 165 patients with 212 lesions were enrolled into the LISA trial. Only 76 patients with 83 lesions (39%) had paired post-stent and 9-month follow-up IVUS and were therefore enrolled into this substudy. Finally, 83 lesions were divided into PB-PES and PF-PES groups (41 lesions; 43 lesions). IVUS, intravascular ultrasound; PB-PES, polymer-based paclitaxel-eluting stent; PF-PES, polymer-free paclitaxel-eluting stent.

PF-PES and PB-PES at 9-month follow-up.

Methods

Study Design and Subjects

This was a substudy of the Late Incomplete Stent Apposition Evaluation trial (LISA; www.clinicaltrial.gov, NCT01375855).[19] Briefly, this trial was a prospective, randomized, single-blinded, multicenter trial comparing PF-PES with the PB-PES. All the patients who met all the inclusion/exclusion criteria were randomized 1:1 to receive either the PF-PES (AXXION™; Biosensors International, Kampong, Singapore) or the PB-PES (TAXUS Express™; Boston Scientific, Natick, MA, USA) for the treatment of coronary lesions. Eligible patients with a diagnosis of stable or unstable angina or non ST-elevation myocardial infarction or silent ischemia were included. Patients were eligible if they had atherosclerotic coronary artery disease including native and de novo lesions with a diameter stenosis ≥50% reference vessel diameters ranging from 2.25 to 4.0 mm on quantitative coronary angiogram with objective evidence of ischemia. Patients with acute coronary syndrome within 72 h before admission or creatine kinase 2-fold over the upper normal limit, previous brachytherapy or DES implantation in the target lesion, restenotic lesion, allergy to aspirin or thienopyridine, by-pass graft lesions, true bifurcation lesion (stenosis in the proximal and/or distal segment of the main vessel and in the side-branch vessels), severe renal insufficiency (creatinine clearance <30 ml/min), severe liver failure (aspartate aminotransferase and alanine aminotransferase >3-fold the upper normal limit), or life expectancy <1 year because of other pathologies were excluded from the study. Primary endpoint was angiographic late loss at 9-month follow-up.[19] Intravascular ultrasound (IVUS) was done after the procedure and at 9-month follow-up. All patients provided written informed consent for their inclusion. The institutional Ethics Committee of each center approved the study protocol.

All the patients with paired IVUS after stent implantation and at 9-month follow-up were included in this substudy.

Devices

The whole surface of PF-PES (AXXION™) stent is coated with synthetic glycocalix, which is a permanent biocompatible carbohydrate of glycoproteins and glycolipid. Paclitaxel is spray-coated onto the synthetic glycocalix substrate on the abluminal surface of the stent only. The thickness of the coating is approximately 2 nm and the drug dosage is approximately 2.7 μg/mm^2. Approximately 40–50% of drug is released within the first week and the remainder is released in the next 3 weeks.

PB-PES (TAXUS Express™)'s thickness of coating is approximately 16 μm. The coating is composed of 1 μg/mm^2 of the antiproliferative drug paclitaxel and a poly(styrene-b-isobutylene-b-styrene), which provides controlled biphasic release. The first release of paclitaxel (approximately 38% of the 10-day dose) occurs during the first 48 h after implantation, and in the second phase paclitaxel is slowly released over the next 10 days.

IVUS

IVUS was done after stent implantation and at 9-month follow-up, and was carried out after 200 μg intracoronary nitroglycerin

Table 1. Baseline Patient Characteristics

Patients (n=76)	PB-PES (n=38)	PF-PES (n=38)	P-value
Age (years)	66.4±10.5	67.1±8.5	0.740
Male	24 (63.2)	24 (63.2)	1.000
Hypertension	29 (76.3)	28 (73.7)	1.000
Hypercholesterolemia	24 (63.2)	23 (60.5)	1.000
Diabetes mellitus	10 (26.3)	12 (31.6)	0.801
Insulin-dependent	2 (5.3)	3 (7.9)	0.897
Smoking history	7 (18.4)	4 (10.5)	0.516
Prior MI	14 (36.8)	11 (28.9)	0.626
Prior PCI	13 (34.2)	13 (34.2)	1.000
Prior CABG	1 (2.6)	3 (8.1)	0.358
Clinical indication			
Stable or silent angina	19 (50.0)	28 (73.7)	0.580
Unstable angina/NSTEMI	19 (50.0)	10 (26.3)	
Vessel disease			
1-vessel	34 (89.5)	32 (84.2)	0.346
2-vessel	3 (7.9)	6 (15.8)	
3-vessel	1 (2.6)	0	
Lesions (n=84)	**PB-PES (n=41)**	**PF-PES (n=43)**	**P-value**
Treated vessel			
Left anterior descending	31 (75.6)	28 (65.1)	0.363
Left circumflex	4 (9.8)	9 (20.9)	
Right coronary artery	6 (14.6)	6 (14.0)	
Left main	0	0	
Lesion type			
A	1 (2.4)	5 (11.6)	0.208
B1	9 (22.0)	9 (20.9)	
B2	26 (63.4)	20 (46.5)	
C	5 (12.2)	9 (20.9)	
Stent number	1.12±0.39	1.16±0.47	0.409
Stent length (mm)	19.70±9.18	20.74±9.2	0.651
Stent diameter (mm)	3.06±0.42	3.02±0.41	0.727
Post-dilatation	14 (34.1)	20 (46.5)	0.274

Data given as mean±SD or n (%). CABG, coronary artery bypass graft; MI, myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; PB-PES, polymer-based paclitaxel-eluting stent; PCI, percutaneous coronary intervention; PF-PES, polymer-free paclitaxel-eluting stent.

injection using a rotating 40-MHz transducer within a 2.5-F imaging sheath (Galaxy2; Boston Scientific). The ultrasound catheter was advanced at least 5 mm beyond the stent into the distal vessel up to an anatomical landmark, and the transducer was withdrawn at an automatic pullback speed of 0.5 mm/s up to an anatomical landmark at least 5 mm proximal to the stent. All IVUS data were recorded on compact disc and analyzed offline by an expert analyst, who was blinded to stent type, in the independent core laboratory of the Hospital Clinic, Barcelona. Cross-sections at 1-mm intervals 5 mm proximal and distal to the stent edges were analyzed. External elastic membrane (EEM) and lumen contours were detected using dedicated software (QCU version 2.0; Medis Medical Imaging Systems, Leiden, The Netherlands): EEM area and lumen area (LA) were automatically drawn with minor modification made whenever necessary. Plaque area was obtained as EEM area minus LA. Differences in IVUS parameters between baseline and follow-up were calculated in terms of absolute difference (follow-up minus post-stent implantation baseline) and relative difference (follow-up minus post-stent implantation baseline/follow-up×100). To evaluate intraobserver variability, the observer repeated the analysis 3 months later.

Clinical Outcome

Clinical data were obtained at 9-month follow-up. All-cause death included non-cardiac and cardiac death. Cardiac death was defined as any death due to immediate cardiac cause (myocardial infarction, low-output failure and fatal arrhythmia), death related to the procedure or death of unknown cause. Target lesion revascularization (TLR) was defined as either percutaneous coronary intervention or coronary artery bypass grafting owing to restenosis or other complication of the target lesion. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel was defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself. Stent thrombosis was assessed according to Academic Research Consortium criteria.[20] An event committee blinded to treatment allocation adjudicated all adverse events.

Table 2. Stent Segment IVUS Data

Lesions (n=84)	PB-PES (n=41)	PF-PES (n=43)	P-value
Baseline (after procedure)			
Mean VA (mm^2)	14.99±4.49	14.47±3.90	0.651
Mean SA (mm^2)	7.44±2.33	7.38±2.13	0.900
Mean LA (mm^2)	7.46±2.39	7.40±2.15	0.936
Minimum LA (mm^2)	6.15±2.06	6.15±1.93	0.918
Mean PSA (mm^2)	7.55±2.74	7.09±2.39	0.543
% PSA (%)	50.01±6.33	48.55±8.05	0.303
ISA	4 (9.7)	5 (11.6)	1.000
9-month follow-up			
Mean VA (mm^2)	15.92±4.80	14.77±4.01	0.281
Mean SA (mm^2)	7.69±2.45	7.56±2.12	0.844
Mean LA (mm^2)	7.12±2.45	6.29±2.34	0.130
Minimum LA (mm^2)	5.42±2.33	4.45±2.12	0.026
Mean PSA (mm^2)	8.23±2.79	7.21±2.39	0.092
% PSA (%)	51.49±6.02	48.43±7.09	0.033
Mean NIHA (mm^2)	0.56±0.64	1.26±0.99	0.001
% NIHA (%)	7.28±8.02	18.06±14.44	<0.001
ISA	5 (12.1)	4 (9.3)	0.735
Persistent ISA	3 (7.3)	3 (7.3)	1.000
LISA	2 (4.8)	1 (2.4)	0.611
Resolved ISA	1 (2.4)	2 (4.8)	1.000

Data given as mean±SD or n (%).
ISA, incomplete stent apposition; IVUS, intravascular ultrasound; LA, lumen area; LISA, late complete stent apposition; NIHA, neointimal hyperplasia area; PSA, peri-stent area; SA, stent area; VA, vessel area. Other abbreviations as in Table 1.

Table 3. Stent Edge IVUS Data (Paired-Lesion Analysis)

	PB-PES (n=41)	PF-PES (n=43)	P-value
Proximal segment			
VA (mm^2)			
After procedure	16.77±5.20	15.97±4.27	0.450
9-month follow-up	16.46±6.32	15.90±4.23	0.781
P-value†	0.604	0.909	
Plaque area (mm^2)			
After procedure	7.58±2.85	6.95±2.47	0.301
9-month follow-up	7.48±3.17	7.43±2.62	0.744
P-value†	0.418	0.134	
Lumen area (mm^2)			
After procedure	9.18±3.68	9.02±3.06	0.865
9-month follow-up	9.22±4.14	8.47±3.05	0.700
P-value†	0.846	0.040	
Distal segment			
VA (mm^2)			
After procedure	11.59±4.91	11.03±4.74	0.546
9-month follow-up	11.76±4.85	11.07±4.73	0.485
P-value†	0.389	0.625	
Plaque area (mm^2)			
After procedure	4.97±3.06	4.39±2.73	0.385
9-month follow-up	4.98±3.01	4.78±2.63	0.872
P-value†	0.928	0.004	
Lumen area (mm^2)			
After procedure	6.61±2.86	6.64±2.89	0.869
9-month follow-up	6.78±2.54	6.28±2.87	0.222
P-value†	0.241	0.096	

Data given as mean±SD. †P=baseline vs. follow-up. Abbreviations as in Tables 1,2.

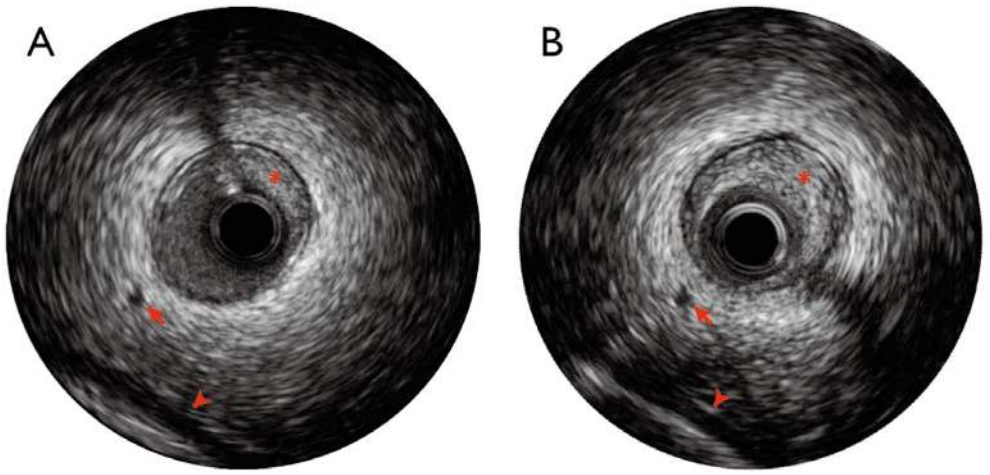

Figure 2. IVUS findings: distal edge of polymer-free paclitaxel-eluting stent (PF-PES). (**A**) Baseline, after the procedure; (**B**) 9-month follow-up IVUS assessment of corresponding cross-sectional images with a small branch (arrow) and epicardium (arrowhead) selected as anatomical landmarks. (**A**) Plaque (asterisk) in the distal edge of the PF-PES implanted in the mid-segment of the left anterior descending coronary artery. (**B**) Significant plaque increase (asterisk) and significant lumen reduction.

Statistical Analysis

Categorical variables are presented as numbers and percentages and were compared between groups with the chi-squared or the Fisher exact tests, when appropriate. Continuous data are shown as mean±SD or median (interquartile range) as appropriate and compared using Mann-Whitney test or Wilcoxon signed rank test. Intraobserver reproducibility of IVUS measurements was calculated with intraclass correlation coefficient for repeated measurements. Two-sided P<0.05 was considered statistically significant. All statistical analysis was done using SPSS (version 20.0, SPSS, Chicago, IL, USA).

Results

Baseline Characteristics and Procedures

From October 2007 to April 2009, a total of 165 patients with 212 lesions were enrolled in the LISA trial.[19] The LISA trial was prematurely stopped due to the higher rate of TLR in the PF-PES as compared to PB-PES. Only 76 patients with 84 lesions (46%) had paired IVUS, due to premature discontinuation of the trial and were therefore enrolled into this substudy. Of them, 38 patients (41 lesions) received PB-PES, whereas the remaining 38 patients (43 lesions) received PF-PES (**Figure 1**). Baseline patient and lesion characteristics were similar between the 2 groups (**Table 1**). There were no differences between patients included in this analysis and those excluded.

IVUS

The intraobserver reproducibility for IVUS measurements was 0.957. No differences between groups were found in terms of the various IVUS parameters either after stent implantation or at 9-month follow-up. **Table 2** lists IVUS findings with regards to stent segment. Of note, neointimal hyperplasia area was higher in PF-PES than PB-PES (P=0.001).

At the proximal edge of PB-PES, there were no significant changes in vessel area (VA) (P=0.604), plaque area (P=0.418) or LA (P=0.846) between baseline and follow-up. At the proximal edge of PF-PES, from baseline to follow-up there were no significant changes in VA (P=0.909) or in plaque area (P=0.134), while there was a significant decrease in LA from baseline to follow-up (from 9.02±3.06 mm^2 to 8.47±3.05 mm^2; P=0.040; **Table 3**).

At the distal edge of PB-PES, there were no significant changes in VA (P=0.389), in plaque area (P=0.926) or in LA (P=0.241) from baseline to follow-up. At the distal edge of PF-PES, there were no significant changes in VA (P=0.625), with a significant increase in plaque area from baseline to follow-up (from 4.39±2.73 mm^2 to 4.78±2.63 mm^2; P=0.004) and a trend towards a reduction in LA (P=0.096; **Table 3**).

Comparing the 2 groups, at distal edge there was a significant increase in plaque area with PF-PES as compared to PB-PES (median, +8.0%; IQR: –143.8 to +41.5, vs. median, –0.6%; IQR: –51.7 to +32.6; P=0.015) with subsequent reduction in LA (median, –5.2%, IQR: –70.0 to +25.7, vs. median, +6.0%; IQR: –43.5 to +39.2; P=0.024; **Figures 2,3**).

Clinical Outcome at 9-Month Follow-up

At 9 months, a composite endpoint of all-cause death, any myocardial infarction and TVR was 39.0% for PF-PES and 15.7% for PB-PES (P=0.038), mainly driven by the higher rate of TVR in the PF-PES group compared to PB-PES (39.4% vs. 13.1%; P=0.017; **Table 4**). There were no significant differences between groups in terms of TVR at the proximal (5.2% vs. 10.5%; P=0.600) or distal edge (0% vs. 7.8%; P=0.240). TLR was also higher in the PF-PES than PB-PES group (36.8% vs. 13.1%; P=0.017). One definite stent thrombosis was observed at 205 days in the PF-PES group.

Discussion

PB-PES and PF-PES had different EVR at 9-month follow-up; in particular (1) at the proximal edge there was a significant lumen decrease in PF-PES; (2) at the distal edge a significant plaque increase was observed in PF-PES; and (3) a notable reduction in LA was also observed at the distal edge of PF-PES compared to PB-PES.

The pattern of vascular response after device implantation

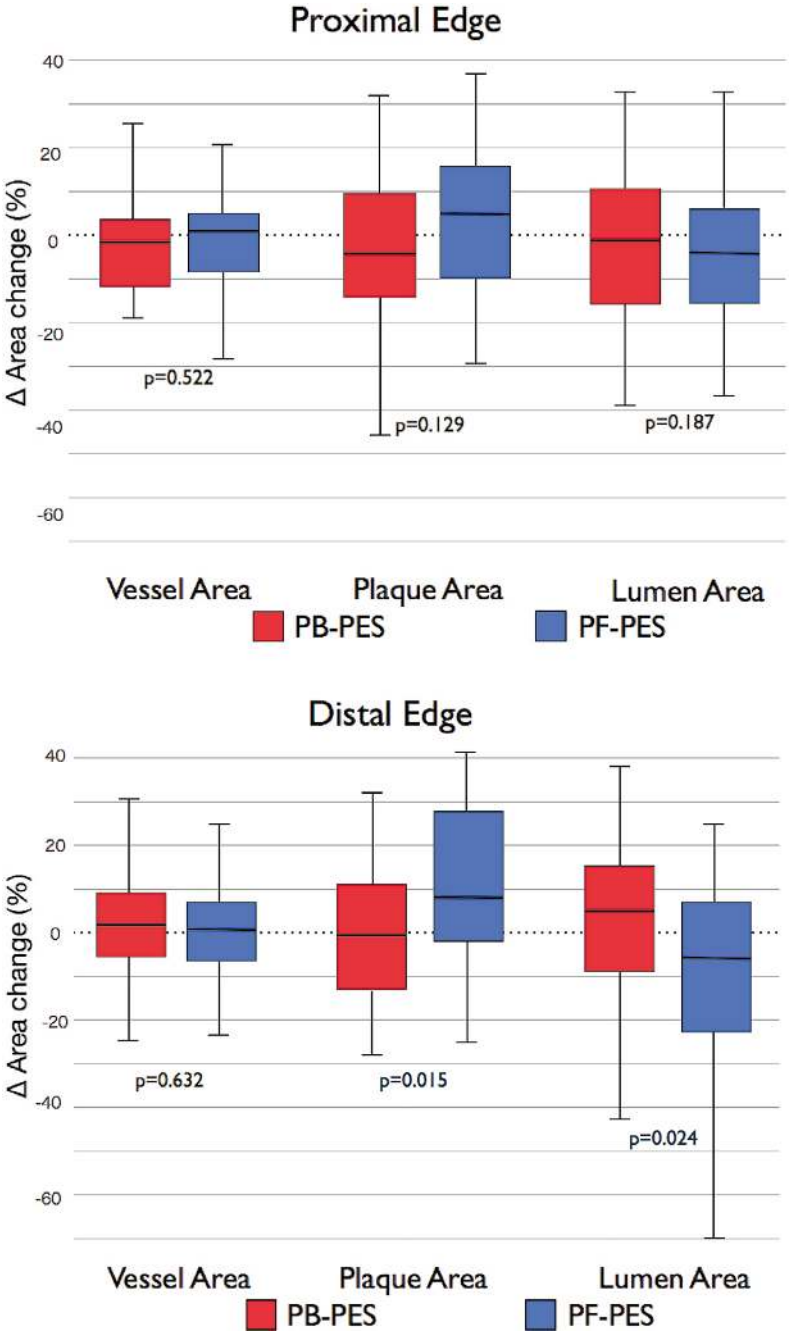

Figure 3. Area changes. There was a significant increase in plaque area with polymer-free paclitaxel-eluting stent (PF-PES) compared to polymer-based paclitaxel-eluting stent (PB-PES; P=0.015) with subsequent reduction in lumen area (P=0.024).

manifests either as in-stent vascular response or as EVR. Each of those responses has important prognostic implications.[21] Abnormal EVR may indeed provoke edge restenosis that requires repeat revascularization or even vessel occlusion. With the introduction of DES, a different EVR was identified between the proximal and distal stent edges: the higher downstream concentration of the drug at the distal edge compared to the proximal edge probably contributed to a lower restenosis rate at the distal than at the proximal edge.[1] This study investigated the contribution of polymer to EVR.

With regards to PB-PES, we did not find any significant change in various IVUS parameters either at the proximal or distal edges during 9-month follow-up. Previous studies reported contrasting results: whereas in the first-in-man TAXUS I trial no edge effect was seen with the slow-release polymer formulation of the PES,[22] in other later studies some plaque increase without positive remodeling or even with constrictive remodeling was seen at distal edge.[14–16,23] It is of note that the use of platforms with different drug-release kinetics may have influenced these contrasting vascular responses in all these studies.

With regard to PF-PES, in the present study lack of polymer together with a higher paclitaxel dose, as compared to PB-PES, produced an ominous EVR, with plaque increase at the distal edge and lumen reduction at both edges. In the ASPECT trial, which compared a PF paclitaxel platform vs. BMS at 6 months,

Table 4. Clinical Results at 9-Month Follow-up

Patients (n=76)	PB-PES (n=38)	PF-PES (n=38)	P-value
Death/Non-fatal MI/TVR†	2 (5.2)	13 (34)	0.002
Death (all-cause)	0	0	–
Cardiac	0	0	–
Non-cardiac	0	0	–
Any MI	0	1 (2.6)	1.000
TVR	2 (5.2)	13 (39.4)	0.002
TLR	2 (5.2)	12 (36.8)	0.002
TVR at proximal edge	2 (5.2)	4 (10.5)	0.600
TVR at distal edge	0	3 (7.8)	0.240
TVR for edge disease	2 (5.2)	7 (18.4)	0.152
PCI on the non-target vessel	0	0	–
Stent thrombosis†	0	1 (2.6)	1.000
Definite	0	1 (2.6)	1.000
Probable	0	0	–
ISR pattern (Mehran classification)			1.000
A	0	0	
B	1 (2.6)	2 (5.2)	
C	0	3 (7.8)	
D	0	0	
II	1 (2.6)	3 (7.8)	
III	0	3 (7.8)	
IV	0	1 (2.6)	

Data given as n (%). †Combined (hierarchical) of death, non-fatal MI or TVR.
TLR, target lesion revascularization; TVR, target vessel revascularization. Other abbreviations as in Tables 1,2.

there was no evidence of lumen decrease or plaque increase in the PF-PES group either at the proximal or at the distal edge.[24,25] Of note is the higher risk profile of patients/lesions enrolled in the present study as compared with the ASPECT trial, which may partially explain these differing results. The present patients had, for example, a higher rate of diabetes (31.6% vs. 7.0%) and also higher lesion complexity (ratio of B2/C lesions: 67.4% vs. 4.0%) than the subjects in that previous study.[24,25]

An increase in plaque area at the distal edge with subsequent reduction in LA was also clinically reflected by a higher rate of TVR at the distal edge in the PF-PES group compared to PB-PES (0% vs. 7.8%; P=0.240), which was not statistically significant due to small sample size. In any case the overall rate of TVR was higher in PF-PES than in PB-PES, indicating that lack of polymer may negatively influence neointimal response also inside the stent.

Although PF-PES is no longer available on the market, new DES based on PF technology are still under development; unfortunately whether the PF technology concerns, raised in the present study, can be globalized is unknown. Nevertheless, they should be taken into account for PF-DES design. With regard to this, a PF amphilius-eluting stent, which uses abluminal reservoirs for drug elution (Cre8™ stent; CID, Saluggia, Italy), has been found to have a lower late loss than PB-PES with similar clinical outcome at 1 year.[26] No data on EVR have so far been reported for this stent.

Study Limitations

This study had several limitations. First, this is a substudy, which itself has inherent limitations. But it is the only analysis existing on comparison of the effects of PF vs. PB stents on edges. Finally, the PF-PES used in the present study is no longer available on the market. Therefore, the present results will not be translated directly into clinical practice, but they may provide important insights into PF-DES technology for the manufacturing of new stents.

Conclusions

PF-PES had a different EVR compared to PB-PES. Compared with PB-PES, there was significant plaque increase with lumen reduction at the distal edge in PF-PES, probably due to differences in polymer-based drug-release kinetics between the 2 platforms.

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