Coronary Arterial Remodeling and Out-Stent Plaque Change After Drug-Eluting Stent Implantation – Comparison Between Zotarolimus-Eluting Stents and Paclitaxel-Eluting Stents –

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Background: Out-stent plaque characteristics and eosinophilic inflammatory response, which correlates with positive remodeling after first-generation drug-eluting stent implantation, may be associated with late restenosis and very late stent thrombosis. The differences of out-stent plaque characteristics were compared between paclitaxel-eluting stents (PES) and zotarolimus-eluting stents (ZES), using integrated backscatter-intravascular ultrasound (IB-IVUS).

Methods and Results: Of 78 patients enrolled, 25 receiving PES and 25 receiving ZES had adequate IVUS assessment. Volumetric IVUS analysis was performed after stenting and at 8-month follow-up. Out-stent plaque change in the stented segment was compared on IB-IVUS. The relationship between systemic inflammatory response and out-stent plaque change was evaluated. In PES, vessel volume significantly increased ($365\text{--}389\text{ mm}^3$, $P<0.0001$), whereas it did not change in ZES ($315\text{--}314\text{ mm}^3$, $P=0.81$). In culprit lesions at baseline in PES, fibrous plaque tended to increase ($3.1\text{--}3.6\text{ mm}^2$, $P=0.051$) and lipid plaque significantly increased ($4.3\text{--}5.1\text{ mm}^2$, $P=0.02$), whereas in ZES the fibrous plaque significantly increased ($2.9\text{--}4.0\text{ mm}^2$, $P<0.0001$) but lipid plaque significantly decreased ($5.1\text{--}3.6\text{ mm}^2$, $P<0.0001$). Systemic eosinophil increase was significantly correlated with positive remodeling and out-stent lipid plaque increase.

Conclusions: Chronic out-stent plaque change in ZES consisted of less positive remodeling and more favorable effects on out-stent plaque characteristics than PES. Systemic eosinophil change might be a marker of out-stent lipid plaque change. (*Circ J* 2013; **77**: 363–371)

Key Words: Drug-eluting stent; Intravascular ultrasound; Out-stent plaque; Paclitaxel-eluting stent; Zotarolimus-eluting stent

First-generation polymer-based sirolimus (Cypher) and paclitaxel (Taxus) drug-eluting stents (DES) have remarkably reduced angiographic restenosis and target lesion revascularization (TLR) by reducing neointimal hyperplasia compared with bare-metal stents (BMS).^{1,2} Concern about vasculo-toxic effects, however, remains to be resolved. Previous case reports and observational studies showed that late and very late stent thrombosis occurred after DES implantation.^{3,4}

As the main mechanisms of late and very late stent thrombosis, delayed arterial healing (persistent fibrin deposition and

delayed re-endothelialization) due to drugs in DES,^{5–9} and chronic inflammation and hypersensitivity reaction due to drugs and/or durable polymers in DES have been reported in animal and human pathology studies.^{7–12} These studies noted enhanced inflammatory responses consisting predominantly of T lymphocytes and eosinophils around the stent struts and stent malapposition with vessel enlargement after DES implantation.^{7,10–12} In clinical practice, previous intravascular ultrasound (IVUS) in vivo showed that positive coronary arterial remodeling after first-generation DES was associated with late restenosis and very late stent thrombosis. Those studies reported that positive

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vessel remodeling was the main cause of late-acquired incomplete stent apposition (ISA). It was also reported that late-acquired ISA seemed to be associated with late and very late stent thrombosis.^{13–18} Moreover, previous histopathological and IVUS studies showed that eosinophilic infiltrates were associated with evidence of vessel remodeling with late-acquired ISA.^{10,17}

Endeavor™ zotarolimus-eluting stents (ZES; Medtronic Vascular, Santa Rosa, CA, USA), which belong to second-generation DES, have biocompatible characteristics, with cobalt alloy thin-strut stent, phosphorylcholine polymer, and different drug-elution, compared with first-generation DES.¹⁹ Several past randomized trials confirmed the relative safety and efficacy of ZES compared with first-generation DES.^{19–21} IVUS in the Endeavor trials showed that ZES implantation provided relatively complete and uniform neointimal coverage over stent surface, resulting in the low incidence of late-acquired ISA.^{22–24} IVUS analysis from Endeavor IV trial showed that paclitaxel-eluting stents (PES) had significantly increased vessel and out-stent plaque volume (plaque behind the stent struts) in the stented segment during the follow-up period, whereas ZES had no significant changes in vessel or out-stent plaque volume.²⁵ Little is known, however, about the tissue characteristics of chronic out-stent plaque after ZES implantation in vivo. We hypothesized that chronic out-stent plaque change in ZES would have a smaller systemic inflammatory response, accompanied by less positive vessel remodeling and more favorable effects on out-stent plaque characteristics than PES. Recently, integrated backscatter-IVUS (IB-IVUS) has enabled the in vivo tissue characterization of coronary plaque, such as calcification, dense fibrosis, fibrosis, and lipid, using radiofrequency ultrasound backscatter signals.^{26–31} Therefore, we evaluated serial out-stent plaque characteristics after ZES implantation compared with PES implantation, using gray-scale IVUS and IB-IVUS. We also evaluated the correlation between serial systemic inflammatory response and out-stent plaque characteristics.

Methods

Subjects

From May 2009 to March 2010, after excluding patients with acute coronary syndrome, large vessel disease or low compliance with antiplatelet therapy (who were basically BMS candidates), we enrolled 78 consecutive patients with de novo lesions who underwent DES implantation. They were randomly assigned to be treated with PES (n=39) or ZES (n=39). Randomization was performed after diagnostic angiography and before percutaneous coronary intervention (PCI). Sequentially numbered, sealed randomization envelopes were used in accordance with a computer-generated random allocation sequence. Patients were randomized on a 1:1 basis to treatment with PES or ZES. Serial coronary angiography (CAG), gray-scale IVUS and IB-IVUS were performed at baseline and at 8-month follow-up. Blood samples including representative systemic inflammation scores (white blood cell fraction and high-sensitivity C-reactive protein) were similarly collected. Patients with left main trunk disease, in-stent restenosis, and severe calcification lesions at follow-up catheterization were excluded from IVUS analysis. The patients with inadequate IVUS and IB-IVUS imaging due to lack of follow-up CAG and/or the IVUS catheter not crossing the culprit lesion or mechanical trouble were also excluded. The study was approved by the institutional review board. Consecutive and eligible patients signed written informed consent before the in-

terventional procedure.

Quantitative CAG

CAG at baseline, immediately after PCI, and at follow-up was performed in at least 2 orthogonal views to avoid vessel overlapping after i.c. isosorbide dinitrate 1–2 mg. Quantitative CAG (QCA) was performed using an offline QCA system (CAAS QCA for Research2.0, Pie Medical Imaging BV, The Netherlands). The minimal luminal diameter of treated coronary segments, and the reference diameter on the baseline angiogram were determined in the view that demonstrated the lesion to be the most severe and not foreshortened. Then, minimal lumen diameter was measured on final angiogram. Minimal luminal diameter and late lumen loss were measured on follow-up angiogram.

Acquisition of Gray-Scale IVUS and IB-IVUS Data

All gray-scale IVUS and IB-IVUS was performed after i.c. isosorbide dinitrate 1–2 mg. Gray-scale IVUS and ultrasound signals were acquired with a commercially available IVUS imaging system (VISIWAVE, Terumo, Tokyo, Japan) using a 43-MHz mechanically rotating IVUS catheter (View IT, Terumo) with a motorized transducer pullback speed of 0.5 mm/s. During IVUS acquisition, radiofrequency signal, signal trigger, and video image output were automatically exported to a computer equipped with the custom software (IB-IVUS, YD, Nara, Japan) connected to the IVUS system. IB values for each tissue component were calculated as the average power using a fast Fourier transform, measured in decibels (dB), of the frequency component of the backscattered signals from a small volume of tissue. IB-IVUS was also acquired at the interval of 1 image/s using an auto-pullback device (0.5 mm/s). The excellent correlation of IB-IVUS and histology has been reported in the validation studies using not only a previous IVUS imaging system (Galaxy, Boston Scientific/Scimed, Natick, MA, USA) but also a new IVUS imaging system (VISIWAVE, Terumo).^{27,29} After tracing vessel, out-stent plaque, and stent area, gray-scale IVUS images and IB-IVUS color-coded maps were displayed side-by-side on a monitor. Out-stent plaque tissue components were classified into 4 categories: calcification (red), dense fibrosis (yellow), fibrosis (green), and lipid (blue) according to signal level. The range of IB values for each historical category were the same as reported previously:²⁹ –11 to –20 dB, calcification; –20 to –26 dB, dense fibrosis; –26 to –42 dB, fibrosis; and –42 to –130 dB, lipid.

Gray-Scale IVUS and IB-IVUS Parameters

On gray-scale IVUS analysis, cross-sectional images were quantified for stent, vessel, and out-stent plaque areas. Out-stent plaque area was calculated as vessel minus stent area. The percentages of calcification area (calcification area/out-stent plaque area), dense fibrosis area (dense fibrosis area/out-stent plaque area), fibrosis area (fibrosis area/out-stent plaque area), and lipid area (lipid area/out-stent plaque area) were automatically calculated by the IB-IVUS system. Serial quantitative IVUS was performed at baseline and at 8-month follow-up. Baseline and follow-up IVUS and IB-IVUS images were matched by the distances from stent edges. Because stent struts cause artifacts, we excluded the image frames including total shadowing due to struts, from analysis. After cross-sectional analysis was performed in culprit lesion at baseline, volumetric analysis was performed in the whole stent segment at 1-mm intervals. Vascular remodeling was assessed according to the change in vessel size (follow-up vessel area/baseline vessel area, follow-up vessel volume/baseline vessel volume). Posi-

tive vessel remodeling was defined as a 5% increase in vessel size.³² ISA was assessed on qualitative IVUS. ISA was defined as one or more struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches. ISA was classified as persistent, resolved, or late-acquired as previously reported.¹³ We also evaluated the correlation between serial change of systemic inflammation scores and out-stent plaque characteristics. All images were reviewed by 2 independent observers (S.S., K.K.), and adjudication of opinion was based on the consensus of these observers.

Study Endpoints

The primary endpoint was out-stent plaque volume and characteristics change after DES implantation. The secondary endpoint was serial systemic inflammatory response after DES implantation. We also evaluated major adverse cardiac events: death from cardiac causes, myocardial infarction, and TLR. TLR was defined as a repeated revascularization, based on a stenosis within the stent or within the 5-mm borders proximal or distal to the stent. TLR was considered if the stenosis of the target lesion was >50% based on QCA in the presence of ischemic signs or symptoms, or if there was a stenosis of >75% even in the absence of ischemic signs or symptoms.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. Categorical data were compared using chi-squared statistic or Fisher's exact test. For continuous variables, comparisons between ZES and PES were performed with a 2-tailed, unpaired t-test, and comparisons between baseline and follow-up were done with a 2-tailed, paired t-test. Correlation between out-stent plaque change and systemic inflammation scores was analyzed using

Pearson's correlation analysis. $P < 0.05$ was considered statistically significant.

Results

Figure 1 shows the flow of participants through the study. Complete IVUS analysis was obtained in 25 patients receiving PES and in 25 patients receiving ZES.

Baseline clinical characteristics are summarized in **Table 1**. There were no significant differences in age, sex, coronary risk factors, or medication between the 2 groups. CAG findings and procedural results are listed in **Table 2**. More lesions in the left anterior descending artery were treated in ZES, although it was not significant. As for procedure characteristics, there were no significant differences in stent number, diameter, or length between groups. High pressure post-dilatation using non-compliant balloon was performed in both groups. Regarding QCA analysis, all parameters were similar at baseline and follow-up between the 2 groups. There was no cardiac death or myocardial infarction in either group. TLR rate was lower in the ZES group compared with PES, although it was not significant ($P = 0.46$).

Serial changes of laboratory data are listed in **Table 3**. Absolute eosinophils significantly decreased at follow-up in ZES. There were no significant serial changes in other systemic inflammatory scores in either group. Serial eosinophil change, however, was not advanced and largely within the normal range.

IVUS and IB-IVUS

Serial gray-scale IVUS measurements are listed in **Table 4**. In the overall analysis, baseline IVUS measurements were not significantly different between groups. In cross-sectional and

Table 1. Baseline Clinical Characteristics

	PES	ZES	P-value
Clinical			
Age (years)	69±11	70±10	0.73
Gender, male	18 (72)	15 (60)	0.37
Coronary risk factors			
Hypertension	21 (84)	16 (64)	0.20
Dyslipidemia	18 (72)	17 (68)	0.76
Diabetes mellitus	18 (72)	14 (56)	0.24
Smoking	17 (68)	11 (44)	0.09
Hemodialysis	7 (28)	3 (12)	0.29
Previous MI	7 (28)	6 (24)	0.75
Prior PCI or CABG	13 (52)	11 (44)	0.57
Family history	6 (24)	2 (8)	0.25
Medication			
Dual antiplatelet therapy	25 (100)	25 (100)	–
ACEI/ARB	19 (76)	13 (52)	0.08
β-blocker	10 (40)	6 (24)	0.23
Ca channel blocker	13 (52)	11 (44)	0.57
Nicorandil	7 (28)	10 (40)	0.37
Nitrates	4 (16)	5 (20)	0.99
Statins	22 (88)	22 (88)	0.99

Data given as n (%) or mean±SD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent.

Table 2. Coronary Angiography and Procedure Results

	PES	ZES	P-value
Target vessel			
LAD	11 (44)	18 (72)	0.06
LCX	3 (12)	0 (0)	
RCA	11 (44)	7 (28)	
ACC/AHA lesion type			
A/B1	5 (20)	7 (28)	0.51
B2/C	20 (80)	18 (72)	
Procedural characteristics			
Stent number	1.2±0.4	1.2±0.4	0.74
Use of multiple stents	6 (24)	5 (20)	0.73
Stent diameter (mm)	3.1±0.3	3.1±0.2	0.75
Stent length (mm)	30.6±11.3	27.7±10.0	0.34
Maximum pressure (atm)	20±3	21±2	0.10
QCA results			
Reference diameter (mm)	2.1±0.5	2.3±0.4	0.31
Minimal lumen diameter (mm)			
Before intervention	0.7±0.3	0.7±0.2	0.73
After intervention	2.2±0.4	2.3±0.4	0.53
8-month follow-up	1.5±0.6	1.6±0.5	0.28
Late lumen loss (mm)	0.7±0.5	0.6±0.5	0.55
Binary restenosis	6 (24)	4 (16)	0.73
TLR	6 (24)	3 (12)	0.46

Data given as n (%) or mean±SD.

LAD, left anterior descending; LCX, left circumflex; QCA, quantitative coronary angiography; RCA, right coronary artery; TLR, target lesion revascularization. Other abbreviations as in Table 1.

Table 3. Laboratory Data (Serial Change)

	Baseline	Follow-up
WBC		
PES	7,308±2,512	6,644±2,092
ZES	5,844±1,741	5,800±1,818
Neutrophils (/mm³)		
PES	5,027±2,186	4,413±1,572
ZES	3,630±1,356	3,714±1,406
Eosinophils (/mm³)		
PES	186±137	201±151
ZES	223±153	169±145*
Monocytes (/mm³)		
PES	400±220	345±126
ZES	365±102	352±131
hsCRP		
PES	0.6±1.7	0.2±0.2
ZES	0.5±0.6	0.3±0.6

Data given as mean±SD. *P<0.05, follow-up vs. baseline.

hsCRP, high-sensitivity C-reactive protein; WBC, white blood cells. Other abbreviations as in Table 1.

volumetric analysis, vessel size was significantly augmented in PES with significant increase in out-stent plaque (17.5±4.2 mm² to 19.0±4.5 mm², P<0.0001; 365±234 mm³ to 389±247 mm³, P<0.0001), whereas it did not change in ZES (18.3±3.6 mm² to 18.2±3.6 mm², P=0.49; 315±120 mm³ to 314±119 mm³, P=0.81). Serial change in out-stent plaque was significantly larger in PES than in ZES (+1.5±1.4 mm² vs. −0.1±0.6 mm², P<0.0001; 24.2±23.5 mm³ vs. −0.4±8.9 mm³, P<0.0001). Remodeling index was significantly larger in PES than in ZES (vessel area, 1.09±0.08 vs. 0.99±0.03, P<0.0001; vessel volume, 1.06±0.05 vs. 0.99±0.03, P<0.0001). The incidence of positive vessel remodeling was significantly higher in PES than in ZES (56%, n=14 vs. 4%, n=1; P=0.0001 for both vessel area and volume). On qualitative IVUS, there were 2 ISA at baseline in PES and 4 ISA at baseline in ZES. Although most ISA at baseline resolved at 8-month follow-up, there were 2 late cases of ISA at follow-up in PES, whereas there were no such cases in ZES. Representative 2-D IB-IVUS color-coded maps of out-stent plaque in culprit site in each group are given in **Figure 2**. Serial IB-IVUS measurements are given in **Table 5**. In PES, fibrous plaque tended to or significantly increased (3.1±1.2 mm² to 3.6±1.0 mm², P=0.051; 56.4±34.5 mm³ to 70.3±39.7 mm³, P=0.0011) and lipid plaque tended to or significantly increased (4.3±3.0 mm² to 5.1±3.2 mm², P=0.02; 85.3±90.0 mm³ to 91.2±97.6 mm³, P=0.12), whereas fibrous plaque significantly increased (2.9±0.5 mm² to 4.0±1.2 mm², P<0.0001; 54.1±21.2 mm³ to 67.4±27.7 mm³, P<0.0001) and lipid plaque significantly decreased (5.1±2.9 mm² to 3.6±2.8 mm², P<0.0001; 65.0±41.4 mm³ to 47.5±35.9 mm³, P=0.0001) in ZES. Serial lipid plaque change showed increased response in PES, while it showed decreased response in ZES (0.8±1.6 mm² vs. −1.5±1.1 mm², P<0.0001; 5.9±18.3 mm³ vs. −17.5±18.8 mm³, P<0.0001 for both vessel area and volume).

In addition, we examined the relationship between systemic eosinophil change and out-stent plaque change, although fluctuations in eosinophil number after PES or ZES implantation were not advanced and largely within the normal range. Increase in eosinophils was significantly correlated with positive vessel remodeling (r=0.45, P=0.001) and increase in out-stent lipid plaque (r=0.47, P=0.0006) at follow-up (**Figure 3**). There

	PES		ZES	
	Mean±SD	FU-BL	Mean±SD	FU-BL
Culprit site				
Vessel area (mm ²)				
Baseline	17.5±4.2		18.3±3.6	
Follow-up	19.0±4.5*	1.5±1.4 [†]	18.2±3.6	−0.1±0.6
Remodeling index	1.09±0.08 [†]		0.99±0.03	
Out-stent plaque area (mm ²)				
Baseline	7.9±3.2		8.2±2.9	
Follow-up	9.4±3.3*	1.5±1.3 [†]	8.2±3.0	−0.1±0.6
Stent area (mm ²)				
Baseline	9.7±2.3		10.1±1.6	
Follow-up	9.7±2.3	0.01±0.5	10.1±1.7	−0.01±0.4
Whole stent segment				
Vessel volume (mm ³)				
Baseline	365±234		315±120	
Follow-up	389±247*	24.2±23.5 [†]	314±119	−0.4±8.9
Remodeling index	1.06±0.05 [†]		0.99±0.03	
Out-stent plaque volume (mm ³)				
Baseline	152±125		128±60	
Follow-up	174±135*	22.7±18.1 [†]	128±58	0.05±8.4
Stent volume (mm ³)				
Baseline	213±121		187±69	
Follow-up	215±122	1.5±9.3	186±69	−0.7±7.5

*P<0.0001, FU vs. BL; [†]P<0.0001, PES vs. ZES.

BL, baseline; FU, follow-up; IVUS, intravascular ultrasound. Other abbreviations as in Table 1.

Figure 2. Representative 2-D integrated backscatter-intravascular ultrasound color-coded maps of out-stent plaque at the culprit site at baseline for (A) paclitaxel-eluting stent (PES) and (B) zotarolimus-eluting stent (ZES). Red, calcification; yellow, dense fibrosis; green, fibrosis; blue, lipid. Each out-stent plaque component is described as a percentage. Fibrous plaque apparently decreased but lipid plaque apparently increased in PES, whereas fibrous plaque apparently increased but lipid plaque apparently decreased in ZES, at follow-up.

Table 5. IB-IVUS Data				
	PES		ZES	
	Mean±SD	FU-BL	Mean±SD	FU-BL
Culprit site				
Calcification area (mm ²)				
Baseline	0.1±0.1	0.05±0.2	0.1±0.1	0.08±0.2
Follow-up	0.2±0.2		0.2±0.1*	
Dense fibrosis area (mm ²)				
Baseline	0.3±0.2	0.1±0.2	0.3±0.2	0.2±0.3
Follow-up	0.4±0.3*		0.5±0.2*	
Fibrosis area (mm ²)				
Baseline	3.1±1.2	0.6±1.3	2.9±0.5	1.1±1.0
Follow-up	3.6±1.0		4.0±1.2*	
Lipid area (mm ²)				
Baseline	4.3±3.0	0.8±1.6†	5.1±2.9	−1.5±1.1
Follow-up	5.1±3.2*		3.6±2.8*	
Whole stent segment				
Calcification volume (mm ³)				
Baseline	3.0±1.9	0.9±1.9	2.3±1.6	1.3±2.3
Follow-up	4.0±2.5*		3.6±2.5*	
Dense fibrosis volume (mm ³)				
Baseline	6.9±3.9	14.3±3.8	6.4±3.4	18.7±4.3
Follow-up	8.9±4.7*		9.3±4.9*	
Fibrosis volume (mm ³)				
Baseline	56.4±34.5	13.9±18.7	54.1±21.2	13.3±13.3
Follow-up	70.3±39.7*		67.4±27.7*	
Lipid volume (mm ³)				
Baseline	85.3±90.0	5.9±18.3†	65.0±41.4	−17.5±18.8
Follow-up	91.2±97.6		47.5±35.9*	

*P<0.05, FU vs. BL; †P<0.0001, PES vs. ZES.

IB, integrated backscatter. Other abbreviations as in Tables 1,4.

Figure 3. (A) Remodeling index vs. systemic eosinophil change. (B) Out-stent lipid plaque change vs. systemic eosinophil change.

were no cases of late or very late stent thrombosis up to 30-month follow-up in either group.

Discussion

The main results of this study are as follows. First, out-stent plaque change was different between PES and ZES. Serial gray-scale IVUS showed that vessel size significantly increased in PES, whereas it did not change in ZES on both culprit site and volumetric analysis within the stents. Remodeling index was significantly larger and the rate of positive vessel remodeling was significantly higher in PES than in ZES. Serial IB-IVUS showed that fibrous plaque significantly increased and lipid plaque significantly increased in PES, whereas fibrous plaque significantly increased but lipid plaque significantly decreased in ZES, at the culprit site. And second, increase in eosinophils was significantly correlated with positive vessel remodeling and increase in out-stent lipid plaque at follow-up.

Although first-generation DES had dramatically reduced angiographic restenosis and TLR by decreasing neointimal hyperplasia compared with BMS,^{1,2} late and very late stent thrombosis, a life-threatening complication of this technology, has emerged as a major safety concern.^{3,4} As the main mechanisms of late and very late stent thrombosis, delayed arterial healing (persistent fibrin deposition and delayed re-endothelialization) due to drugs in DES⁵⁻⁹ and chronic inflammation and hypersensitive reactions due to drugs and/or durable polymers in DES, have been reported in animal and human pathological studies.⁷⁻¹² These studies found enhanced inflammatory responses consisting predominantly of T lymphocytes and eosinophils around stent struts and stent malapposition with vessel enlargement after DES implantation.^{7,10-12} In clinical practice, previous in vivo IVUS showed that positive vessel remodeling after first-generation DES was associated with late and very late stent thrombosis. Those studies reported that positive vessel remodeling was the main cause of late-acquired ISA. It was also reported that late-acquired ISA seemed to correlate with late and very late stent thrombosis.¹³⁻¹⁸ Cook et al also reported that very late DES thrombosis was associated with histopathological signs of inflammation and IVUS evidence of vessel remodeling. Eosinophilic infiltrates were predominantly observed in thrombus aspirates, which suggested an immunologic reaction in response to the implanted DES.¹⁷ Furthermore, recent pathology suggested that neoatherosclerosis occurred in both DES and BMS, but it was observed more frequently and earlier in DES compared with BMS. That study also suggested that neoatherosclerosis could be accelerated in DES and, in rare cases, contributed to very late thrombotic events.³³ In previous angioscopic clinical studies, DES showed poor neointimal coverage and promoted formation of yellow plaque in stented lesions at chronic phase.^{34,35}

Endeavor™ ZES (Medtronic Vascular), second-generation DES, have biocompatible characteristics with low-profile, thin-strut, cobalt-alloy Driver stent, phosphorylcholine polymer, and different drug-elution, compared with first-generation DES.¹⁹ According to several randomized trials, ZES was found to have relative safety and efficacy compared with first-generation DES.¹⁹⁻²¹ Previous optical coherence tomography and angioscopic clinical studies demonstrated that ZES provided adequate neointimal coverage and that late-acquired ISA was not found after stenting, which indicated arterial endothelial healing after stenting.³⁶⁻³⁸ Moreover, the angioscopic study reported that ZES-implanted vessels were associated with significantly less yellow plaques than first-generation DES.³⁸ This finding suggests that ZES may provide stabilization of residual plaque.

IVUS analyses from Endeavor trials showed that ZES implantation provided relatively complete and uniform neointimal coverage over the stent surface, resulting in low incidence of late-acquired ISA.²²⁻²⁴ IVUS analysis from the Endeavor IV trial showed that PES had significantly increased vessel and out-stent plaque volume in stented segments during the follow-up period, whereas ZES had no significant changes in vessel and out-stent plaque volume.²⁵

In the present study, QCA showed that there were no significant differences in any parameters or in the TLR rate between the 2 groups. Chronic out-stent plaque change after ZES implantation, however, was different from that after PES implantation. ZES had less positive vessel remodeling and more favorable changes in out-stent plaque characteristics (fibrous plaque increase and lipid plaque decrease) in comparison with PES. Owing to rapid drug-elution, much less chronic inflammation and allergy caused by durable polymers, sufficient neointimal coverage, composed mainly of smooth muscle cells and collagen fibers, can occur to seal the residual plaque behind stent struts. This suggests that favorable arterial healing will occur after stenting. Moreover, it is expected that favorable arterial healing may lead to the stabilization of residual plaque with less positive vessel remodeling. Out-stent fibrous plaque increase and lipid plaque decrease on IB-IVUS analysis may suggest that favorable arterial healing and stabilization of residual plaque will occur. In addition, almost all patients received statin treatment. Several previous studies of lipid-lowering therapy found that statin treatment significantly decreased atheromatous plaque volume and lipid components.³⁹ These results are thought to be due to lipid-lowering action and pleiotropic effects. It is possible that statin treatment may have made some contribution to the stabilization of residual plaque after stent implantation in this study. In contrast, PES caused positive vessel remodeling and unfavorable changes in out-stent plaque characteristics (lipid plaque increase). Because of delayed arterial healing due to drugs, chronic inflammation and hypersensitivity reaction caused by drugs and/or durable polymers, incomplete neointimal coverage, that is, a deficiency of smooth muscle cells and collagen fiber progression, and an abundance of vulnerable tissue, such as thrombus, fibrin, and proteoglycan can occur. Recent pathological and IVUS studies suggested that positive vessel remodeling after PES implantation was caused by vascular toxicity (tissue necrosis and apoptosis) due to excessive drug elution and hypersensitive reactions due to drugs and/or durable polymers.^{25,40,41} What is worse, it is possible that residual plaque can cause progression of atherosclerosis in the early phase. Increase of vessel size and out-stent lipid plaque on IVUS and IB-IVUS may suggest the presence of vulnerable tissue, such as thrombus, fibrin, and proteoglycan and the progression of atherosclerosis.

Regarding eosinophil change, because there could be multiple factors in the increase or decrease of eosinophils, eosinophils may increase after PES implantation in some cases, while eosinophils may decrease in others. Similar results were also observed after ZES implantation in this study. It is difficult to conclude that PES or ZES has a bidirectional influence on eosinophil number according to the present results. Although eosinophil number significantly decreased after ZES implantation, the change was not advanced and largely within the normal range. Possible reasons for the reduced eosinophils after ZES implantation are as follows: (1) a plaque-sealing effect of out-stent plaque inflammation due to favorable arterial healing and sufficient neointimal coverage; and (2) lipid-lowering action and pleiotropic effects due to statin treatment. Further studies are necessary to evaluate this point.

Despite these, we consider that eosinophil number fluctuations after PES or ZES implantation, although not advanced and largely within normal range, are important. Increase in eosinophils was significantly correlated with positive vessel remodeling and increase in out-stent lipid plaque at follow-up. There is a possibility that residual drug and/or durable polymers were associated with chronic inflammation and allergy. Statin treatment may not be able to produce favorable vessel response.

Study Limitations

This study had several limitations. It was a small randomized study performed at a single medical center, raising the possibility of selection bias. Although QCA and IVUS analysis were performed independently by 2 experienced blinded observers, there were big differences among QCA-derived reference diameter and post-intervention minimal lumen diameter, and actual stent diameter. In the previous IVUS study, the difference between QCA and IVUS was >0.5 mm when reference diameter on angiography was <2.5 mm.⁴² In IVUS analysis, vessel measurement was performed only for lesions for which vessel borders were clearly visible. Lesions in which vessel borders were not clearly visible on IVUS (heavily calcified lesions) were excluded in this study. Large vessel size as well as existence of neointima and stent struts may affect the results of out-stent plaque characterization because of echo attenuation. We believe, however, that we conducted the measurements under the same conditions, that is, in exactly the same place and using the same method, so that we could minimize the effect of this. Moreover, the IB-IVUS system in itself can correct the effect of attenuation.²⁹ Supportive evidence of chronic coronary arterial response after DES implantation in humans is mostly derived from autopsy studies. IVUS and IB-IVUS are the only systems that enable vessel and out-stent plaque change to be observed in vivo.⁴³ Therefore, we evaluated the differences of vessel response between ZES and PES using IVUS and IB-IVUS. Validation on pathology is needed in the future. Because radiofrequency quality greatly deteriorates behind the stent, we excluded from analysis the image frames including total shadowing due to struts. It was difficult to distinguish between thrombus and other plaque components on IB-IVUS. Follow-up IVUS was limited to a mid-term period of 8 months. The impacts of vessel remodeling and out-stent plaque change on clinical outcome are still unclear. Further studies with longer-term follow-up are necessary for more adequate assessment of these findings.

Conclusions

Chronic out-stent plaque change in ZES involved less positive vessel remodeling and more favorable effects on out-stent plaque characteristics than PES. Serial systemic eosinophil response largely in the normal range in PES might be associated with increase of vessel remodeling and out-stent lipid plaque. Further studies are required to confirm the clinical impact of these findings.

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