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Impact of out-stent plaque characteristics on vascular response after second generation drug-eluting stent implantation: iMAP-intravascular ultrasound and angioscopic study

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ABSTRACT

Purpose: The purpose of this study is to elucidate the impact of out-stent plaque characteristics on vascular response after implantation of second generation drug-eluting stent (G2-DES).
Methods: Enrolled were 37 patients with 39 coronary artery lesions into which three types of G2-DES were successfully implanted (9 Nobori biolimus-, BES; 15 Xience everolimus-, EES; 15 Resolute zotarolimus-eluting stents; R-ZES). Immediately after (baseline) and one year after the implantation (follow-up), iMAP-intravascular ultrasound (IVUS) was performed to measure out-stent plaque volume (OSPV) and its components. Percent OSPV and vulnerable plaque index (VPI) were defined as percentile of OSPV to vessel volume and as percentile of lipidic plus necrotic volume to OSPV. Coronary angioscopy at follow-up rated the degree of arterial repair by neointimal stent coverage (NSC).
Results: Poor NSC was found in approximately 60% of each G2-DES. In BES, % OSPV at baseline was significantly greater in poor NSC than in good NSC (36.2 ± 3.9 vs. 27.3 ± 4.0%, P = 0.01). In EES, %OSPV was significantly greater in poor NSC than in good NSC (41.0 ± 4.1 vs. 32.6 ± 2.7%, P < 0.01). In R-ZES implantation, there was no significant difference with regards to %OSPV between poor and good NSC. In BES, VPI at baseline was significantly greater in poor NSC than good NSC (54.0 ± 5.8 vs. 42.2 ± 5.1%, P = 0.02). There was no significant difference with regards to VPI between poor and good NCS in EES and R-ZES.
Conclusions: Impact of out-stent plaque characteristics on vascular response was different among the three types of G2-DES.
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1. Introduction

Although arterial repair after intracoronary implantation of drug-eluting stents (DES) depends not only on bio-suppressive drug elution from stent struts but also on solvent polymer [1], impact of out-stent plaque characteristics on arterial repair has been controversial [2]. Pathology revealed the delayed arterial repair after implantation of the first generation drug-eluting stents (G1-DES) in comparison with bare metal stents [3]. This delay was angioscopically characterized by poor neointimal stent coverage (NSC) and in-stent yellow plaque [4,5]. Autopsy revealed that NSC after G1-DES implantation delayed in cadavers with acute myocardial infarction in comparison with those with stable angina pectoris [6]. The delayed arterial repair might cause very late stent thrombosis, a serious complication of DES implantation.

In this study, we performed one-year followed up of arterial repair after implantation of the second generation drug-eluting stents (G2-DES) into patients with coronary artery disease. We employed coronary angioscopy as well as iMAP™-intravascular ultrasound (IVUS) to assess plaque characteristics [7]. The purpose of this study was to elucidate the impact of out-stent plaque volume (OSPV) and plaque vulnerability on vascular response after implantation of three types of G2-DES.

2. Methods

2.1. Study population

From July 2012 to July 2013, enrolled were consecutive 40 patients with coronary artery diseases who received successful implantation of G2-DES at their culprit lesions. For this period, we did not fail to implant G2-DES. Implanted stents were composed of Xience everolimus-eluting stents (EES, Xience®, Abbott-vascular Co., Abbott Park, IL, USA), Resolute zotarolimus-eluting stents (R-ZES, Resolute Integrity®, Medtronic Co., Minneapolis, MN, USA), and biolimus-eluting stents (BES, Nobori®, Terumo Co., Tokyo, Japan). Selection of G2-DES depended on operator's preference. Immediately after the stent implantation, iMAP-IVUS were performed (baseline). When a patient received two stents, we implanted the same G2-DES as the first one. In other words, cases with hybrid stenting (bare-metal stent/DES and different types of G2-DES) were excluded from the enrollment. Dual antiplatelet therapy, 75 mg clopidogrel and 100 mg aspirin, had been continued at least for one year until follow-up coronary angiography (CAG). Two patients were withdrawn from the follow-up because of stroke and non-cardiac death.

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Follow-up CAG was performed at one year after the stent implantation, revealing in-stent restenosis in a patient who was withdrawn from further intracoronary imaging analyses. Subsequently, 39 stents in 37 patients, i.e. 18 acute coronary syndrome (ACS) and 19 stable angina pectoris (SAP), were subjected to iMAP™-IVUS and coronary angioscopy (follow-up). The study protocol was approved by our institutional review board. A written informed consent was obtained from each patient before his or her participation.

2.2. iMAP-IVUS analyses

IVUS was performed by iMAP™-system (Boston Scientific Corp, Fremont, CA, USA). A 3.6 Fr 40 MHz IVUS catheter (Atrantis SR Pro 2; Boston Scientific Corporation, Minneapolis, MN) was introduced into a coronary artery. First, gray-scale IVUS provided planimetric data throughout stent length at every 0.5 mm interval. Vessel area was defined as inner area within outer border of sonolucent zone. Vessel volume and stent volume were calculated by integral from distal to proximal edge of each stent (Fig. 1). Out-stent plaque volume (OSPV) was defined as subtraction of stent volume from vessel volume. Percent OSPV (%OSPV), a representative parameter for plaque burden, was calculated as ratio of OSPV to vessel volume.

Second, iMAP system provided the tissue characterization of out-stent plaques [7]. On the cross section images, iMAP coded the out-stent plaques as light-green (fibrotic), yellow (lipidic), pink (necrotic), light-blue (calcified), and artifact area. Artifact area was caused by interference of guide wires (ignored area). Employing EchoPlaque Analysis software (INDEC Medical Systems, Santa Clara, CA), fractions of each component in out-stent plaques were calculated by integral throughout stent length at every 0.5 mm interval (Fig. 1). To assess out-stent plaque vulnerability, we tentatively defined vulnerable plaque index (VPI) as ratio of lipidic plus necrotic volume to total OSPV.

2.3. Coronary angioscopy

Coronary angioscopy (Visible™, Fiber-tech, Tokyo) was performed through a 6 Fr sheath under continuous flush of 3% dextran 40 as described previously [8,9]. It visualized in-stent appearance, i.e. grade of neointimal stent coverage (NSC), presence of yellow plaque, and mural thrombus. NSC was classified into two grades, poor or good coverage [10]. Poor NSC was corresponded to grade 0–1, and good NSC was corresponded to grade 2–3 according to previous report methods [2,5]. When both grades were observed in a stent, dominant grade of NSC was assigned to the grade of the entire stented segment. All angioscopic data were evaluated by 2 angioscopic specialists blinded to the patient characteristics.

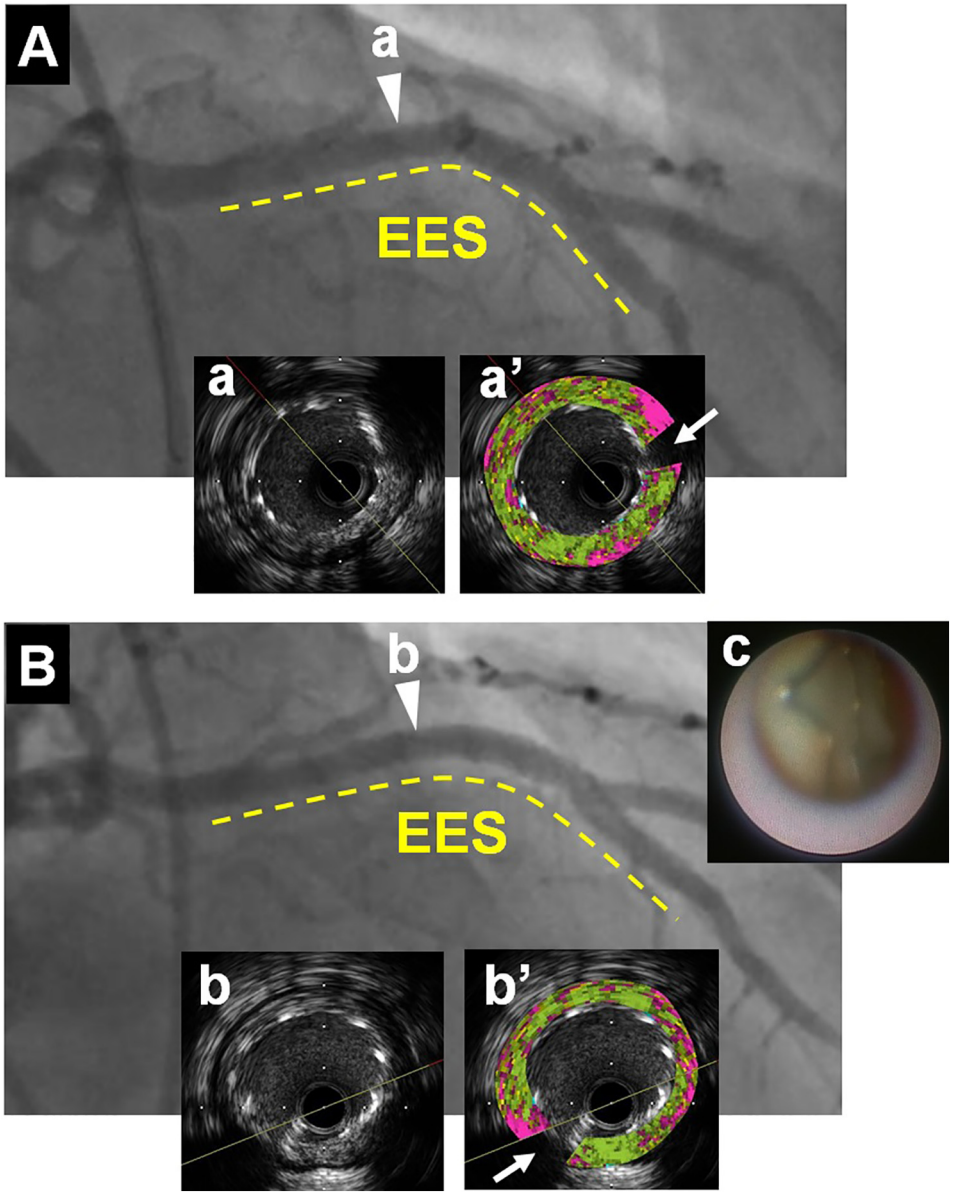

Fig. 1. A representative case. At baseline (A), EES (dotted line) was successfully implanted into proximal LAD, a culprit lesion of anterior acute myocardial infarction, in a 70-year-old male. At the center of EES (arrowhead), cross sectional images of gray-scale IVUS (a) and iMAP-IVUS (a') were shown. Planimetry of out-stent plaque was done in the former. The out-stent plaque was colorized on the basis of tissue characteristics (a'). Artifact area caused by guide wire interference was excluded for iMAP analysis (arrow). Integral of each area throughout the stent gave each volume. At follow-up (B), cross sectional images of gray-scale IVUS (b) and iMAP-IVUS (b') were shown. From baseline to follow-up, %OSPV reduced from 55.7 to 42.8%. VPI reduced from 61 to 56%. Coronary angioscopy was performed only at follow-up, showing yellow plaque and stent struts covered with thin transparent neointima (poor coverage) (c).

2.4. Statistical analyses

Categorical variables were presented as numbers and percentages. Continuous variables were presented as mean ± standard deviation. For categorical variables, we employed chi-square test. In comparison of continuous variables among three groups, we employed ANOVA. In comparison between the good coverage and poor coverage groups (Figs. 2 and 3), we employed unpaired *t*-test. Difference with $P < 0.05$ was considered significant. All statistical analysis was performed using SPSS software (SPSS, Chicago, IL).

3. Results

3.1. Patients and stented lesions

Thirty-nine G2-DES (9 BES, 15 EES, 15 R-ZES) were implanted into 37 patients. In coronary risk factors, dyslipidemia was significantly more frequent in patients implanted with the R-ZES group than those with BES and EES. Five of 7 patients of the BES group were patients with ACS (Table 1). Stent diameter of BES (3.4 ± 0.3 mm) was significantly greater than those of EES (3.0 ± 0.5 mm) and R-ZES (3.1 ± 0.4 mm, P = 0.03; see Table 2).

3.2. IVUS analyses

In gray-scale volumetric analysis (Fig. 1A-a and B-b), both OSPV and %OSPV reduced from baseline to follow-up only in EES (153.2 ± 93.4 to 145.8 ± 83.5 mm^3, 38.2 ± 5.5 to 36.8 ± 4.5%, $P < 0.05$) but not in BES or R-ZES (Table 3). In iMAP tissue characterization analysis (Fig. 1A-a' and B-b'), necrotic fraction at baseline was the greatest in BES in comparison with EES and R-ZES (36.6 ± 5.6 vs. 32.9 ± 6.6 vs. 29.2 ± 5.1%, P = 0.02, see Table 4). Fibrotic faction at baseline was the lowest in BES in comparison with EES and R-ZES (40.7 ± 8.0 vs. 44.4 ± 6.5 vs. 48.7 ± 6.4%, P = 0.04) (Table 4). VPI at baseline was the greatest in BES in comparison with EES and R-ZES (50.1 ± 7.9 vs. 44.5 ± 11.8 vs. 40.9 ± 6.7%, P = 0.04), being compatible with prevalence of ACS in the BES patients (Table 3). There was no significant difference with regards to VPI at follow-up among the three G2-DES.

3.3. Coronary angioscopy at chronic phase

Coronary angioscopy revealed poor NSC in 67% of BES, 67% of EES, and 60% of R-ZES (Table 5). YP was observed most frequently in BES (56%) in comparison with EES (7%) and R-ZES (7%, P = 0.004). Although thrombus was detected only in one BES-implanted lesion, no statistical difference was found among three types of G2-DES (P = 0.18).

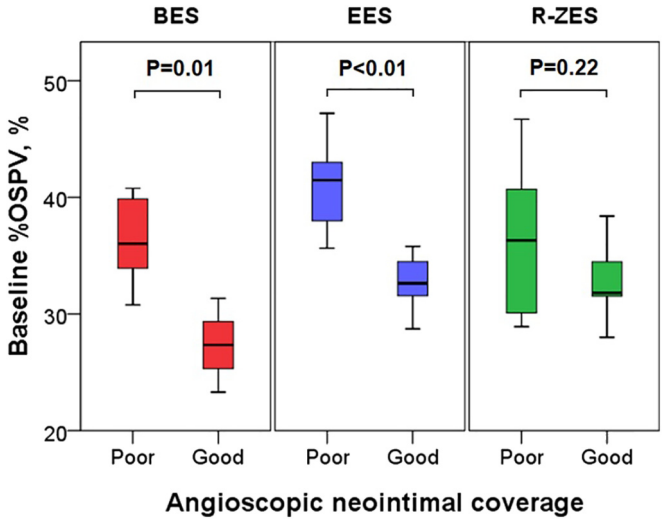

Fig. 2. Relationship between baseline %OSPV and angioscopic findings. In BES and EES, %OSPV was significantly greater in poor neointimal stent coverage (NSC) group than in good NSC group (A). In R-ZES, there was no relationship between %OSPV and angioscopic neointimal coverage.

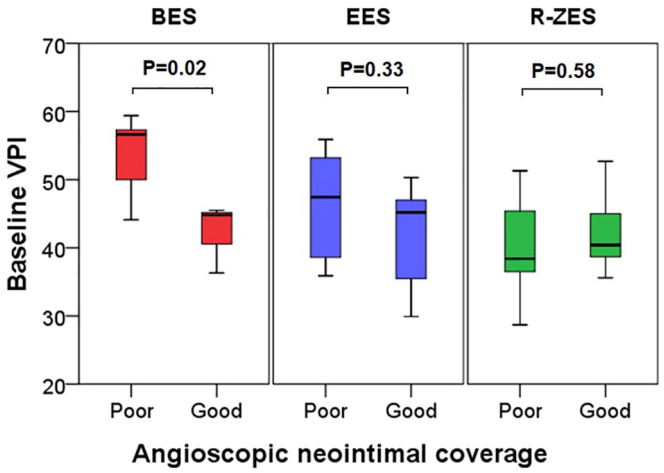

Fig. 3. Relationship between baseline VPI and angioscopic findings. In BES, VPI was significantly greater in poor neointimal stent coverage (NSC) group than in good NSC group. In EES and R-ZES, there was no significant relationship between VPI and angioscopic findings.

3.4. Impact of plaque burden on NSC

In BES, %OSPV at baseline was significantly greater in poor NSC than in good NSC (36.2 ± 3.9 vs. 27.3 ± 4.0%, P = 0.01, see Fig. 2). In EES, %OSPV was significantly greater in poor NSC than in good NSC (41.0 ± 4.1 vs. 32.6 ± 2.7%, $P < 0.01$). In R-ZES implantation, there was no significant difference with regards to %OSPV between poor and good NSC (36.4 ± 6.4 vs. 32.7 ± 3.5%, P = 0.22).

3.5. Impact of plaque vulnerability at acute phase on NSC

In BES, VPI at baseline was significantly greater in poor NSC than good NSC (54.0 ± 5.8 vs. 42.2 ± 5.1%, P = 0.02, see Fig. 3). There was no significant difference with regards to VPI between poor and good NCS in EES (46.0 ± 7.9 vs. 41.6 ± 8.5%, P = 0.88) and R-ZES (40.0 ± 7.4 vs. 42.1 ± 6.0%, P = 0.57).

Table 1
Patient characteristics.

	BES (n = 7)	EES (n = 15)	R-ZES (n = 15)	P-value
Age, years	72.9 ± 7.1	67.4 ± 10.7	68.1 ± 8.6	0.33
Gender, male (%)	6 (86)	13 (87)	12 (80)	0.87
Clinical diagnosis				0.38
ACS, (%)	5 (71)	7 (47)	6 (40)	
SAP, (%)	2 (29)	8 (53)	9 (60)	
Coronary risk factors				
Hypertension, (%)	7 (100)	13 (87)	12 (80)	0.44
Dyslipidemia, (%)	6 (86)	8 (53)	14 (93)	0.03
Diabetes mellitus, (%)	4 (57)	5 (33)	6 (40)	0.57
CKD, (%)	0 (0)	1 (7)	1 (7)	0.78
Current smoker, (%)	5 (71)	11 (73)	10 (67)	0.92
Medication†				
ACEI/ARB, (%)	5 (71)	7 (47)	10 (67)	0.42
β-blocker, (%)	5 (71)	7 (47)	8 (53)	0.55
Statin	6 (86)	7 (47)	11 (73)	0.14
Dual antiplatelet therapy	7 (100)	14 (93)	11 (73)	0.14

Categorical data are expressed as percentage in 37 patients. Continuous variables are expressed as mean ± SD. †Medication at one-year after stenting. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Dual anti-platelet therapy, 100 mg aspirin plus 75 mg clopidogrel.

Table 2
Lesion and stent characteristics.

	BES (n = 9)	EES (n = 15)	R-ZES (n = 15)	P-value
Follow-up period, days	375.0 ± 32.3	350.8 ± 29.6	359.0 ± 27.4	0.61
Stent diameter (mm)	3.4 ± 0.3	3.0 ± 0.5	3.1 ± 0.4	0.03
Total stent length (mm)	30.0 ± 13.2	30.3 ± 13.4	27.5 ± 12.2	0.37
Target vessel				0.06
LAD, (%)	3 (33)	10 (67)	11 (73)	
LCX, (%)	1 (11)	3 (20)	3 (20)	
RCA, (%)	5 (56)	2 (13)	1 (7)	
ACC/AHA lesion type[†]				0.25
A/B1, (%)	0 (0)	1 (7)	3 (20)	
B2/C, (%)	9 (100)	14 (93)	12 (80)	

Categorical data are expressed as numbers in 39 lesions. Continuous variables are expressed as mean ± SD. [†]Lesion types were defined in Methods. EES, everolimus-eluting stent; R-ZES, Resolute zotarolimus-eluting stent; and BES, Nobori biolimus-eluting stent; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Table 4
iMAP-IVUS analyses.

	Phase	BES (n = 9)	EES (n = 15)	R-ZES (n = 15)	P-value
Fibrotic (%)	Baseline	40.7 ± 8.0	44.4 ± 6.5	48.7 ± 6.4	0.04
	Follow-up	44.4 ± 6.5	48.3 ± 9.5	53.6 ± 7.1	0.90
	Δ	7.6 ± 4.7	3.9 ± 6.0	4.9 ± 7.1	0.32
Lipidic (%)	Baseline	13.7 ± 2.8	11.6 ± 2.13	11.7 ± 2.8	0.12
	Follow-up	11.2 ± 2.0	10.1 ± 3.9	8.9 ± 1.9	0.09
	Δ	−2.4 ± 2.9	−14.7 ± 3.18	−2.7 ± 2.6	0.52
Necrotic (%)	Baseline	36.6 ± 5.6	32.9 ± 6.6	29.2 ± 5.1	0.02
	Follow-up	30.8 ± 6.5	28.9 ± 8.5	25.1 ± 6.2	0.12
	Δ	−5.8 ± 4.9	−4.0 ± 6.3	−4.4 ± 5.3	0.78
VPI (%)	Baseline	50.1 ± 7.9	44.5 ± 11.8	40.9 ± 6.7	0.04
	Follow-up	41.7 ± 7.7	38.7 ± 11.8	40.9 ± 6.7	0.08
	Δ	−8.4 ± 6.6	−5.8 ± 9.1	−6.9 ± 7.1	0.81
Calcified (%)	Baseline	2.4 ± 1.2	2.9 ± 1.4	3.2 ± 1.4	0.21
	Follow-up	3.0 ± 1.4	4.2 ± 1.9	4.0 ± 2.7	0.33
	Δ	0.6 ± 1.7	1.3 ± 1.6	0.8 ± 2.4	0.48
Ignored (%)	Baseline	6.6 ± 1.3	8.1 ± 2.9	7.2 ± 1.9	0.28
	Follow-up	7.2 ± 2.7	8.7 ± 3.1	7.6 ± 3.8	0.43

Continuous variables are expressed as mean ± SD. VPI, Vulnerable plaque index was defined as ratio of lipidic plus necrotic to total OSPV.

4. Discussion

In this study with iMAP-IVUS and coronary angioscopy, we first reported the relationship between out-stent plaque characteristics and arterial repair after implantation of three types of G2-DES. We found: 1) %OSPV decreased at one-year after EES implantation, whereas it increased after BES and R-ZES implantation; 2) The greater %OSPV immediately after BES and EES implantation was associated with the poor NSC at follow-up; 3) VPI at baseline was associated with the poor NSC at follow-up after BES implantation; and 4) Neither %OSPV and VPI at baseline was associated with NSC at follow-up after R-ZES implantation.

Impact of out-stent plaque characteristics on arterial repair at follow-up was stent-specific. A previous autopsy study argued that NSC after G1-DES (Sirolimus- or paclitaxel-eluting stent) implantation delayed at the vulnerable plaques, not at stable plaques [6], suggesting the impact of out-stent plaque vulnerability on arterial repair after stent implantation. A previous gray-scale IVUS study argued that reduction of out-stent plaque volume at chronic phase was associated with less in-stent intimal hyperplasia in patients with implantation of sirolimus-eluting stent or bare-metal stent [11]. A previous integrated backscatter-IVUS study clarified the difference between Taxus paclitaxel-eluting stent and Endeavor ZES with regards to out-stent plaque volume and vulnerability at chronic phase [12]. Recent angioscopic studies revealed the different patterns of vascular response at chronic phase among different types of G2-DES [2,13]. In the present study, arterial repair after BES implantation was most affected by out-stent plaque characteristics. Arterial repair after EES was affected by out-stent plaque volume. Arterial repair after R-ZES implantation was not affected by out-stent plaque characteristics (Figs. 2 and 3).

Out-stent plaque volume regressed at follow-up after EES implantation (%OSPV 38.2 ± 5.5 to 36.8 ± 4.5, P = 0.03), whereas OSPV increased after BES and R-ZES implantation (Table 3). The reason for this phenomenon may be explained by EES specific performance. First, it is regarded that EES has anti-inflammatory and antithrombotic effect after stent placement [14–17], and these characteristic properties of EES may be relate to reduction of underlying plaque volume. Second, it has been widely accepted that the aggressive lowering of LDL-cholesterol led to regression of coronary plaques [18]. In this study, morbidity of dyslipidemia in patients with EES implantation was significantly lower than in those with BES and R-ZES implantation (53% vs. 86 and 93%, respectively; P = 0.03). Rate of statin use was only 47% in patients with EES implantation (Table 1). Unfortunately, we did not measure serum LDL cholesterol level in all the studied patients. Further study with more patients must be done to conclude the regression of plaque volume after EES implantation.

There were several limitations in this study. First, this study was conducted in a single-center with a small number of G2-DES. Second, coronary angioscopy was not performed at baseline so that we did not know the presence of yellow plaques and thrombi at acute phase. Third, arterial healing after stent implantation was evaluated only at one year after the implantation. We know that arterial repair after DES implantation gradually proceeded through a decade [1]. Fourth, stent selection was not randomized so that baseline profiles of the three groups were significantly different (prevalence of dyslipidemia, stent diameter, and VPI). This might affect our results.

In conclusion, impact of out-stent plaque characteristics on vascular response was different among BES, EES, and R-ZES.

Conflict of interest

The Authors declare that there is no conflict of interest.

Table 3
IVUS volumetric analyses.

	Phase	BES (n = 9)	EES (n = 15)	R-ZES (n = 15)	P-value
Stent volume (mm^3)	Baseline	321.8 ± 141.8	239.3 ± 124.2	209.8 ± 99.1	
	Follow-up	335.2 ± 157.3	244.2 ± 127.0	216.9 ± 90.5	
	Δ	13.4 ± 25.9	5.0 ± 24.0	7.1 ± 25.3	0.62
Vessel volume (mm^3)	Baseline	489.3 ± 221.7	392.5 ± 212.9	323.3 ± 145.2	
	Follow-up	520.9 ± 261.1	390.2 ± 207.6	338.8 ± 140.6	
	Δ	31.7 ± 57.6	−2.4 ± 36.6	15.5 ± 36.3	0.25
OSPV (mm^3)	Baseline	167.5 ± 85.7	153.2 ± 93.4	113.5 ± 50.0	
	Follow-up	185.8 ± 106.9	145.8 ± 83.5	121.9 ± 57.0	
	Δ	18.3 ± 33.6	−7.4 ± 21.2	8.4 ± 25.6	0.03
%OSPV (%)	Baseline	33.3 ± 5.8	38.2 ± 5.5	34.9 ± 5.6	
	Follow-up	34.6 ± 4.8	36.8 ± 4.5	35.1 ± 6.3	
	Δ	1.3 ± 2.2	−1.5 ± 3.6	0.2 ± 5.7	0.04

Continuous variables are expressed as mean ± SD. OSPV, out-stent plaque volume.

Table 5
Angioscopic comparison among 3 types of G2-DES.

	BES (n = 9)	EES (n = 15)	R-ZES (n = 15)	P-value
Poor NSC (%)	6 (67)	10 (67)	9 (60)	0.92
Presence of YP (%)	5 (56)	1 (7)	1 (7)	0.004
Presence of Th (%)	1 (11)	0 (0)	0 (0)	0.18

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