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Comparison of Neointimal Tissue Characteristics Between Bare-metal and Second-generation Drug-eluting Stents Nine Months after Implantation in Patients with ST-segment Elevation Myocardial Infarction

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Abstract

Background: Neointimal tissue characteristics after implantation of stents are related to late/ very late stent thrombosis and/ or restenosis of target lesion. However, the difference of them has not been fully elucidated among bare-metal stents (BMS) and second-generation drug-eluting stents (DES).

Methods: The present study uses optical coherence tomography (OCT) to compare neointimal tissue characteristics among BMS (n = 22), Endeavor zotarolimus - (E-ZES; n = 21), everolimus - (EES; n = 22) and biolimus A9 - (BES; n = 23) eluting stents in the patients with STEMI who underwent follow-up coronary angiography at nine months after stent implantation.

Results: Quantitative coronary angiography revealed significantly higher restenosis rates for BMS and E-ZES than EES and BES. OCT showed significantly lower and higher rates for covered and uncovered EES, respectively, than for BMS and E-ZES. The malapposition rate for E-ZES was significantly lower than those of other two types of DES. The neointima of EES and BES was significantly thinner than that of BMS and E-ZES. Evagination was more prevalent in BES among the four stents, and the rate of evagination/strut significantly correlated with positive remodeling (r = 0.312, p = 0.006).

Conclusion: Neointimal tissue characteristics were different among BMS and second-generation DES at nine months after implantation into patients with STEMI. This might be related to the differences of future cardiac events.

Keywords: Optical coherence tomography; Intravascular ultrasound; Neointimal coverage; Evagination

Introduction

Drug eluting stents (DES) reduce target-vessel revascularization more effectively than bare metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) [1,2]. However, the risk of late and very late stent thrombosis is potentially higher for these devices [3-7]. The first-generation DES, namely sirolimus (SES) and paclitaxel- (PES) eluting stents are associated with an increased risk of ST caused by delayed healing, uncovered struts, persistent fibrin deposition, late acquired malapposition and neoatherosclerosis [8-10]. Indeed, the risk is likely to be increased in patients with STEMI because implanting metallic devices within a thrombotic environment caused by plaque disruption in the setting of myocardial infarction could enhance thrombus formation [11]. Evaluations of primary outcomes including target lesion failure and a composite of cardiac death, myocardial infarction and target-lesion revascularization have shown that second-generation DES such as zotarolimus- (ZES), everolimus- (EES) and biolimus A9 - (BES) eluting stents are safer and more effective than BMS and/or first-generation DES for patients with STEMI [12-14]. However, it is not fully understood about differences in morphological features among second-generation DES implanted in STEMI patients.

Optical coherence tomography (OCT) is a novel intravascular imaging modality that allows clear visualization of the features of intracoronary plaque and deployed stents such as endothelial coverage and late acquired stent malapposition that are linked to late stent thrombosis [15].

Here, we used OCT to compare neointimal coverage, stent strut apposition, microvessels and evagination among second-generation DES [Endeavor-ZES (E-ZES), EES and BES] and BMS in patients with STEMI at nine months after implantation.

Methods

Study population

We prospectively evaluated patients who underwent percutaneous coronary intervention (PCI) using BMS (Driver; Medtronic, Santa Rosa, CA, USA; n = 22), E-ZES (Endeavor; Medtronic, Santa Rosa, CA, USA; n = 21), EES (Xience V; Abbott Vascular, Santa Clara, CA, USA; n = 22), or BES (Nobori; Terumo, Tokyo, Japan; n = 23) within 24 h of the onset of STEMI at Sasebo City General Hospital between

October, 2011 and April, 2013. They were also assessed by coronary angiography (CAG) and OCT at nine months after implantation. The type of stent deployed was changed every 2 – 3 months in each of 4 successive groups consisting of approximately 20 patients. We defined STEMI as chest pain that persisted for >30 minutes, new ST-segment elevation of at least 0.1 mV in two or more contiguous leads on 12-lead electrocardiograms and total creatine kinase levels that were more than twice the normal upper limit [16]. The exclusion criteria comprised left main trunk disease, bypass grafts, cardiogenic shock, low ejection fraction (≤35%), renal insufficiency with baseline creatinine ≥2.0 mg/dL, in-stent lesions and <2.3 or >3.75 mm of reference vessel diameter according to quantitative coronary angiography. This study complied with the Declaration of Helsinki with regard to investigations in humans, and the Ethics Committee of Sasebo City General Hospital approved the protocol. All participants provided written, informed consent before enrollment in the study.

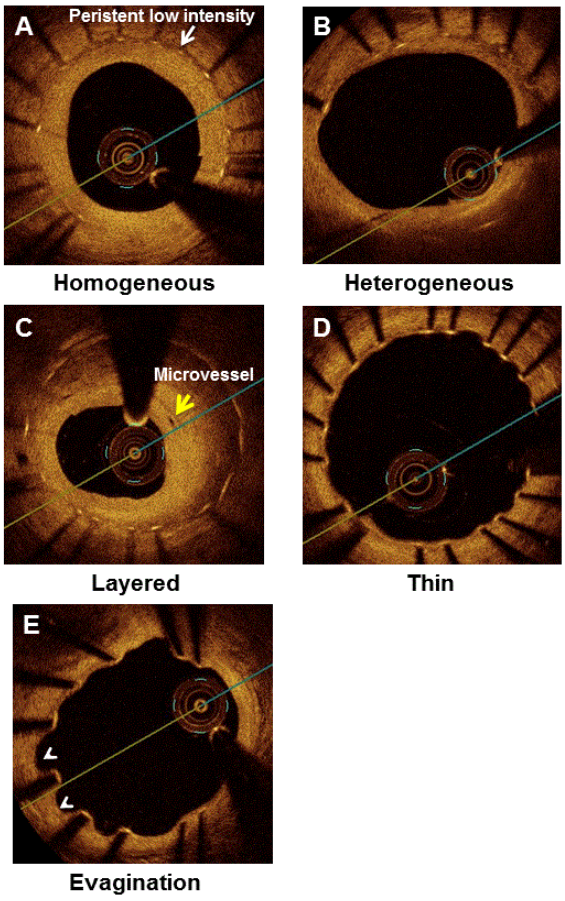

Figure 1: Neointimal structure assessed using optical coherence tomography. Homogeneous (A) and heterogeneous (B) neointimal intensity. Layered neointima comprises higher-, inside lower-intensity tissue (C). Thin neointima (D). Evagination (E, white arrowhead). Peri-stent low intensity around strut (white arrow). Microvessel (<200 μm) has low intensity within intima (yellow arrow).

Percutaneous coronary intervention (PCI)

All patients were administered with aspirin (100 mg) and clopidogrel (300 mg) before PCI started, and heparin (5000-IU bolus) was administered as required during PCI. Most patients underwent thrombus aspiration. The apposition of stent struts was confirmed by intravascular ultrasound (IVUS). The patients started daily dual antiplatelet therapy with aspirin (100 mg) and clopidogrel (75 mg) from the day after PCI.

Angiographic analysis

The minimum lumen diameter (MLD) and reference vessel diameter (RVD) were measured by quantitative coronary angiography using the CAAS System (Pie Medical Instruments, Maastricht, The Netherlands) and then % diameter stenosis, acute gain, and late loss were calculated.

IVUS image acquisition and analysis

We acquired IVUS images using the Galaxy 2 IVUS imaging system (Boston Scientific, Natick, MA, USA) and a 40-MHz Atlantis Pro Imaging catheter (Boston Scientific) during automated motorized pullback at 1.0 mm/s. Images were digitally stored for subsequent offline analysis.

The IVUS data were analyzed using validated EchoPlaque 3.0 software (INDEC Medical Systems, Santa Clara, CA, USA) according to the American College of Cardiology Clinical Expert Consensus Document [17]. Lumen cross-sectional area (CSA) and external elastic membrane (EEM) were quantified on cross-sectional images and plaque area was calculated as EEM minus lumen CSA. Plaque area rates were calculated as plaque plus media divided by EEM CSA. The remodeling index (RI) was defined as EEM CSA at the target lesion divided by EEM CSA at the average reference, and RI > 1.05 was taken as positive remodeling [18].

Acquisition and analysis of OCT images

Patients were assessed by OCT using an ILUMIENTM OCT Imaging System (LightLab Imaging Inc., Westford, MA, USA) with a C7 DragonflyTM imaging catheter at nine months after PCI. The OCT images were acquired using automated pullback at a rate of 20 m/s immediately after contrast medium was infused via an auto-injector at a rate of 3 - 4.5 mL/s.

An experienced observer who was blinded to the patients' information analyzed the OCT data using an offline review workstation (LightLab Imaging Inc., Westford, MA, USA). Images of cross sections were analyzed at 1-mm intervals (every 5 frames). The number of stent struts, rates of covered/uncovered struts, malapposed covered/uncovered struts and of covered/uncovered branches as well as neointimal thickness/area were evaluated. An uncovered strut was defined as a strut without intima inside the stent. Malapposition was defined as separation of the center of the stent strut from the inner lumen by a distance that exceeded the thickness of the polymer plus the stent strut (BMS, E-ZES, EES and BES: 91, 110, 90 and 135μm, respectively).

We classified structure according to neointimal intensity and thickness as homogeneous, heterogeneous, layered or thin (Figure 1) [19]. The intensity of the intima was defined as homogeneous or heterogeneous. A higher intensity within a lower-intensity intima was

defined as layered. Intima in which detailed properties could not be evaluated was defined as thin.

Low intensity around a stent strut was defined as peri-stent low intensity. Round structures of <200 μm and with low intensity within intima were defined as microvessels.

	BMS	E-ZES	EES	BES	P
	(n = 22)	(n = 21)	(n = 22)	(n = 23)	
Baseline					
Age (y)	65.0 ± 12.2	68.6 ± 12.8	67.2 ± 14.3	72.9 ± 10.6	NS
Male	16 (72.7%)	16 (76.2%)	14 (63.6%)	16 (69.6%)	NS
Hypertension	15 (68.2%)	15 (71.4%)	15 (68.2%)	17 (73.9%)	NS
Diabetes	8 (36.4%)	5 (23.8%)	10 (45.5%)	5 (21.7%)	NS
Dyslipidemia	18 (81.8%)	18 (85.7%)	19 (86.4%)	18 (78.3%)	NS
Smoking	15 (68.2%)	11 (52.4%)	9 (40.9%)	11 (47.8%)	NS
Myocardial injury factors					
Onset-to-balloon duration (min)	622.3 ± 1010.1	457.6 ± 518.8	340.9 ± 404.5	335.7 ± 330.0	NS
Max creatine kinase (mg/dL)	2694.6 ± 2206.5	2270.9 ± 2144.7	2373.9 ± 2137.8	3243.7 ± 2895.6	NS

BMS: Bare Metal Stents; BES: Biolimus A9-Eluting Stent; EES: Everolimus-Eluting Stent; E-ZES: Endeavor Zotarolimus-Eluting Stent; Hba1c: Hemoglobin A1c; LDL: Low-Density Lipoprotein; NS: No Significant Difference.

Table 1: Baseline demographics of patients.

A coronary evagination was defined as the presence of an outward bulge in the luminal vessel contour between apposed struts with a maximum depth of the bulge exceeding that of the actual strut thickness [20,21]. Evagination/strut was calculated as evagination number divided by stent strut number. The diameter and area of stents and the lumen were also measured. Overlapping sites of stents were excluded from evaluation.

Statistical analysis

The normal distribution of continuous values was tested using the Shapiro-Wilk's test and results are expressed as means ± SD and. Categorical variables were compared using the chi-square test or Fisher's exact test. Multiple groups of independent were analyzed a one-way ANOVA followed by Tukey's post hoc test (acute gain, RVD, MLD, EEM CSA, and plaque area) or the Kruskal-Wallis test followed by post hoc Steel-Dwass multiple comparison tests. Correlations between two variables were evaluated using Spearman's rank correlation coefficient. All data were statistically analyzed using JMP Pro10.0 for Windows (SAS Institute, Tokyo, Japan,). $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the baseline clinical demographics of the patients implanted with the four types of stents. Age, the proportions of males and risk factors for coronary artery diseases including hypertension, diabetes, and dyslipidemia did not differ among the patients. Factors associated with myocardial injury, onset-to-balloon duration and maximum creatine kinase levels also did not significantly differ. Parameters associated with PCI, target lesion, diameter of stenosis, number of stents, thrombolysis in myocardial infarction grades and mean stent diameter/length did not significantly differ among the groups. The IVUS findings before vasodilation at the acute phase, such as EEM CSA, lumen CSA, plaque area, remodeling index, and the number of attenuations were comparable among the groups (Table 2). Significant differences in RVD, MLD and diameter stenosis before and after PCI at the acute phase were not identified by quantitative coronary angiography (Table 3).

Among the medical agents administered at the follow-up CAG, the proportion of dual antiplatelet therapy was lower in the BMS than in the other groups. Ejection fraction determined by echocardiography, lipid profiles, glucose metabolism and renal function did not significantly differ (Table 4). Follow-up quantitative coronary angiography revealed a significantly smaller in-stent MLD, and significantly larger in-stent late loss and in-stent diameter stenosis in BMS than EES and BES. Furthermore, in-stent MLD was significantly smaller for E-ZES than BES, and significantly larger in-stent late loss and in-stent diameter stenosis than EES and BES (Table 3). Target-vessel revascularization rates tended to be higher in BMS and E-ZES than in EES and BES (13.6%, 4.8%, 0% and 0%, respectively).

We used OCT to evaluate neointimal tissues in 490, 564, 536 and 622 cross-sections and in 6510, 7952, 6516 and 6858 BMS, E-ZES, EES and BES struts, respectively, at nine months of follow-up. The E-ZES have more crowns and thus more struts than EES. Table 5 and Figure 2 show the OCT findings. The rates of covered and uncovered struts did not differ between BMS and E-ZES, whereas those of EES were significantly lower and higher, respectively, among the four types of stents. No E-ZES struts were malapposed. The malapposition rate was significantly higher for EES and BES than for E-ZES. The rates of covered and uncovered struts in malapposed portions were significantly higher in EES than in E-ZES, and the rates of covered BES were higher than those of E-ZES. Mean stent areas and mean lumen

areas tended to be smaller and larger, respectively, in EES and BES than in BMS and E-ZES, but the difference did not reach statistical significance. The maximum neointimal area was significantly larger in BMS than in EES and BES, and that of E-ZES was also significantly larger than that of BES. Mean neointimal area was the largest and the neointima was thicker in the order of BMS, E-ZES, EES and BES. Significant differences were evident between BMS vs. EES or BES, and between E-ZES vs. EES or BES (all $p < 0.001$).

	BMS	E-ZES	EES	BES	P
	(n =22)	(n =21)	(n =22)	(n = 23)	
Target lesion					NS
Right coronary artery	12 (54.5%)	6 (28.6%)	7 (31.8%)	7 (30.4%)	
Left anterior descending artery	6 (27.3%)	13 (61.9%)	9 (40.9%)	13 (56.5%)	
Left circumflex artery	4 (18.2%)	2 (9.5%)	6 (27.3%)	3 (13.0%)	
Number and size of stents					
Number of stents	1.0 ± 0.21	1.1 ± 0.36	1.2 ± 0.53	1.2 ± 0.39	NS
Mean stent diameter (mm)	3.31 ± 0.52	3.20 ± 0.32	3.05 ± 0.38	3.05 ± 0.37	NS
Mean stent length (mm)	21.1 ± 5.8	24.9 ± 5.0	21.6 ± 4.5	23.0 ± 4.2	NS
Coronary angiographic findings					
Diameter stenosis (%)a	98.3 ± 3.0	99.2 ± 1.2	99.0 ± 1.9	99.1 ± 2.3	NS
TIMI grade	0.91 ± 1.3	0.95 ± 1.1	1.0 ± 1.3	0.52 ± 0.9	NS
Intravascular ultrasound findings					
EEM CSA (mm2)	17.9 ± 6.9	15.1 ± 4.8	17.1 ± 5.6	16.8 ± 6.0	NS
Lumen CSA (mm2)	2.42 ± 1.14	1.92 ± 0.78	2.14 ± 0.50	1.75 ± 0.57	NS
Plaque area (mm2)	15.3 ± 6.6	13.1 ± 4.7	15.0 ± 5.6	15.3 ± 5.7	NS
Plaque area rate (%)	0.85 ± 0.06	0.87 ± 0.06	0.87 ± 0.04	0.89 ± 0.04	NS
Remodeling index	1.15 ± 0.26	1.24 ± 0.33	1.26 ± 0.25	1.31 ± 0.24	NS
Attenuation	10 (47.6%)	7 (38.9%)	10 (55.6%)	9 (39.1%)	NS

BMS: Bare Metal Stents; BES: Biolimus A9-Eluting Stent; CSA: Cross-Sectional Area A Diameter Stenosis According to American Heart Association Classification; EEM: External Elastic Membrane; EES: Everolimus-Eluting Stent; E-ZES: Endeavor Zotarolimus-Eluting Stent; NS: No Significant Difference; TIMI: Thrombolysis In Myocardial Infarction.

Table 2: Coronary angiographic and intravascular ultrasound findings at baseline.

	BMS	E-ZES	EES	BES	P
	(n = 22)	(n = 21)	(n = 22)	(n = 23)	
Before PCI					
Reference vessel diameter (mm)	2.82 ± 0.48	2.80 ± 0.42	2.79 ± 0.47	2.88 ± 0.78	NS
Minimum lumen diameter (mm)	0.05 ± 0.10	0.02 ± 0.04	0.03 ± 0.05	0.02 ± 0.05	NS
Diameter stenosis (%)	98.3 ± 3.0	99.2 ± 1.3	99.1 ± 1.9	99.1 ± 2.3	NS
After PCI (In-stent)					
Reference vessel diameter (mm)	3.24 ± 0.49	3.11 ± 0.31	2.94 ± 0.33	3.01 ± 0.42	NS
Minimum lumen diameter (mm)	2.91 ± 0.42	2.77 ± 0.27	2.64 ± 0.34	2.65 ± 0.40	NS
Acute gain (mm)	2.87 ± 0.40	2.74 ± 0.25	2.58 ± 0.37	2.64 ± 0.40	NS

Diameter stenosis (%)	9.60 ± 6.06	10.90 ± 5.61	10.36 ± 5.55	11.43 ± 4.98	NS
Follow-up CAG(In-stent)					
Reference vessel diameter (mm)	3.00 ± 0.68	2.87 ± 0.33	2.86 ± 0.36	2.99 ± 0.41	NS
Minimum lumen diameter (mm)	1.86 ± 0.62	2.09 ± 0.53	2.43 ± 0.42a	2.53 ± 0.40c,e	< 0.001
Late loss (mm)	1.05 ± 0.49	0.68 ± 0.46	0.26 ± 0.25b,d	0.15 ± 0.20c,f	< 0.001
Diameter stenosis (%)	38.2 ± 19.0	27.1 ± 17.1	14.9 ± 8.0b,d	14.8 ± 4.9c,e	< 0.001

BMS: Bare Metal Stents; BES: Biolimus A9-Eluting Stent; CAG: Coronary Angiography EES: Everolimus-Eluting Stent; E-ZES: Endeavor Zotarolimus-Eluting Stent; NS: No Significant Difference; PCI: Percutaneous Coronary Intervention. AP < 0.05: BMS Vs. EES; BP < 0.01: BMS Vs. EES; CP < 0.01: BMS Vs. BES; DP < 0.05: E-ZES Vs. EES; EP < 0.05: E-ZES Vs. BES; FP < 0.01: E-ZES Vs. BES.

Table 3: Quantitative coronary angiographic findings before and after percutaneous coronary intervention and at follow-up coronary angiography.

	BMS	**E-ZES**	**EES**	**BES**	**P**
	(n =22)	**(n = 21)**	**(n = 22)**	**(n = 23)**	
Follow-up duration (days)	274.0 ± 16.2	278.3 ± 15.2	279.3 ± 30.17	286.5 ± 16.9	NS
Medicines					
Anti-hypertension drugs	17 (77.3%)	15 (71.4%)	15 (68.2%)	17 (73.9%)	NS
Calcium antagonists	7 (31.8%)	11 (52.4%)	8 (36.4%)	9 (39.1%)	NS
Angiotensin II receptor blockers	14 (63.6%)	11 (52.4%)	15 (65.2%)	13 (56.5%)	NS
Statins	18 (81.8%)	18 (85.7%)	18 (81.8%)	18 (78.3%)	NS
Oral diabetic drugs	4 (18.2%)	2 (9.5%)	7 (31.8%)	3 (13.0%)	NS
Insulin	1 (4.5%)	2 (9.5%)	2 (9.1%)	0 (0%)	NS
Dual antiplatelet therapy	19 (86.4%)a	21 (100%)	22 (100%)	23 (100%)	0.025
Blood data					
HbA1c (%)	6.26 ± 0.86	6.10 ± 1.09	6.12 ± 0.67	6.09 ± 0.66	NS
LDL-cholesterol (mg/dL)	108.8 ± 34.9	109.8 ± 28.2	105.6 ± 30.0	119.8 ± 39.0	NS
eGFR (ml/min/1.73 mm2)	67.7 ± 17.6	67.0 ± 22.4	64.1 ± 23.8	58.5 ± 11.9	NS
Cardiac function					
Ejection fraction by echocardiography (%)	58.7 ± 11.3	59.0 ± 10.2	57.5 ± 13.2	57.3 ± 11.9	NS

BMS: Bare Metal Stents; BES: Biolimus A9-Eluting Stent; EES: Everolimus-Eluting Stent; EGFR: Estimated Glomerular Filtration Rate; E-ZES: Endeavor Zotarolimus-Eluting Stent; Hba1c: Hemoglobin A1c; LDL: Low-Density Lipoprotein; NS: No Significant Difference.

Asignificant Difference: BMS Vs. E-ZES: EES: And BES.

Table 4: Medicines, blood data and cardiac functions of patients at follow-up coronary angiography.

The neointimal structure was most frequently homogeneous and the neointima was thin only in BES. The proportion of peri-stent low intensity was similar among the four stents. Significantly more microvessels were evident in BMS and E-ZES than in EES and BES and evagination was more prevalent and deeper in BES than in the other three stents. Evagination was significantly more frequent in EES than in E-ZES. In addition, remodeling index significantly correlated with evagination/strut (r = 0.312, p = 0.006; Figure 3). Table 1 shows the baseline clinical demographics of the patients implanted with the four types of stents. Age, the proportions of males and risk factors for coronary artery diseases including hypertension, diabetes, and dyslipidemia did not differ among the patients. Factors associated with myocardial injury, onset-to-balloon duration and maximum creatine kinase levels also did not significantly differ. Parameters associated with PCI, target lesion, diameter of stenosis, number of stents, thrombolysis in myocardial infarction grades and mean stent diameter/length did not significantly differ among the groups. The IVUS findings before vasodilation at the acute phase, such as EEM

CSA, lumen CSA, plaque area, remodeling index, and the number of attenuations were comparable among the groups (Table 2). Significant differences in RVD, MLD and diameter stenosis before and after PCI at the acute phase were not identified by quantitative coronary angiography (Table 3).

	BMS	E-ZES	EES	BES	P
	(n = 22)	(n = 21)	(n = 22)	(n = 23)	
Strut analysis					
Covered rate (%)	98.4 ± 3.0	99.0 ± 1.6	93.7 ± 4.4b,f	96.4 ± 4.6g,i	< 0.001
Uncovered rate (%)	0.17 ± 0.40	0.18 ± 0.49	3.58 ± 2.11b,f	0.99 ± 1.19c,h,j	< 0.001
Malapposed rate (%)	0.82 ± 2.65	0	1.73 ± 3.42f	1.77 ± 3.95h	< 0.001
Malapposed/ covered rate (%)	0.46 ± 1.04	0	1.1 ± 2.83e	1.73 ± 3.94h	0.001
Malapposed/ uncovered rate (%)	0.36 ± 1.71	0	0.63 ± 1.29e	0.05 ± 0.16	0.001
Branch covered rate (%)	0.55 ± 0.81	0.79 ± 1.17	0.81 ± 0.80	0.84 ± 1.02	NS
Branch uncovered rate (%)	0.05 ± 0.19	0.08 ± 0.16	0.15 ± 0.37	0.02 ± 0.07	NS
Measurement of lumen and neointima					
Mean stent area (mm2)	9.37 ± 3.18	8.47 ± 1.66	7.76 ± 2.12	7.96 ± 1.91	NS
Mean lumen area (mm2)	6.13 ± 2.33	6.05 ± 1.52	6.93 ± 2.09	7.29 ± 1.93	NS
Minimum lumen area (mm2)	4.18 ± 1.96	4.33 ± 1.89	5.43 ± 1.95	5.66 ± 1.95	NS
Maximum neointimal area (mm2)	20.90 ± 22.04	7.68 ± 12.16	8.11 ± 10.96a	3.51 ± 8.03d,h	< 0.001
Mean neointimal area (mm2)	3.25 ± 1.30	2.43 ± 1.01	0.85 ± 0.43b,f	0.67 ± 0.29d,h	< 0.001
Mean neointimal area rate (%)	35.2 ± 10.8	28.5 ± 10.1	11.5 ± 5.5b,f	9.2 ± 4.8d,h	< 0.001
Mean neointimal thickness (μm)	346.8 ± 116.2	267.0 ± 121.6	93.4 ± 45.5b,f	73.4 ± 34.3d,h	< 0.001
Neointimal structure					
Main tissue structure (homo/ hetero/ layered/thin)	21/ 1/ 0/ 0	21/ 0/ 0/ 0	18/ 2/ 2/ 0	19/ 0/ 1/ 3	NS
Peri-stent low-intensity	16 (72.7%)	16 (76.2%)	16 (72.7%)	14 (60.9%)	NS
Microvessels	8 (36.4%)	9 (42.9%)	0 (0%)b,f	0 (0%)d,h	0.005
Evagination (total number/lesion)	2.32 ± 4.55	0.10 ± 0.30	8.05 ± 15.03f	25.96 ± 40.45d,h,i	<0.001
Evagination/strut (%)	0.80 ± 1.63	0.02 ± 0.07	2.45 ± 4.78e	8.12 ± 10.03d,h,i	<0.001
Mean evagination depth (μm)	61.0 ± 87.2	17.1 ± 55.0	93.7 ± 89.6e	168.5 ± 62.8d,h,i	<0.001

BMS: Bare Metal Stents; BES: Biolimus A9-Eluting Stent; EES: Everolimus-Eluting Stent; E-ZES: Endeavor Zotarolimus-Eluting Stent. A P < 0.05: BMS Vs. EES; B P < 0.01: BMS Vs. EES; C P < 0.05: BMS Vs. BES; D P < 0.01: BMS Vs. BES; E P < 0.05: E-ZES Vs. EES; F P < 0.01: E-ZES Vs. EES; G P < 0.05: E-ZES Vs. BES; H P < 0.01: E-ZES Vs. BES; I P < 0.05: EES Vs. BES; J P < 0.01: EES Vs. BES.

Table 5: Optical coherence tomographic findings at follow-up coronary angiography.

Among the medical agents administered at the follow-up CAG, the proportion of dual antiplatelet therapy was lower in the BMS than in the other groups. Ejection fraction determined by echocardiography, lipid profiles, glucose metabolism and renal function did not significantly differ (Table 4). Follow-up quantitative coronary angiography revealed a significantly smaller in-stent MLD, and significantly larger in-stent late loss and in-stent diameter stenosis in BMS than EES and BES. Furthermore, in-stent MLD was significantly smaller for E-ZES than BES, and significantly larger in-stent late loss and in-stent diameter stenosis than EES and BES (Table 3). Target-vessel revascularization rates tended to be higher in BMS and E-ZES than in EES and BES (13.6%, 4.8%, 0% and 0%, respectively).

We used OCT to evaluate neointimal tissues in 490, 564, 536 and 622 cross-sections and in 6510, 7952, 6516 and 6858 BMS, E-ZES, EES and BES struts, respectively, at nine months of follow-up. The E-ZES have more crowns and thus more struts than EES. Table 5 and Figure 2 show the OCT findings. The rates of covered and uncovered struts did not differ between BMS and E-ZES, whereas those of EES were

significantly lower and higher, respectively, among the four types of stents. No E-ZES struts were malapposed. The malapposition rate was significantly higher for EES and BES than for E-ZES. The rates of covered and uncovered struts in malapposed portions were significantly higher in EES than in E-ZES, and the rates of covered BES were higher than those of E-ZES. Mean stent areas and mean lumen areas tended to be smaller and larger, respectively, in EES and BES than in BMS and E-ZES, but the difference did not reach statistical significance. The maximum neointimal area was significantly larger in BMS than in EES and BES, and that of E-ZES was also significantly larger than that of BES. Mean neointimal area was the largest and the neointima was thicker in the order of BMS, E-ZES, EES and BES. Significant differences were evident between BMS vs. EES or BES, and between E-ZES vs. EES or BES (all $p < 0.001$).

The neointimal structure was most frequently homogeneous and the neointima was thin only in BES. The proportion of peri-stent low intensity was similar among the four stents. Significantly more microvessels were evident in BMS and E-ZES than in EES and BES and evagination was more prevalent and deeper in BES than in the other three stents. Evagination was significantly more frequent in EES than in E-ZES. In addition, remodeling index significantly correlated with evagination/strut ($r = 0.312$, $p = 0.006$; Figure 3).

Discussion

The main findings of this study were as follows. Neointimal proliferation was more prevalent and rates of covered struts and microvessels were higher in BMS and E-ZES whereas rates of uncovered and malapposed struts were higher in EES and BES. Evagination was most prevalent in BES among the four types of stents. In addition, evagination was associated with positive remodeling of the target lesion. The intensity of most neointimal structures assessed by OCT was homogeneous. A thin structure was evident only in BES.

Primary PCI with stents is the currently recommended treatment for STEMI. Coronary stents reduce target-vessel revascularization in STEMI compared with balloon angioplasty [22,23]. Furthermore, a study found that the incidence of in-stent restenosis and subsequent target-vessel revascularization was significantly lower for first-generation DES than for BMS, although a benefit in terms of death and/or reinfarction was not identified [24]. This could be due to increased risk of stent thrombois, which is considered a main cause of late cardiac death [4] and deploying DES in patients with STEMI might put them at increased risk for stent thrombosis. The inhibition of neointimal formation by DES can lead to delayed neointimal coverage and incomplete endothelialization, which might in turn be associated with an increased proportion of uncovered stent struts and the subsequent occurrence of stent thrombosis [8,10]. This concern is particularly relevant to first-generation DES. Second-generation DES have upgraded stent materials and more biodurable polymers that have increased their safety and efficacy compared with first-generation DES [25,26]. In the present study, we did not investigate differences in the incidence of stent thrombosis among the second-generation DES because stent thrombosis did not arise during the first nine months follow-up.

OCT can visualize neointimal tissue characteristics and stent malapposition, which allows accurate in vivo strut-level analysis with higher resolution than angioscopy and other imaging modalities. OCT has associated a thicker neointima and a lower frequency of uncovered and malapposed struts with EES compared with SES in patients with STEMI, although both types of stents equally suppress intimal proliferation in culprit lesions [27]. The features of E-ZES and BMS determined by OCT in the present study were similar, namely lower rates of uncovered and malapposed struts, but more neointimal coverage and microvessels, as well as a thicker neointima than the other two DES. These results agreed with the findings of the Optical Coherence Tomography in Acute Myocardial Infarction (OCTAMI) study that found no differences between E-ZES and BMS in the ratio (%) of uncovered/malapposed struts, maximum length of uncovered/malapposed segments, and neointimal responses [28].

Nishinari et al. found an obviously increased rate of neointimal coverage between two and four weeks after E-ZES deployment and that coverage with a thicker neointima was 99.2% complete by 10 weeks thereafter in patients with stable angina pectoris [26]. The cumulative five-year incidence of MI and combined cardiac death/MI were significantly lower, and that of definite/probable stent thrombosis tended to be lower for E-ZES than for first-generation DES, whereas target-lesion revascularization was comparable between the two groups [25].

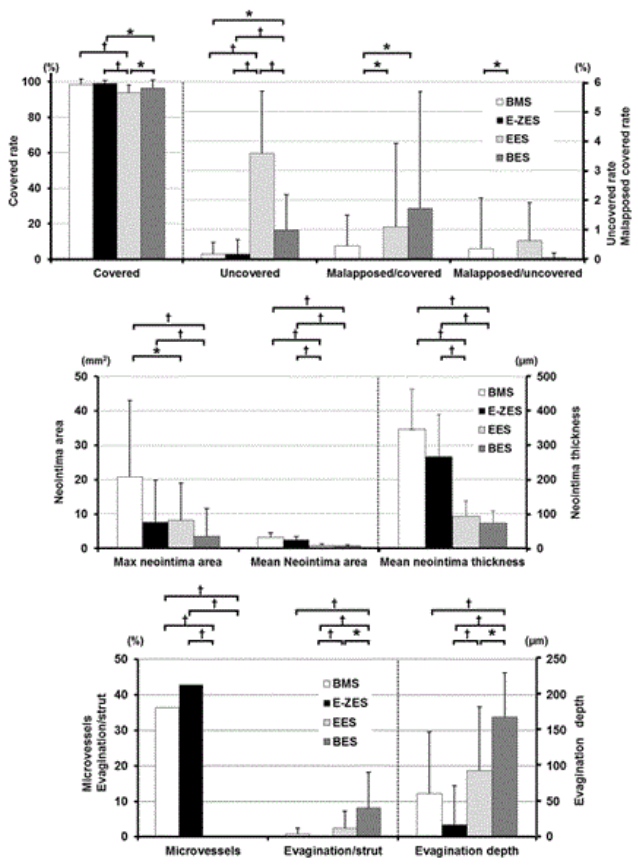

Figure 2: Comparison of neointimal tissue characteristics and strut malapposition assessed by optical coherence tomography. BES, biolimus A9-eluting stent; BMS, bare metal stent; EES, everolimus-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent. * $p < 0.05$; † $p < 0.01$.

The overall incidences of target lesion failure and definite stent thrombosis at one year after unrestricted ZES and EES deployment determined from a real-world registry were low and comparable, indicating that these second-generation DES were equally safe and effective [13]. In contrast, a meta-analysis demonstrated that E-ZES was inferior to other limus-eluting stents in terms of target-lesion revascularization [29].

Evagination or late acquired malapposition has been identified after the deployment of first-generation DES [30], and they are linked to increased risk for late stent thrombosis [20,31]. We found more frequent evagination and a thin neointima with BES among the four stents. This might be due to BES having thick struts with a large amount of biodegradable polymer (polylactic acid) coated only on the abluminal side of the stent surface [32]. Recent network meta-analyses have shown that biodegradable polymer-BES was associated with a higher risk of stent thrombosis than durable polymer-EES [33,34]. In addition, we found that evagination was significantly associated with positive remodeling. Radu et al. showed that major evagination detected by OCT is essentially absent in E-ZES and EES and that it is associated with positive vessel remodeling [21]. Furthermore, a higher remodeling index is an independent predictor of late stent thrombosis caused by DES [31]. Thus, late or very late stent thrombosis might occur in patients implanted with BES. A longitudinal, prospective study is needed to determine whether the increased evagination in BES is associated with the occurrence of stent thrombosis.

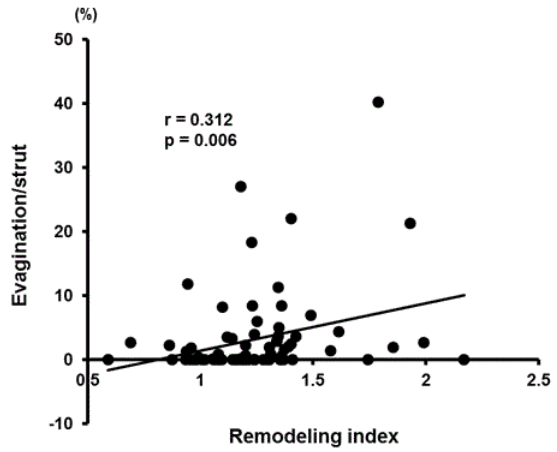

Figure 3: Correlation between remodeling index and evagination.

This study had a number of limitations. This study included a small patient cohort from a single center, and the follow-up period was quite short. The selection of stents depended on the period of primary PCI for patients with STEMI, but the characteristics of the patients implanted with the four types of stents and of target lesions did not significantly differ. Only STEMI patients were enrolled in this study. Kubo, et al. demonstrated using OCT that compared with stable angina patients after implantation of SES, unstable patients had a higher prevalence of intracoronary thrombus before the implantation and a significantly greater incident of inadequately apposed stent and partially uncovered stent by neointima at 9 months' follow-up [35]. Furthermore, Garcia-Garcia et al. reported that the volume of post-procedural intra-stent structure such as prolapse and thrombus positively correlated with neointima formation at 6 months' follow-up, although thrombus aspiration did not affect OCT parameters, such as stent/ lumen areas, percentage of malapposed struts and covered struts, at both post-procedure and 6 months' follow-up in STEMI patients [36]. Thus, intracoronary thrombus in acute phase may have some effects on neointimal tissue characteristics at the follow-up. Finally, conclusions regarding clinical outcomes cannot be definitive because death, cardiac death, MI (de novo at other lesions and/or recurrence) and late or very late stent thrombosis did not occur in our patients.

Conclusions

Neointimal tissue characteristics differed according to OCT among BMS and three types of second-generation DES (E-ZES, EES and BES) at nine months after deployment in patients with STEMI. These differences might be associated with future clinical events, such as late/ very late stent thrombosis, target-lesion revascularization, cardiac/ non-cardiac death and major adverse cardiac events. In addition, differences in neointimal coverage among DES might be associated with differences in the duration of dual antiplatelet therapy administration. A randomized, large-scale study with a longer follow-up is required to identify the most effective second-generation DES for deployment in patients with STEMI.

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