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ORIGINAL PAPER

Early vessel healing after implantation of biodegradable-polymer and durable-polymer drug-eluting stent: 3-month angioscopic evaluation of the RESTORE registry

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Abstract

The purpose of this study was to evaluate the vessel healing status 3 months after stent implantation of bioresorbable-polymer drug-eluting stents (BP-DESs) in comparison with durable-polymer DESs (DP-DESs) by angioscopy. Study design was a single-center all-comer prospective cohort study: the RESTORE registry (UMIN000033009). All patients who received successful angioscopic examination at planned 3-month follow-up after the DES implantation in the native coronary artery were enrolled. We evaluated main, maximum, minimum strut coverage grades and coverage heterogeneity score defined as a difference between maximum and minimum coverage grades. All lesions were divided into three segments: proximal, mid, and distal segments. A total of 108 patients (66.6 ± 10 years) with 124 lesions were analyzed (BP-DES 57 patients 61 lesions 226 segments vs. DP-DES 57 patients 63 lesions 203 segments; six patients had both BP-DES and DP-DES). Patient and lesion demographics, procedural characteristics were well balanced. Main coverage grade (mean ± standard error; 1.08 ± 0.02 vs. 1.05 ± 0.03, p = 0.354) and minimum coverage grade (1.00 ± 0.00 vs. 1.00 ± 0.00, p > 0.999) were not significantly different between BP-DES and DP-DES groups. Maximum coverage grade was significantly higher in the BP-DES than in the DP-DES (1.45 ± 0.04 vs. 1.35 ± 0.04, p = 0.049). Coverage heterogeneity score did not differ between BP-DES and DP-DES groups (1.05 ± 0.07 vs. 0.90 ± 0.07, p = 0.162). At 3-month follow-up, the current BP-DES had higher maximum stent coverage than the contemporary DP-DES, while main and minimum coverage grades and heterogeneity of the neointimal coverage were comparable. Further prospective randomized trials should be conducted to evaluate the clinical significance of the present imaging results.

Keywords Coronary angioscopy · Drug-eluting stent · Biodegradable polymer · Durable polymer

Abbreviations

BP-DES	Bioresorbable-polymer DESs
DES	Drug eluting stent
DP-DES	Durable-polymer DESs
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention

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Introduction

Metallic drug-eluting stent (DES) platforms have evolved towards percutaneous devices with highly compatible antiproliferative drugs and biocompatible durable polymers, supported by thinner backbones. Durable-polymer DESs (DP-DESs), however, had delayed neointimal coverage when compared with bare metal stent (BMS) [1]. The contemporary biodegradable-polymer drug-eluting stents (BP-DESs) have been expected to overcome some of the drawbacks of DP-DESs [2–4]. Abluminal coating technology of the contemporary BP-DESs, Synergy™ (Boston Scientific Corporation, Natick, MA, USA) and Ultimaster™ (Terumo Corp., Tokyo, Japan) is expected to enhance the early neointimal coverage. An imaging study on Ultimaster™ BP-DES presented almost complete coverage of struts at 3-month follow-up on optical coherence tomography (OCT) [5], which could

be interpreted as the expected early vessel healing. This theoretical expectation of the early vessel healing after implantation of the contemporary BP-DES may be supported by a large randomized controlled trial comparing BP-DES with BMS [6]. The SENIOR trial reported that the superiority of Synergy™ BP-DES over BMS in short-term outcomes even with 1-month dual antiplatelet therapy, suggesting that the contemporary BP-DES has, at least, comparable or even better neointimal healing as compared to the BMS [6].

Coronary angioscopy provides substantial information pertaining to macroscopic pathology in living patients. On coronary angioscopy, we can evaluate neointimal coverage, presence of thrombus and atherosclerosis as a yellow plaque [7, 8]. It is easy to differentiate healthy endothelium from fibrin or thrombus deposition based on the color of the neointima on stent struts. Coronary angioscopy would be, therefore, advantageous over OCT especially for the assessment of neointimal coverage. However, there are few reports presenting the intra-coronary angioscopy assessment of the contemporary BP-DESs in comparison with the current DP-DESs.

The purpose of the present study is to evaluate the healing status 3 months after stent implantation of the contemporary BP-DESs as compare to the DP-DESs on coronary angioscopy.

Methods

Study design and population

Study design was a single-center all-comer prospective cohort study: the RESTORE registry (UMIN000033009). No particular exclusion criteria were specified. All patients who received successful angioscopic examination at planned 3 months follow-up (± 1 month) after the DES implantation in the native coronary artery irrespective of clinical presentation (silent myocardial ischemia, stable or unstable angina, ST elevation myocardial infarction, or non-ST elevation myocardial infarction) without any earlier event of stent failure were enrolled from May 2016 to April 2018. Synergy™ and Ultimaster™ were defined as BP-DESs, while Resolute Onyx™ zotarolimus-eluting stent (Medtronic CardioVascular, CA, USA), Xience™ cobalt chromium everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) were categorized as DP-DESs. Written informed consent was obtained from all enrolled patients. This study was approved by the Osaka Police Hospital Ethical Committee.

Procedure

Percutaneous coronary intervention (PCI) strategy was left to the discretion of the individual operators. Dual antiplatelet therapy (DAPT, aspirin and $P2Y_{12}$ inhibitor) was encouraged to keep at least 6 months after the PCI. All patients and treating physicians were asked to adhere to the Guideline of the Japanese Society of Cardiology in terms of tobacco usage, exercise, healthy food intake, maintenance of an adequate body weight, and medications for the achievement of target blood lipid concentrations, and blood pressure control. Three months invasive follow-up (± 1 month) of coronary angiography mainly via radial approach was planned for all patients. Imaging assessment of the stented segment was routinely performed with coronary angioscopy.

Angioscopic examination

The present study aimed to evaluate the status of vessel endothelialization by angioscopy 3 months (± 1 month) after implantation of contemporary DESs. For segment analysis, we divided all stents into three segments, proximal, mid and distal segments. We evaluated neointimal coverage, thrombus and yellow color grade at each segment on angioscopy. The non-occlusion type of angioscopy, VISIBLE (FiberTech Co., Ltd., Tokyo, Japan) was used. Angioscopic observation of the stented lesions was done while blood was cleared away from the viewing area by the injection of 3% dextran-40 [9]. The cases with complete pull back and good image quality as defined by > 70% of analyzable stent lengths were included in this analysis [10]. We repeatedly performed angioscopic observation until we obtained the sufficient image quality. When we cannot achieve the sufficient image quality, these lesions were excluded from the analysis. Figure 1 summarizes the imaging evaluation of angioscopy. Yellow color grade was classified into four grades (0: white, 1: slight yellow, 2: yellow, and 3: intensive yellow) compared with the standard colors [8]. Neointimal coverage was classified into three grades (0: no coverage, 1: poor coverage, 2: complete coverage) [11]. Thrombus was defined as white or red material that had cotton-like or ragged appearance or that presented fragmentation with or without protrusion into lumen or adherent to the luminal surface [12]. Maximum and minimum neointima coverage grade, maximum yellow color grade, and presence or absence of thrombus was determined for each stented lesion. The coverage heterogeneity score was defined as follows: maximum neointimal coverage grade minus minimum neointima coverage grade in each segment [13]. Presence of yellow plaque was defined as the maximum yellow color grade ≥ 2 [14]. Four analysts of angioscopy (SS, YS, TK, and YH) who were blinded to patients' characteristics evaluated the angioscopic images. The inter-observer and intra-observer reproducibility (percent agreement) for the interpretation of angioscopic images in our institution was 95% and 95% for stent coverage, 85% and 95% for plaque color, and 90% and 100% for thrombus, respectively [14].

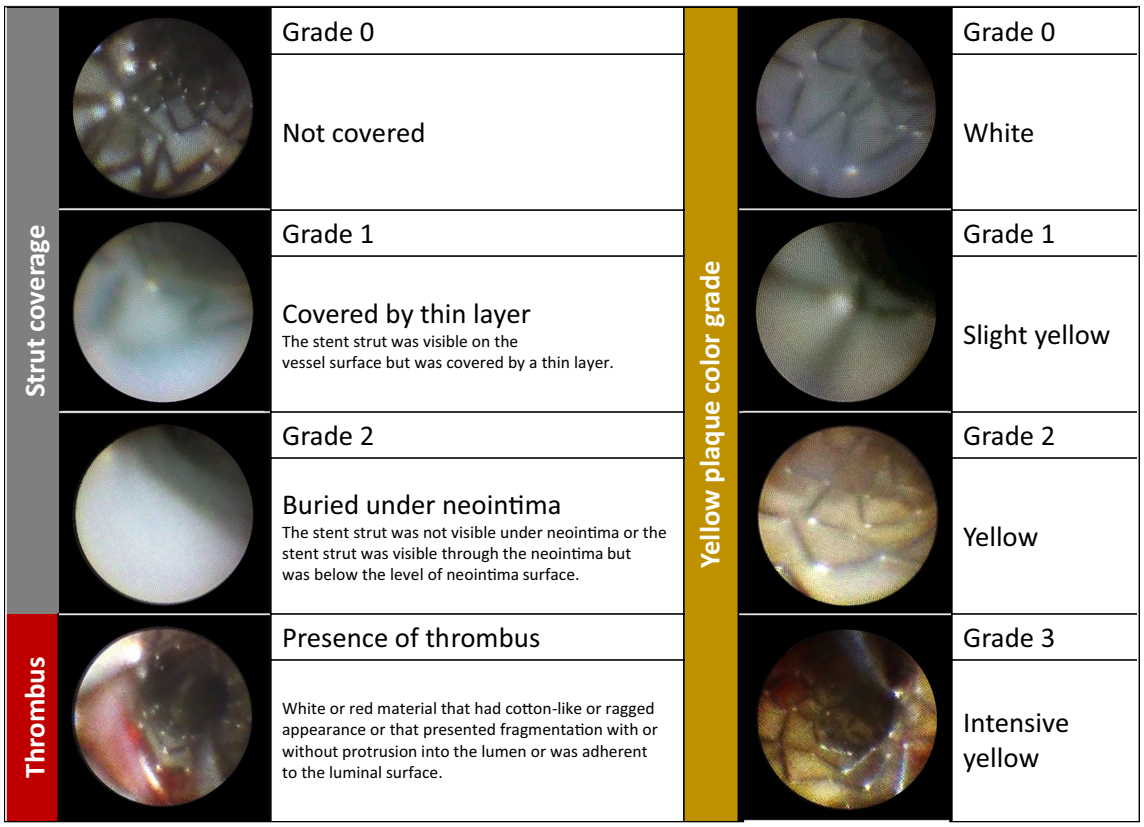

Fig. 1 Image examples of angioscopic evaluation

Statistical analysis

Study population was divided into two groups, BP-DES (Synergy™ and Ultimaster™) vs. DP-DES (Xience™ and Resolute Onyx™) groups. Normality of data distribution was tested by the Kolmogorov–Smirnov test. Data are expressed as mean ± SD or median and inter-quartile range. Group means for continuous variables with normal and non-normal distributions were compared using Student's *t* tests and Mann–Whitney U tests, respectively. Categorical variables were compared using the Pearson's Chi square test or Fischer's exact test, as appropriate. Regarding the angioscopic continuous values, mixed linear model with an assumed Gaussian distribution was used for the comparisons of continuous variables to take into an account the clustered nature of > 1 segment analyzed from the same lesions and patients, which might result in unknown correlations among measurements within the clusters. All statistical analyses were performed with SPSS (version 24.0.0, IBM, New York).

Results

Study population

A total of 110 patients with 126 lesions were enrolled from May 2016 to April 2018. Sufficient image quality of CAS was obtained in 124 lesions out of 126 lesions (98.4%). As a result, a total of 108 patients with 124 lesions (mean age 66.6 ± 10 years) were analyzed (BP-DES 57 patients 61 lesions vs. DP-DES 57 patients 63 lesions; *six patients had both BP-DES and DP-DES) (Fig. 2). The median invasive follow-up duration was 104.6 days [interquartile range: 93, 113.3 days]. Table 1 shows patient and lesion demographics, risk factors, and medication. Serum profiles including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides are not different between both groups. Lesion and procedural characteristics were overall well-balanced (Table 2). Approximately half of the lesions were left anterior descending artery.

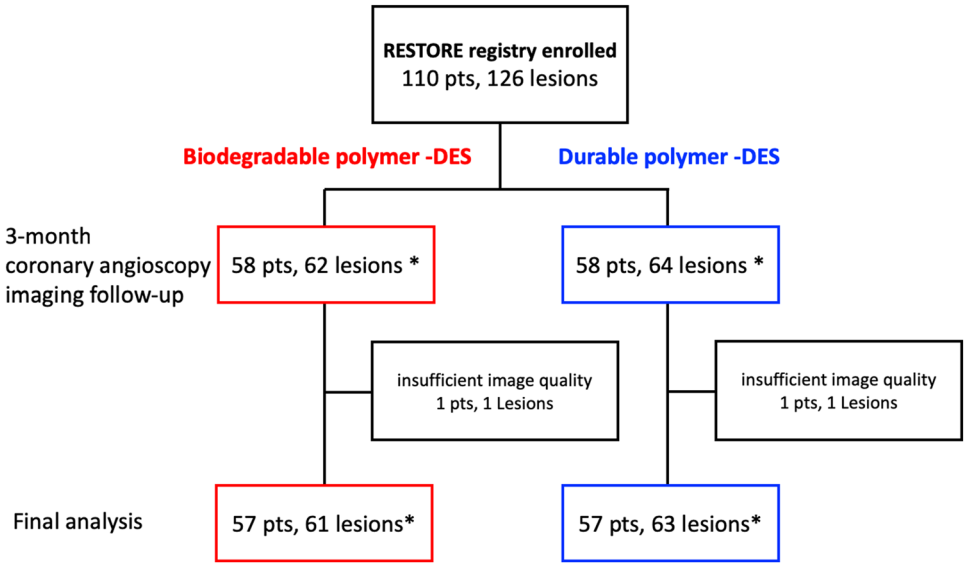

Fig. 2 Patient flowchart. A total of 110 patients with 126 lesions were enrolled from May 2016 to April 2018. Sufficient image quality of CAS was obtained in 124 lesions out of 126 lesions (98.4%). As a result, a total of 108 patients with 124 lesions were analyzed (biodegradable polymer-DES 57 patients 61 lesions vs. durable polymer-DES 57 patients 63 lesions).*Six patients had both BP-DES and DP-DES. Abbreviations: coronary angioscopy, CAS; drug-eluting stent, DES

Table 1 Baseline characteristics

	BP-DES Patient number = 57*	DP-DES Patient number = 57*	P value
Age (years)	65.4 ± 10.01, 67.00 [59.00, 74.00]	67.63 ± 9.56, 68.00 [62.00, 75.00]	0.360
Body mass index (kg/m^2)	24.59 ± 3.89, 24.10 [21.87, 26.55]	25.39 ± 3.34, 25.00 [22.70, 27.70]	0.179
Male	48/57 (84.2)	50/57 (87.7)	0.788
diabetes mellitus	30/57 (52.6)	32/57 (56.1)	0.851
Hypertension	44/57 (77.2)	49/57 (86.0)	0.218
Current smoker	45/57 (78.9)	42/57 (73.7)	0.660
Serum lipid profile at 3-month follow-up (mg/dl)			
Low-density lipoprotein cholesterol	85.86 ± 23.64, 83.50 [66.00, 101.25]	80.26 ± 20.30, 79.00 [68.00, 98.00]	0.180
High-density lipoprotein cholesterol	49.61 ± 15.25, 45.50 [40.75, 56.00]	45.93 ± 12.14, 43.00 [38.00, 53.00]	0.185
Triglycerides	156.84 ± 119.87, 120.50 [87.50, 204.75]	138.88 ± 80.88, 115.00 [86.00, 177.00]	0.619
Medication at 3-month follow-up			
Statin	44 (77.2)	50 (87.7)	0.218
Aspirin	57 (100.0)	57 (100.0)	> 0.999
Clopidogrel	20 (35.1)	24 (42.1)	0.564
Prasugrel	34 (59.6)	34 (59.6)	> 0.999
Follow-up duration, day	105.51 ± 19.48, 102.00 [93.00, 113.00]	105.02 ± 18.16, 105.00 [95.00, 114.00]	0.696

Data are expressed as mean ± standard deviation, median [interquartile range], and number (percentage)

*Six patients had both BP-DES and DP-DES

Only pre-dilatation balloon diameter was significantly larger in the DP-DES group than in the BP-DES group.

Angioscopic findings

Angioscopic findings at 3-month follow-up are presented in Fig. 3 and Table 3 (BP-DES 226 segments vs. DP-DES 203 segments). Vessel healing status in terms of main coverage grade (1.080 ± 0.023 vs. 1.048 ± 0.026, p = 0.354) and minimum coverage grade (1.00 ± 0.00 vs. 1.00 ± 0.00, p > 0.999) was not significantly different between BP-DES and DP-DES groups. Maximum coverage grade was significantly higher in the BP-DES than in the DP-DES (1.45 ± 0.035 vs. 1.35 ± 0.037, p = 0.049). Coverage heterogeneity score did not differ between BP-DES and DP-DES groups (0.50 ± 0.035 vs. 0.44 ± 0.037, p = 0.244). Incidence of in-stent thrombus [47/226 (20.8%) vs. 50/203 (24.6%), p = 0.357] and yellow plaque [35/226 (15.5%) vs. 42/203 (19.7%), p = 0.255] was comparable between both groups. In-stent thrombus observed in the present study was all

Table 2 Procedural characteristics

	BP-DES	DP-DES	P value
Lesion number	N = 61	N = 63	
Acute coronary syndrome	13/61 (21.3)	17/63 (27.0)	0.188
Target vessel			
Right coronary artery	22/61 (36.1)	19/63 (30.2)	0.723
Left anterior descending artery	28/61 (45.9)	29/63(46.0)	
Left circumflex artery	9/61 (14.8)	10/63 (15.9)	
Left main trunk	2/61 (3.3)	5/63 (7.9)	
Bifurcation lesion*	38/61 (62.3)	39/63 (61.9)	> 0.999
Branch number[a]	0.73 ± 0.65, 1.00 [0.00, 2.00]	0.79 ± 0.71, 1.00 [0.00, 2.00]	0.703
Pre-dilatation performed	53/61 (86.9)	57/63 (90.5)	0.580
Pre-dilatation balloon diameter (mm)	2.50 ± 0.52, 2.50 [2.00, 3.00]	2.86 ± 0.69, 2.75 [2.50, 3.00]	0.005
Pre-dilatation balloon pressure (atm)	12.57 ± 2.76, 12.00 [12.00, 14.00]	12.33 ± 3.84, 12.00 [11.00, 14.00]	0.758
Stenting			
Stent number	1.16 ± 0.37, 1.00 [1.00, 1.00]	1.30 ± 0.49, 1.00 [1.00, 2.00]	0.100
Stet diameter (mm)	3.02 ± 0.47, 3.00 [2.75, 3.50]	3.05 ± 0.50, 3.00 [2.50, 3.50]	0.860
Stent length (mm)	41.08 ± 19.10, 38.00 [28.00, 52.00]	36.67 ± 23.39, 30.00 [22.00, 38.00]	0.253
Stent implantation pressure (atm)	13.23 ± 2.66, 14.00 [12.00, 14.00]	14.03 ± 2.46, 14.00 [12.00, 16.00]	0.084
Post-dilatation performed	49/61 (80.3)	50/63 (79.4)	> 0.999
Post-dilatation balloon diameter (mm)	3.23 ± 0.62, 3.00 [2.75, 3.75]	3.41 ± 0.70, 3.25 [3.00, 3.75]	0.188
Post-dilatation pressure (atm)	16.29 ± 3.98, 16.00 [14.00, 20.00]	16.35 ± 3.57, 16.00 [14.00, 20.00]	0.785
Stent type			
Synergy	29/61 (47.5)	–	
Ultimaster	32/61 (52.5)	–	
Xience	–	30/63 (47.6)	
Resolute onyx	–	33/63 (52.4)	

Data are expressed as mean ± standard deviation, median [interquartile range], and number (percentage)

*Bifurcation lesion was defined as a bifurcation with a significant side branch

[a]A significant side branch was defined as a vessel with a reference vessel diameter of 1.5 mm or more by visual assessment on angiography

mural and not-clinically relevant at least up to 3-month follow-up.

Clinical outcomes

One patient in the DP-DES group experienced target lesion revascularization. No death, no myocardial infarction, no stent thrombosis was observed in the study population.

Discussion

Main findings of the present study are as follows: (1) At 3-month follow-up on coronary angioscopy, the current BP-DES had higher maximum stent coverage than the contemporary DP-DES, while main and minimum coverage grades were comparable; (2) Coverage heterogeneity score was not significantly different between BP-DES and DP-DES groups; (3) Incidence of thrombus and yellow plaque did not significantly differ between both groups.

In general, neointimal coverage after stent implantation is complicatedly influenced by lesion characteristics and biomechanical properties of the device such as strut design and thickness, polymer type and its coating technology, antiproliferative drug type and release duration, etc. Angioscopic evaluation of early vessel healing after implantation of BP-DES and DP-DES was previously performed in a few clinical studies. When comparing the BP-DES (biolimus A9-eluting stent, Terumo Corporation, Tokyo, Japan, strut thickness 125 μm, N = 15) and the 1st-generation DP-DES (Cypher, Cordis, Miami Lakes, FL, USA, strut thickness 140 μm, N = 16), both devices presented comparable dominant neointimal coverage grade at 9 months, but with a significantly higher heterogeneity of the neointimal coverage in the DP-DES as compared to the BP-DES [15]. On the other hand, another relatively large study presented better neointimal coverage in the BP-DES group (EXCEL™, Biosensor/Jiwei, Shandong, China, N = 94, strut thickness 119 μm) than in the DP-DES group (Cypher, N = 81) at 9 months [16]. Both studies, however, evaluated the 1st-generation DP-DES

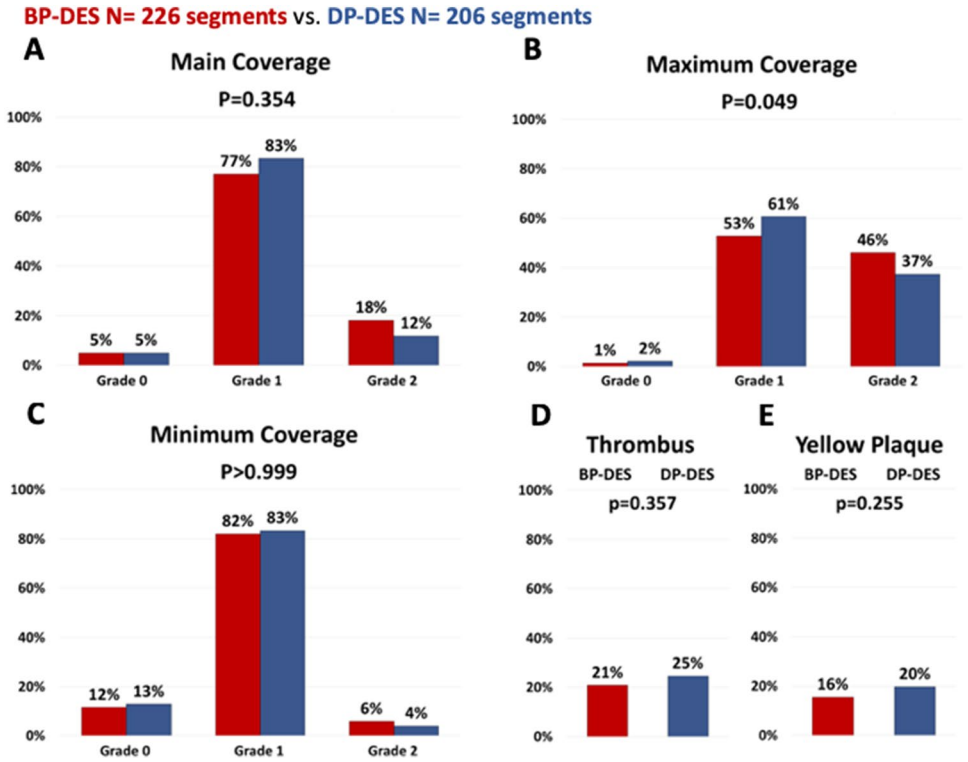

Fig. 3 Angioscopic findings at 3-month follow-up. All data are expressed as percentage at segment level (BP-DES 226 segments vs. DP-DES 206 segments). Main coverage grade (**a**) and minimum coverage grade (**c**) were comparable between BP-DES and DP-DES groups, while maximum coverage grade (**b**) was significantly higher in the BP-DES than in the DP-DES. Incidence of in-stent thrombus (**d**) and yellow plaque (**e**) was not significantly different between both groups

Table 3 Neointimal coverage on angioscopy

	BP-DES 57 patients/61 lesions/226 segments	DP-DES 57 patients/63 lesions/203 segments	P value*
Main coverage grade	1.08 ± 0.02	1.05 ± 0.03	0.354
Maximum coverage grade	1.45 ± 0.04	1.35 ± 0.04	0.049
Minimum coverage grade	1.00 ± 0.00	1.00 ± 0.00	> 0.999
Coverage heterogeneity score	1.05 ± 0.07	0.90 ± 0.07	0.162

Data are expressed as mean ± standard error. Main, maximum and minimum coverage grade were analyzed at segment level, whereas heterogeneity score was at lesion level

*Mixed linear model with an assumed Gaussian distribution was used for the comparisons of continuous variables to take into an account the clustered nature of > 1 segment analyzed from the same lesions and patients, which might result in unknown correlations among measurements within the clusters

Cypher and the BP-DES with relatively large strut thickness as compared to the contemporary DES. Nishimoto et al. reported better stent coverage of the 2nd-generation DP-DES over the BP-DES (Nobori™, Terumo, Tokyo, Japan) [13]. Neointimal coverage of the BP-DES was more homogeneous than that of the DP-DES. Nevertheless, it would be complicated to interpret these results since these previous studies compared the different devices having different strut thickness, different polymer, and different antiproliferative drug. It was still unclear if the biodegradable polymer contributed to the homogeneous neointimal coverage.

The present study evaluated the devices with similar strut thickness which can be the most powerful determinant of the neointimal coverage (Synergy™ 74 μm; Ultimaster™ 80 μm; Xience™ 81 μm; Resolute Onyx™ 81 μm). In contrast to the previous studies [13], our study demonstrated that the contemporary BP-DESs have slightly but significantly higher maximum neointimal coverage grade at 3 months when compared with the current DP-DESs. Considering the similar strut thickness, higher maximum neointimal coverage grade of the BP-DES group would be attributed to the biodegradable polymer and/or abluminal polymer coating, although it is still unknown which factor mainly influenced. Heterogeneity of the neointima was comparable between both devices in the present study, suggesting that similar strut thickness rather than polymer type might have stronger impact on the heterogeneity of the neointimal coverage.

Clinical implication

Main and minimum coverage grade was comparable between the BP-DES and the DP-DES groups. Thrombus was also similarly observed between both groups, but without any clinical adverse events. Approximately 90% of the stented segments presented minimum coverage grade ≥ 1 at 3-month follow-up, suggesting that the both contemporary BP-DES and DP-DES have favorable vessel healing status in acute phase. This fact would support the ultra-short DAPT strategy (1 month) or even monotherapy with P2Y12 inhibitor in the upcoming decade.

The higher maximum coverage grade in the BP-DES might imply the earlier vessel healing in comparison with the DP-DES. However, clinical significance of this difference should be assessed in a prospective randomized manner. Possible neointimal "quality" difference between BP-DES and DP-DES would also be a next scientific interest. Quantitative assessment approach such as light property analysis is desirable for the objective comparison [17].

Study strength and limitations

One of the possible drawbacks of the OCT assessment of neointimal coverage would be the difficulty in differentiation between the fibrin/thrombus deposition and healthy endothelial coverage. The animal study suggested that BP-DES might have healthier neointimal coverage than DP-DES in acute phase [18]. Angioscopy would be advantageous over OCT, in the sense that neointimal coverage assessment on angioscopy would be influenced by not only the thickness of the neointima but also the quality (permeability, density, morphology, color, etc.). The present study would be, to date, the first angioscopic prospective analysis of the contemporary BP-DES and DP-DES.

Some limitations should to be acknowledged. First, the RESTORE Registry was single-center prospective cohort study. Invasive serial imaging observation delayed the patient enrollment, resulting in a selection bias. Although serial imaging observations at 6–12 months would also be scientifically intriguing, it was challenging to perform in individual patients. Second, patients with tortuous or small vessels not suitable for angioscopic examination were excluded, also resulting in selection bias. Third, coronary angioscopy could not acquire the images of whole vessel wall due to the limited field of view and might have missed some yellow plaques and thrombus and resulted in some misclassification of neointimal coverage. Fourth, no baseline angioscopy evaluation was performed which downgrades the validity of the results. Finally, the current results would be hypothesis-generating and should be interpreted with caution due to the non-randomized study design. Further prospective randomized trials would be warranted.

Conclusions

The present coronary angioscopic study demonstrated that, at 3-month follow-up, the current BP-DES had higher maximum stent coverage than the contemporary DP-DES, while main and minimum coverage grades and heterogeneity of the neointimal coverage were comparable between both devices. Incidence of in-stent thrombus and yellow plaque did not significantly differ between BP-DES and DP-DES. The present results support the ultra-short DAPT strategy or even monotherapy with P2Y12 inhibitor in the upcoming decade. Further prospective randomized trials should be conducted to evaluate the clinical significance of the present imaging results.

Compliance with ethical standards

Conflict of interest Y. Sotomi, S. Nakatani, and Y. Higuchi received speaker honoraria from Abbott Vascular Japan, Boston Scientific Japan, TERUMO, Cardinal Health, and Medtronic. Y. Sakata reports grants and personal fees from Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. A. Hirayama reports grants and personal fees from Boston Scientific Japan, Abbott Vascular Japan, Japan Lifeline, and Medtronic. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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