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Early- and middle-phase arterial repair following bioresorbable- and durable-polymer drug-eluting stent implantation: An angioscopic study☆,☆☆

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ABSTRACT

Background: Bioresorbable-polymer drug-eluting stent (BP-DES) demonstrates comparable clinical outcomes compared to durable-polymer drug-eluting stent (DP-DES). However, early- and middle-phase arterial repair following deployment of BP-DES and DP-DES has not been elucidated to date.
Methods: We extracted coronary angioscopy (CAS) findings covering early phase (4 ± 1 months) or middle phase (10 ± 2 months) between January 2010 and February 2018 from the database of Kansai Rosai Hospital. Neointimal coverage (NIC), yellow color intensity of the stented segment and incidence of thrombus adhesion were compared between BP-DES (Synergy or Ultimaster) and DP-DES (Promus or Resolute or Xience) in early (39 BP-DES of 33 lesions from 24 patients and 83 DP-DES of 74 lesions from 56 patients) and middle (198 BP-DES of 175 lesions from 135 patients and 204 DP-DES of 184 lesions from 149 patients) phases.
Results: In early phase, while NIC was similar in both groups (P = 0.84), the incidence of thrombus adhesion was significantly higher in BP-DES than in DP-DES (67% versus 34%, P = 0.001) even though maximum yellow color was less intense in BP-DES (P = 0.004). In middle phase, while NIC was better in BP-DES (P < 0.001), thrombus adhesion (23% versus 22%, P = 0.81) and maximum yellow color (P = 0.72) were similar in both groups.
Conclusions: Although NIC was similar in the early phase, the incidence of thrombus adhesion was significantly higher in BP-DES than in DP-DES. The incidence of thrombus adhesion reached similar values and NIC improved in BP-DES over that in DP-DES in the middle phase.

1. Introduction

Bioresorbable-polymer drug-eluting stents (BP-DES) such as Synergy (Boston Scientific, Natrick, MA, USA) and Ultimaster (Terumo Corporation, Tokyo, Japan) demonstrate comparable clinical outcomes compared to durable-polymer drug-eluting stents (DP-DES) such as Promus (Boston Scientific, Natrick, MA, USA), Resolute (Medtronic, Minneapolis, MN, USA) and Xience (Abbott Park, Abbott Vascular, IL, USA) [1–3]. In evaluating the safety of drug-eluting stents (DES), it is important to evaluate intravascular status using intravascular imaging devices. Of these, coronary angioscopy (CAS) is only one such imaging device that can observe intra-stent status under direct and full-color vision [4–11]. Arterial healing of BP-DES can be different from that of DP-DES, because BP-DES incorporates a bioresorbable polymer with an abluminal coating. However, early- and middle-phase arterial repair following BP-DES has not been elucidated to date.

2. Methods

2.1. Patients

This was a single-center, retrospective observational study. We extracted the CAS findings of DES evaluated in the early phase (4 ± 1 months after implantation; 122 stents in 107 lesions from 80 patients) or in the middle phase (10 ± 2 months after implantation; 402 stents in 359 lesions from 284 patients) from January 2010 to February 2018 from the database of Kansai Rosai Hospital. We then compared the CAS findings in BP-DES and DP-DES in each phase; early phase: 39 BP-DES [Synergy 25 stents, Ultimaster 14 stents] from 33 lesions in 24 patients and 83 DP-DES [Promus 4 stents, Resolute 42 stents, Xience 37 stents] from 74 lesions in 56 patients; middle phase: 198 BP-DES [Synergy 157 stents, Ultimaster 41 stents] from 175 lesions in 135 patients and 204 DP-DES [Promus 51 stents, Resolute 42 stents, Xience 111 stents] from 184 lesions in 149 patients. All DESs were implanted in de novo lesions in native coronary arteries. We excluded patients who exhibited any event of earlier stent failure such as in-stent restenosis, or who could not receive successful angioscopic evaluation. Although angioscopic evaluation at follow-up angiography as well as staged percutaneous coronary intervention (PCI) for other lesions was recommended for all patients, this was not performed when informed consent could not be obtained, or when a

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specialist for angioscopic evaluation was not available. The elective patients received ticlopidine (200 mg/day), clopidogrel (75 mg/day), or prasugrel (3.75 mg/day) in addition to aspirin (100 mg/day) at least 1 week before PCI. For the emergent patients, the antiplatelet drugs (aspirin: 200 mg and clopidogrel: 300 mg or prasugrel: 20 mg) were loaded before PCI. Most patients continued to receive dual antiplatelet therapy during the follow-up period. The Medical Ethics Committee of Kansai Rosai Hospital approved the study, and all patients provided written informed consent.

2.2. Angiographic and angioscopic follow-up

CAS was performed after administration of unfractionated heparin (5000 IU) into the radial or femoral artery via the inserted sheath, and isosorbide dinitrate (2.5 mg) into the coronary artery. CAS was subsequently performed using a Fullview NEO angioscopic catheter (FiberTech, Tokyo, Japan) as previously described from January 2010 to September 2016 [4,5]. Briefly, an optical fiber was placed at the distal segment of the coronary artery and manually pulled back from the distal edge of the stent to the proximal edge under careful angioscopic and angiographic guidance. Since October 2016, we have been using a smart-i angioscopic catheter (i Heart Medical, Tokyo, Japan) because the Fullview NEO was discontinued. Using guide extension catheters such as GuideLiner (Japan Lifeline, Tokyo Japan), Guidezilla (Boston Scientific, Natrick, MA, USA) and guideplus (NIPRO, Osaka, Japan), we blocked blood flow by flushing with low molecular weight dextran. Both angioscopic images consisted of 3000 pixels with full color and were digitally stored for off-line analysis.

2.3. Angioscopic analysis

Angioscopic images were analyzed to determine the following: 1) dominant degree of neointimal coverage (NIC) over the stent; 2) heterogeneity of NIC; 3) yellow color grade of stented segment; and 4) presence of intra-stent thrombus. Neointimal coverage over the stent was classified into 4 grades as previously described: grade 0, stent struts fully visible, similar to immediately after implantation; grade 1, stent struts bulging into the lumen and although covered, still transparently visible; grade 2, stent struts embedded in the neointima, but translucently visible; grade 3, stent struts fully embedded and invisible on angioscopy [6]. Heterogeneity of NIC has been defined previously [7]. Briefly, NIC was evaluated throughout entire stented segments, and was judged as heterogeneous when differences in the NIC grade became apparent. Struts crossing the side branch and located in the overlapped segment were excluded from grading. In addition, stent edges were excluded from the heterogeneity analysis. The yellow color was graded as follows: grade 0, white; grade 1, light yellow; grade 2, yellow; grade 3, intensive yellow (Supplementary Figure). Thrombus was defined based on criteria adopted by the European Working Group on Coronary Angioscopy [8]. The inter- and intra-observer κ coefficient for evaluating CAS findings was determined for randomly selected 30 cases. The estimated inter- and intra-observer κ coefficients were 0.84 and 0.95, respectively for dominant degree of NIC over the stent, 0.84 and 0.83 for heterogeneity of NIC, 0.82 and 0.86 for yellow color grade of stented segment and 0.93 and 1.0 for presence of intra-stent thrombus.

2.4. Statistical analysis

All results are expressed as mean ± SD unless otherwise stated. Continuous variables with and without homogeneity of variance were analyzed by Student's *t*-test and Welch *t*-test, respectively. Categorical variables were analyzed with Fisher's exact test for 2 × 2 comparisons. For more than 2 × 2 comparisons, the Mann-Whitney test was used. Multivariate analysis was performed using logistic regression. Statistical significance was defined as $P < 0.05$. All calculations were performed using the IBM SPSS Statistics package Version 20 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patients

Patient, medication, lesion and procedural characteristics are shown in Table 1. Patient and medication characteristics were not significantly

Table 1
Patient, medication, lesion and procedural characteristics.

	Early phase			Middle phase		
	BP-DES	DP-DES	P value	BP-DES	DP-DES	P value
Number of patients	24	56		135	149	
Male, n (%)	21 (88)	45 (80)	0.34	116 (86)	123 (83)	0.52
Age, years	68 ± 10	70 ± 8	0.21	69 ± 11	68 + 10	0.79
Prior PCI, n (%)	5 (21)	24 (43)	0.050	56 (42)	62 (42)	1.0
Hypertension[a], n (%)	20 (83)	53 (95)	0.12	116 (86)	131 (88)	0.73
Dyslipidemia[b], n (%)	18 (75)	47 (84)	0.26	112 (83)	114 (77)	0.19
Diabetes[c], n (%)	11 (46)	22 (39)	0.63	47 (35)	51 (34)	1.0
Current smoking, n (%)	10 (42)	14 (25)	0.18	35 (26)	27 (18)	0.12
Aspirin, n (%)	23 (96)	56 (100)	0.30	126 (93)	146 (98)	0.075
$P2Y_{12}$ inhibitor, n (%)	24 (100)	56 (100)	–	127 (94)	143 (96)	0.59
Statin, n (%)	15 (63)	40 (71)	0.44	101 (75)	100 (67)	0.19
DOAC, n (%)	1 (4)	0 (0)	0.30	6 (4)	4 (3)	0.32
Number of lesions	33	74		175	184	
ACS, n (%)	15 (46)	27 (36)	0.40	54 (31)	49 (27)	0.42
Target vessel, n (%)			0.31			0.64
LAD	11 (33)	38 (51)		80 (46)	89 (48)	
LCX	10 (30)	12 (16)		33 (19)	33 (18)	
RCA	12 (37)	25 (33)		62 (35)	62 (34)	
Type B2/C[d], n (%)	25 (76)	54 (72)	0.82	144 (82)	123 (67)	0.001
Bifurcation, n (%)	18 (55)	16 (21)	0.001	63 (36)	57 (31)	0.32
CTO, n (%)	1 (3)	3 (3)	0.64	9 (5)	18 (10)	0.11
Number of stents	39	83		198	204	
Pre-dilatation, n (%)	33 (85)	47 (57)	0.002	164 (83)	134 (66)	<0.001
Max pre-dilatation balloon diameter, mm	2.7 ± 0.5	2.5 ± 0.3	0.19	2.6 ± 0.5	2.6 ± 0.4	0.90
Max pre-dilatation balloon pressure, atm	13 ± 3	13 ± 4	0.17	13 ± 3	13 ± 4	0.29
Stent diameter, mm	3.1 ± 0.5	3.1 ± 0.4	0.86	3.1 ± 0.5	3.1 ± 0.4	0.70
Stent length, mm	25 ± 9	23 ± 8	0.87	25 ± 9	23 ± 8	0.004
Stent implantation pressure, atm	11 ± 2	10 ± 2	0.019	11 ± 2	10 ± 3	0.20
Post-dilatation, n (%)	35 (90)	68 (82)	0.42	180 (91)	154 (76)	<0.001
Max post-dilatation balloon diameter, mm	3.1 ± 0.6	3.1 ± 0.5	0.84	3.2 ± 0.5	3.2 ± 0.5	0.17
Max post-dilatation balloon pressure, atm	15 ± 3	17 ± 4	0.014	16 ± 3	15 ± 4	0.046

Data are presented as mean ± SD or numbers (%).

[a] Receiving antihypertensive medication, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg.

[b] Treatment with medication, total cholesterol ≥ 220 mg/dL, low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol ≤ 40 mg/dL, or triglycerides ≥ 150 mg/dL.

[c] Oral agent or insulin treatment or HbA_{1C} ≥ 6.5%. ACS = acute coronary syndrome; BP-DES = bioresorbable-polymer drug-eluting stent; CTO = chronic total occlusion; DOAC = direct oral anticoagulant; DP-DES = durable-polymer drug-eluting stent; LAD = left anterior descending artery; LCX = left circumflex artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

[d] Based on the American College of Cardiology/American Heart Association Classification.

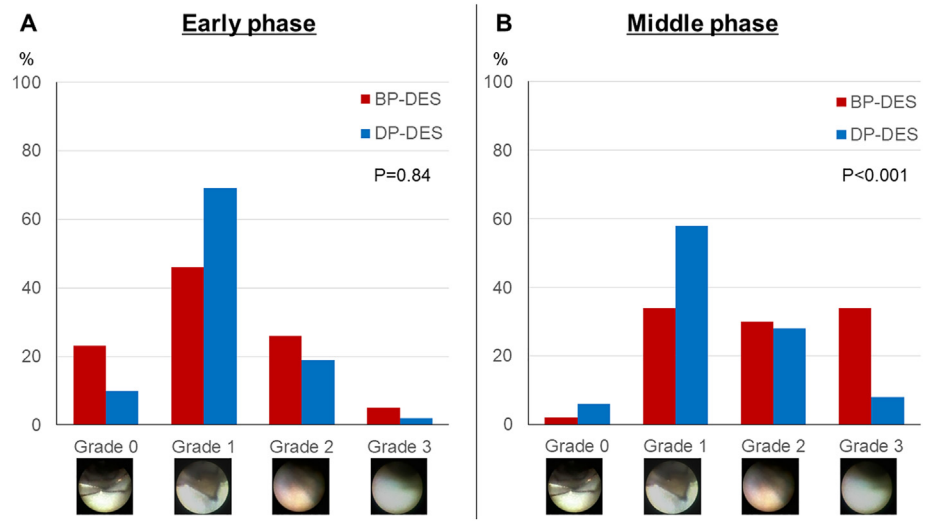

Fig. 1. Dominant neointimal coverage (NIC) grade with bioresorbable-polymer drug-eluting stent (BP-DES) and durable-polymer drug-eluting stent (DP-DES). **A**: Dominant NIC grade in the early phase. Dominant NIC grade was similar in BP-DES and DP-DES ($P = 0.84$). **B**: Dominant NIC grade in the middle phase. The distribution of dominant NIC grade was significantly higher in BP-DES than in DP-DES ($P < 0.001$).

different between BP-DES and DP-DES in the early or middle phases. Lesion characteristics were similar, except for bifurcation lesions in the early phase and Type B2/C lesions in the middle phase. In terms of the procedural characteristics, pre-dilatation was more frequently performed and stent implantation and post-dilatation pressures were higher in BP-DES in the early phase; in addition pre- and post-dilatations were more frequently performed, stent length was longer and post-dilatation pressure was higher in BP-DES.

3.2. Angioscopic findings

Follow-up durations for BP-DES and DP-DES were 108 ± 32 versus 136 ± 22 days in the early phase ($P < 0.001$) and 297 ± 59 versus 294 ± 67 days in the middle phase ($P = 0.67$), respectively. In the early phase, dominant NIC grade as well as NIC heterogeneity were similar between BP-DES and DP-DES (Fig. 1A, Fig. 2A). Incidence of thrombus adhesion was significantly higher in BP-DES than in DP-DES, while maximum yellow color grade was significantly lower in BP-DES (Fig. 2C, Fig. 3A). Even after adjustment of the follow-up duration (adjusted odds ratio (OR): 0.98; confidence interval [CI]: 0.97–0.999) and yellow color grade (adjusted OR: 1.27; CI: 0.78–2.06), multivariate analysis demonstrated that BP-DES usage was an independent predictor for thrombus adhesion in the early phase (adjusted OR: 2.98; CI: 1.14–7.79). In the middle phase, dominant NIC grade was significantly higher in BP-DES, while NIC heterogeneity was similar in BP-DES and DP-DES (Fig. 1B, Fig. 2B). Thrombus adhesion and maximum yellow color grade were similar in BP-DES and DP-DES (Fig. 2D, Fig. 3B).

4. Discussion

The current study has demonstrated the following: 1) the incidence of thrombus adhesion was significant higher in BP-DES than in DP-DES

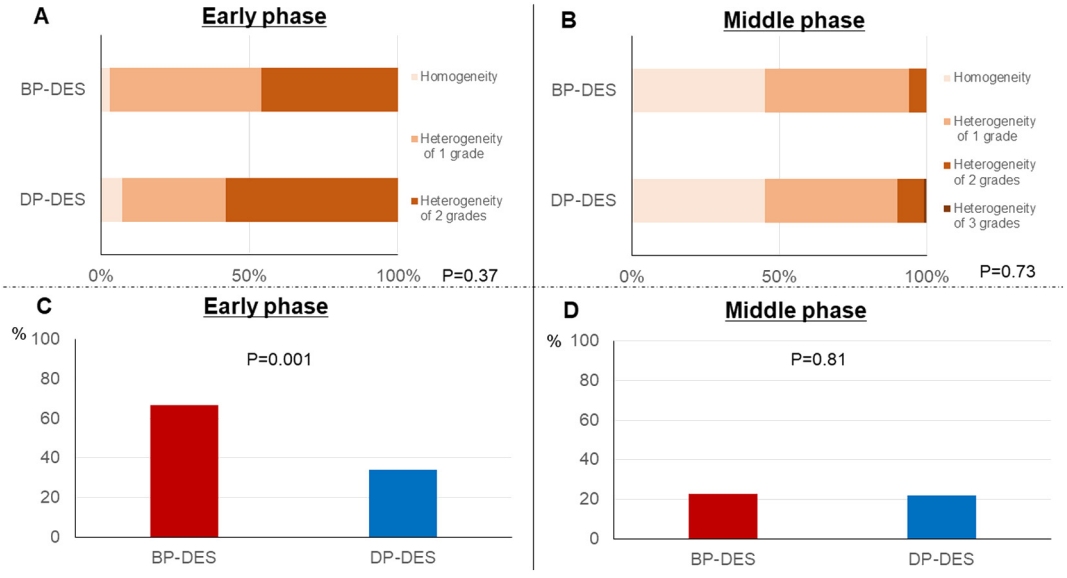

Fig. 2. Heterogeneity of neointimal coverage (NIC) and incidence of thrombus adhesion with bioresorbable-polymer drug-eluting stent (BP-DES) and durable-polymer drug-eluting stent (DP-DES). **A**: Heterogeneity of NIC in the early phase. Heterogeneity of NIC was similar in BP-DES and DP-DES ($P = 0.37$). **B**: Heterogeneity of NIC in the middle phase. Heterogeneity of NIC was similar in BP-DES and DP-DES ($P = 0.73$). **C**: Incidence of thrombus adhesion in the early phase. The incidence of thrombus adhesion was significantly higher in BP-DES than in DP-DES (67% versus 34%, $P = 0.001$). **D**: Incidence of thrombus adhesion in the middle phase. The incidence of thrombus adhesion was similar in BP-DES and DP-DES (23% versus 22%, $P = 0.81$).

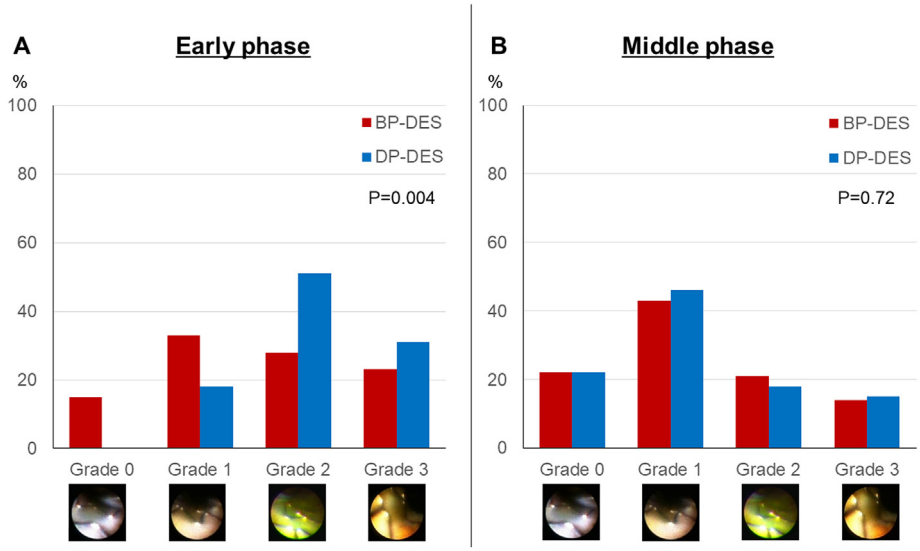

Fig. 3. Maximum yellow color grade of the stented segment with bioresorbable-polymer drug-eluting stent (BP-DES) and durable-polymer drug-eluting stent (DP-DES). **A**: Maximum yellow color grade of the stented segment in the early phase. Maximum yellow color grade was significantly lower in BP-DES than in DP-DES (P = 0.004). **B**: Maximum yellow color grade of the stented segment in the middle phase. Maximum yellow color grade was similar in BP-DES and DP-DES (P = 0.72).

4 months after implantation, while dominant NIC and heterogeneity of NIC were comparable; 2) dominant NIC was significantly better in BP-DES than in DP-DES 10 months after implantation with similar heterogeneity of NIC, severity of YP and incidence of thrombus adhesion. To the best of our knowledge, this is the first report outlining intravascular status after BP-DES in the early and middle phases by CAS.

Thrombus adhesion was more frequently observed in BP-DES than in DP-DES 4 months after implantation, although it was comparable at 10 months. Arterial repair is thought to be incomplete in the stented segment with thrombus adhesion because such adhesion occurs in the initial phase of arterial healing after stent implantation, and thrombus dose not attach to the stented segment where arterial repair is complete because mature endothelial cells have antithrombotic effect [9,12]. It takes 3–4 months for the polymer of Synergy and Ultimaster to resolve [1,2]. On the other hand, resorption of the Absorb everolimus-eluting bioresorbable vascular scaffold (Absorb) is considered complete at 36 months [13]. Optical coherence tomography (OCT) 1 year after implantation has demonstrated a peri-strut low intensity area (PSLIA) in 53% of Absorb cases, while PSLIA was considered as immature neointimal tissue; this was because it included rich proteoglycan/collagen, fibrin and inflammatory cells/macrophage contents and poor smooth muscle cell content [14,15]. Otsuka et al. also demonstrated that inflammation scores were greater in Absorb than in Xience at 6 to 36 months [13]. Judging from these reports, neointimal maturation will rarely be complete in the absorption phase of the scaffold. Similarly, neointimal maturation after Synergy and Ultimaster implantation will not be complete in the absorption phase of the polymer, even taking into account differences in the nature of the polymer between Absorb, Synergy and Ultimaster. Of course, the device itself is different between Absorb and BP-DES: scaffold itself is composed by polymer in Absorb and polymer is loaded between drug and stent strut in BP-DES. This immature neointima has incomplete antithrombogenicity, which would contribute to the higher incidence of thrombus in BP-DES at 4 months in the current study.

On the contrary, the Xience stent polymer has an antithrombotic effect [16], which would contribute to the lower rate of stent thrombosis in the early phase compared to a bare-metal stent in patients with acute myocardial infarction [17]. This may be one reason why the incidence of thrombus adhesion was higher in BP-DES in the early phase as shown in the current study. However, it reached a similar rate at 1 year, which suggests the progression of arterial healing in BP-DES.

In the TRANSFORM-OCT trial, OCT findings 3 months after the implantation were compared between Synergy and Resolute and the maximum length of uncovered struts was similar between Synergy and Resolute [18]. In terms of the NIC, the result was comparable to that in the current study. In contrast, HATTRICK-OCT Trial was a prospective multicenter single-blinded randomized controlled trial which compared neointimal coverage 3 months following the implantation of Orsiro vs. Resolute [19]. The percent uncovered struts was lower in the Orsiro group compared with the Resolute group. Although the net incidence of intra-stent thrombus was higher in Orsiro than in Resolute, it did not reach statistical significance. In terms of neointimal coverage, the result was different from that of the current study. The speculated reasons are as follows: 1) BP-DES included Synergy and Ultimaster in the current study and Orsiro was not included because it was not launched in Japan during the study period. Orsiro has ultra-thin strut, which may cause better neointimal coverage in the HATTRICK-OCT trial; 2) OCT can evaluate neointimal coverage better than CAS, which would cause the difference of neointimal coverage between HATTRIC-OCT trial and the current study. Regarding thrombus adhesion, the incidence in Orsiro was not significantly different than that in Resolute. As CAS is superior to OCT in detecting thrombus [20], it is reasonable of higher incidence to detect thrombus both in BP-DES and DP-DES in the current CAS study. Then, thrombus adhesion was significantly higher in BP-DES than in DP-DES in the early phase.

Although it was similar at 4 months, NIC was better in BP-DES at 10 months. A previous OCT study showed that the absolute value of neointimal thickness was higher in Ultimaster compared to Xience at 9 months, although this difference did not reach statistical significance [21]. Such a result was similar as the current CAS finding which could involve a mechanism whereby BP-DES becomes similar as a bare-metal stent after the resorption of polymer, which in turn progresses NIC.

Yellow color grade was lower in BP-DES at 4 months, which would show the underlying plaque. Therefore, lesion background at the time of stent implantation would be different in BP-DES and DP-DES. Previous CAS studies showed that the incidence of thrombus adhesion was higher at a stent implantation site of yellow color compared to that of one of white color [10], and the incidence of thrombus adhesion increased as yellow color grade became higher [11]. In the current study, after the adjustment of yellow color grade and follow-up duration, BP-DES was an independent predictor of thrombus adhesion at 4 months. We should therefore pay attention to switching of dual-

antiplatelet therapy to mono-antiplatelet therapy equally for all patients receiving BP-DES at 4 months.

4.1. Limitations

This study has several limitations. Firstly, it was a single-center, non-randomized, observational study. However, sample size was enough to permit evaluation of the outcome and was comparable to previous CAS studies. Secondly, we could not evaluate vessel healing process longitudinally in the strict sense because we did not perform CAS evaluation serially. However, patient background was similar in early and middle phases. Thirdly, we did not discuss neoatherosclerosis, which is an unsolved issue in this field, because we did not have CAS findings at the time of stent implantation. Fourthly, angioscopic thrombus did not directly indicate risk of stent thrombosis. Fifth, one of the reason CAS was not performed in all patients was the fact that CAS specialists were not there, which is one of the selection biases. Sixth, the cohort in the current study was not consecutive patients, which is another selection bias. Seventh, some procedural characteristics were different between BP-DES and DP-DES and they could influence NIC. Eighth, although underlying plaque morphology is associated with vessel healing with neointimal formation, we did not evaluate baseline lesion morphology by fixed intravascular imaging devices. Ninth, CAS sometimes could not evaluate whole stented segment completely because of the limitation of visual field of CAS, especially in angulated or tortuous lesions. However, in such cases, changing guidewire sometimes improved the visual field. Finally, further investigation is necessary to evaluate the prognosis and CAS findings of BP-DES implantation.

5. Conclusions

Although NIC was similar, the incidence of thrombus adhesion was significantly higher with BP-DES than with DP-DES at 4 months. However, at 10 months such adhesion reached similar incidence and NIC became better in BP-DES than in DP-DES.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.059.

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