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Original Article

Impact of baseline yellow plaque assessed by coronary angioscopy on vascular response after stent implantation

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ABSTRACT

Background: The relationship between baseline yellow plaque (YP) and vascular response after stent implantation has not been fully investigated.
Methods: This was a sub-analysis of the Collaboration-1 study (multicenter, retrospective, observational study). A total of 88 lesions from 80 patients with chronic coronary syndrome who underwent percutaneous coronary intervention were analyzed. Optical coherence tomography (OCT) and coronary angioscopy (CAS) were serially performed immediately and 11 months after stent implantation. YP was defined as the stented segment with yellow or intensive yellow color assessed by CAS. Neoatherosclerosis was defined as a lipid or calcified neointima assessed by OCT. OCT and CAS findings at 11 months were compared between lesions with baseline YP (YP group) and lesions without baseline YP (Non-YP group).
Results: Baseline YP was detected in 37 lesions (42 %). OCT findings at 11 months showed that the incidence of neoatherosclerosis was significantly higher in the YP group (11 % versus 0 %, $p = 0.028$) and mean neointimal thickness tended to be lower (104 ± 43 μm versus 120 ± 48 μm, $p = 0.098$). CAS findings at 11 months demonstrated that the dominant and minimum neointimal coverage grades were significantly lower ($p = 0.049$ and $P = 0.026$) and maximum yellow color grade was significantly higher ($p < 0.001$) in the YP group.
Conclusions: Baseline YP affected the incidence of neoatherosclerosis as well as poor neointimal coverage at 11 months after stent implantation.

Introduction

Drug-eluting stents (DESs) have been widely used in percutaneous coronary intervention (PCI) for coronary arterial lesions. DESs have dramatically decreased the incidence of restenosis compared to bare-metal stents by inhibiting neointimal proliferation [1]. However, delayed vascular healing and abnormal vascular responses including neoatherosclerosis occasionally occurred after DES implantation, which contributed to late stent failure [2–5]. Although previous studies suggested several risk factors for neoatherosclerosis development, one of the strongest risk factors is a longer time interval from stent implantation to follow-up [5–7]. Although neoatherosclerosis is a time-dependent process, some neoatherosclerosis lesions occur early, ≤12 months after stent implantation [8]. It has been reported that

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early neoatherosclerosis is associated with coronary events, and that hypertension and high low-density lipoprotein (LDL)-cholesterol levels are risk factors for the development of early neoatherosclerosis [8]. However, the impact of baseline lipid plaque at the time of stent implantation on the development of early neoatherosclerosis has not been fully investigated.

Coronary angioscopy (CAS) is the imaging modality that allows observation of intra-stent status by direct and full-color visualization. A previous report revealed a significant negative correlation between yellow color intensity evaluated by CAS and fibrous cap thickness evaluated by optical coherence tomography (OCT) [9]. In addition, there was a significant positive correlation between yellow color intensity and lipid plaque size [9]. Therefore, the evaluation of yellow plaque (YP) by CAS is considered useful to assess lesion morphologies such as lipid-rich plaques or plaque vulnerability. Thus, this study aimed to evaluate the impact of baseline YP on mid-term vascular response after stent implantation.

Methods

Study population

This was a sub-analysis of the COLLABORATION-1 study (multicenter, prospective, observational study); the details of the study protocol are described elsewhere [10]. In brief, the study enrolled patients with chronic coronary syndrome (CCS), multi-vessel disease in native coronary arteries, patients with implantation of a polymer-free and carrier-free biolimus A9-coated stent (PF-BCS) (BioFreedom™, Biosensors Interventional Technologies, Singapore) or a durable polymer everolimus-eluting stent (DP-EES, Xience™, Abbott Vascular, Santa Clara, CA, USA) at the initial PCI, an indication for staged PCI for the residual lesion at 1 ± 0.5 months after the initial PCI, and patients who were scheduled for follow-up coronary angiography 12 ± 2 months after the initial PCI at four hospitals in Japan. All stents were implanted in de novo lesions in native coronary arteries. CAS was performed on target lesions for initial and staged PCI at 1 month and 12 months after the initial PCI, and OCT was performed on target lesions for initial and staged PCI at immediately, 1 month, and 12 months after the initial PCI. The present sub-analysis analyzed target lesions for staged PCI that serially underwent OCT and CAS immediately and 11 months after stent implantation to evaluate the impact of baseline YP on mid-term vascular response after stent implantation. Fig. 1 provides the patient flow chart. Staged PCI was performed for 118 coronary lesions from 105 patients. Of these, 30 lesions were excluded for the following reasons: (1) poor imaging quality of CAS immediately after staged PCI ($n = 8$); (2) lesions could not be followed-up for examination ($n = 11$); and (3) poor imaging quality of OCT data at follow-up (n = 11). Finally, the remaining 88 coronary lesions in 80 patients were analyzed (Fig. 1). This study was approved by each hospital's Ethics Committee, and it adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Angiographic procedure and analysis

Coronary angiography was performed after the administration of unfractionated heparin (5000 IU) into the radial, brachial, or femoral artery via the inserted sheath, and of isosorbide dinitrate into the coronary artery. The view showing the most severe stenosis was selected for quantitative coronary angiography, which was subsequently performed using a computerized angiographic analysis system (QAngioXA 7.3; Medis Medical Imaging Systems, Leiden, the Netherlands) at the same angle of projection before and immediately after PCI [11].

CAS procedure and analysis

CAS was performed for the lesion immediately after PCI and at 11-month follow up using a Smart-i™ angioscopic catheter (i Heart Medical, Tokyo, Japan) or Forwardlooking™ angioscope (Taisho Biomed Instruments, Osaka, Japan). Angioscopic images were analyzed to determine: (1) the dominant, maximum, and minimum degree of neointimal coverage (NIC) over the stent; (2) the yellow color grade of the stented segment; and (3) the presence of intra-stent thrombus. NIC 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, although covered, still transparently visible; grade 2, stent struts embedded in the neointima, but translucently visible; and grade 3, stent struts fully embedded and invisible on angioscopy [12]. The dominant NIC grade was defined as the NIC grade that occupied the largest area in the stented segment. The maximum NIC grade was defined as the NIC grade that was most covered in the stented segment, while the minimum NIC grade was defined as the NIC grade that was least covered in the stented segment. NIC was evaluated throughout entire stented segments, and was judged as heterogeneous when differences in the NIC grade became apparent. The heterogeneity of the grade is presented by the heterogeneity index calculated by maximum–minimum NIC grade [13]. The yellow color was graded as follows: grade 0, white; grade 1, light yellow; grade 2, yellow; grade 3, intense yellow [14]. The maximum yellow color grade was defined as the yellow color grade of the most intensely

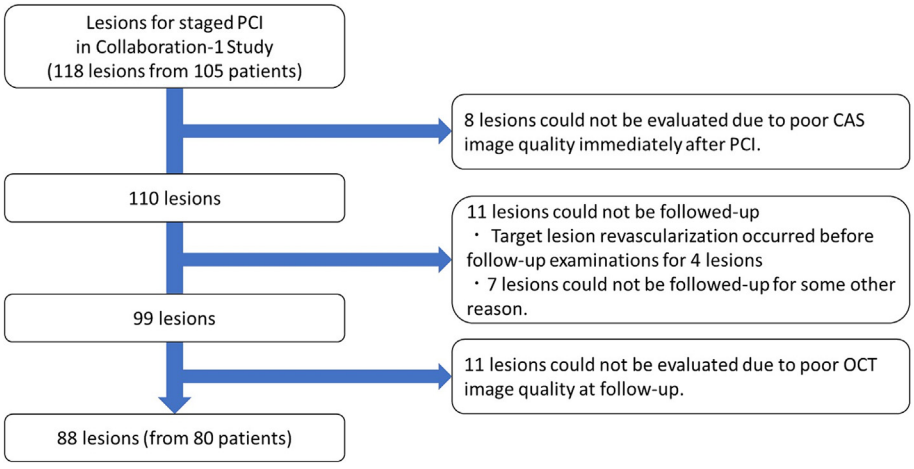

Fig. 1. Study Flow Chart. In total, 105 patients (118 lesions) who underwent percutaneous coronary intervention (PCI) were enrolled. Of these, 30 lesions were excluded for the following reasons: (1) poor imaging quality of coronary angioscopy (CAS) immediately after staged PCI ($n = 8$); (2) follow-up examinations could not be performed ($n = 11$); and (3) poor imaging quality of optical coherence tomography (OCT) data at follow-up (n = 11). Finally, the remaining 88 coronary lesions in 80 patients were analyzed.

Table 1
Patient characteristics.

	YP group ($n = 35$)	Non-YP group ($n = 45$)	p-value
Male, n (%)	28 (80)	34 (76)	0.84
Age, years	72 ± 11	74 ± 9	0.48
Body mass index, kg/m^2	24.2 ± 2.8	23.8 ± 4.0	0.59
Current smoking, n (%)	8 (23)	12 (27)	0.90
Hypertension, n (%)	27 (77)	37 (82)	0.78
Dyslipidemia, n (%)	29 (83)	41 (91)	0.44
Diabetes mellitus, n (%)	18 (51)	18 (40)	0.42
Chronic heart disease, n (%)	3 (9)	3 (7)	1.00
Atrial fibrillation, n (%)	4 (11)	8 (18)	0.54
Previous history of PCI, n (%)	8 (23)	16 (36)	0.33
Previous history of CABG, n (%)	2 (6)	1 (2)	0.58
Medication use at the time of PCI			
Aspirin, n (%)	35 (100)	45 (100)	–
P2Y12 inhibitor, n (%)	35 (100)	45 (100)	–
Anticoagulant drug, n (%)	5 (14)	6 (13)	1.00
Statin, n (%)	30 (86)	42 (93)	0.45
Medication use at 11-month follow-up			
Aspirin, n (%)	29 (83)	35 (78)	0.78
P2Y12 inhibitor, n (%)	30 (86)	39 (87)	1.00
Anticoagulant drug, n (%)	4 (11)	6 (13)	1.00
Statin, n (%)	33 (94)	44 (98)	0.82
Laboratory data at the time of PCI			
Total cholesterol, mg/dL	159 ± 30	147 ± 28	0.09
LDL cholesterol, mg/dl	84 ± 25	78 ± 24	0.50
HDL cholesterol, mg/dL	54 ± 14	50 ± 11	0.21
Triglyceride, mg/dL	130 ± 66	116 ± 54	0.37
HbA1c, %	6.4 ± 0.9	6.3 ± 0.6	0.34
Laboratory data at 11-month follow-up			
Total cholesterol, mg/dL	154 ± 22	147 ± 26	0.16
LDL cholesterol, mg/dl	76 ± 18	74 ± 20	0.79
HDL cholesterol, mg/dL	60 ± 14	53 ± 14	0.043
Triglyceride, mg/dL	113 ± 59	116 ± 74	0.83
HbA1c, %	6.6 ± 1.1	6.4 ± 0.9	0.35

Data are presented as mean ± SD or number (%).
CABG, coronary artery bypass grafting; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; YP, yellow plaque.

yellow part within the stented segment. The presence of YP was defined as the maximum yellow color grade ≥ 2 [15]. Thrombus was defined as a material adhering to the luminal surface or protruding into the lumen [13].

OCT procedure and analysis

OCT was performed for the lesion immediately after PCI and at 11-month follow up using the OPTIS™ Mobile System (Abbott Vascular). At the follow-up, struts were divided into 3 categories: covered (existence of any tissue on the strut), uncovered, and malapposed. In particular, tissue strut coverage with neointimal hyperplasia ≥40 μm was defined as adequate strut coverage [16,17]. The neointima was defined as the tissue between the luminal contour and stent contour and estimated in all frames in the stent. A calcified neointima had a well-delineated, signal-poor region with sharp borders. A lipid neointima had signal-poor regions with diffuse borders and high attenuation [18]. Neoatherosclerosis was defined as the presence of a lipid or calcified neointima [19].

Outcome measures

Outcome measures were OCT and CAS findings 11 months after PCI. These findings were compared between lesions with baseline YP (YP group) and lesions without baseline YP (Non-YP group).

Statistical analysis

Data are shown as mean and standard deviation (SD) for continuous variables or as percentages for discrete variables, unless otherwise indicated. Intergroup differences were tested using the Welch t-test for continuous variables, the Wilcoxon rank sum test for ordinal discrete variables, and the chi-squared test or the Fisher exact test for other discrete variables. The Kaplan-Meier method was used to estimate the cumulative incidences of target lesion revascularization and target vessel revascularization compared by the log-rank test. Ordinal logistic model and linear regression model analyses were performed to determine the impact of YP on OCT and CAS findings at 11 months, respectively. The interaction effect of stent type on the association of YP with the OCT findings and CAS finding was also analyzed using the same model. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria). Values of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics

Baseline YP was detected in 37 lesions (42 %). There were no significant differences in baseline patient characteristics between the groups (Table 1). With respect to lesion characteristics, lesion length was significantly longer in the YP group than Non-YP group (Table 2). For procedural characteristics, stent implantation pressure was higher in the YP group, although the pre- and post-dilatation balloon pressures were similar (Table 2). There were no significant differences in medications at 11-month follow-up between the groups (Table 1). Regarding the

Table 2
Lesion and procedural characteristics.

	YP group ($n = 37$)	Non-YP group ($n = 51$)	p-value
Target vessel, n (%)			0.90
LAD, n (%)	17 (46)	26 (51)	
LCX, n (%)	8 (22)	10 (20)	
RCA, n (%)	12 (32)	15 (29)	
ACC/AHA classification			0.14
A, n (%)	2 (5)	1 (2)	
B1, n (%)	3 (8)	7 (14)	
B2, n (%)	3 (8)	12 (24)	
C, n (%)	29 (78)	31 (61)	
Chronic total occlusion, n (%)	1 (3)	2 (4)	0.62
Pre-PCI QCA data			
Lesion length, mm	31 ± 14	24 ± 12	0.022
Reference vessel diameter, mm	2.58 ± 0.52	2.50 ± 0.47	0.46
Minimum lumen diameter, mm	0.94 ± 0.36	0.87 ± 0.29	0.33
Diameter stenosis, %	64 ± 9	65 ± 10	0.69
Post-PCI QCA data			
Reference vessel diameter, mm	2.98 ± 0.55	2.89 ± 0.45	0.44
Minimum lumen diameter, mm	2.48 ± 0.53	2.45 ± 0.39	0.82
Diameter stenosis, %	17 ± 7	15 ± 6	0.17
11-month follow-up QCA data			
Reference vessel diameter, mm	2.83 ± 0.58	2.65 ± 0.43	0.10
Minimum lumen diameter, mm	2.16 ± 0.50	2.05 ± 0.43	0.25
Diameter stenosis, %	23 ± 10	23 ± 10	0.78
Pre-dilatation, n (%)	35 (95)	48 (94)	1.00
Pre-dilatation balloon diameter, mm	2.66 ± 0.45	2.56 ± 0.39	0.32
Pre-dilatation balloon pressure, atm	12 ± 2	12 ± 3	0.49
Stent diameter, mm	2.91 ± 0.41	2.75 ± 0.33	0.057
Total stent length, mm	37 ± 17	30 ± 13	0.035
Stent implantation pressure, atm	10 ± 3	9 ± 3	0.046
Post-dilatation, n (%)	34 (92)	48 (94)	1.00
Post-dilatation balloon diameter, mm	3.22 ± 0.58	3.20 ± 0.43	0.85
Post-dilatation balloon pressure, mm	17 ± 4	17 ± 4	0.93
Type of stent			0.12
DP-EES, n (%)	23 (62)	22 (43)	
PF-BCS, n (%)	14 (38)	29 (57)	

Data are presented as mean ± SD or number (%).
ACC/AHA classification, American College of Cardiology/American Heart Association classification; DP-EES, durable polymer everolimus-eluting stent; LAD, left anterior descending artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; PF-BCS, polymer-free and carrier-free biolimus A9-coated stent; QCA, quantitative coronary angiography; RCA, right coronary artery; YP, yellow plaque.

Table 3
Optical coherence tomography findings at 11-month follow-up.

	YP group (n = 37)	Non-YP group (n = 51)	*p*-value
Minimum lumen area, mm^2	2.89 ± 2.00	2.67 ± 1.17	0.55
Maximum lumen area, mm^2	12.15 ± 5.25	10.49 ± 4.99	0.14
Mean lumen area, mm^2	6.14 ± 2.21	5.86 ± 2.18	0.55
Minimum lumen diameter, mm	1.83 ± 0.56	1.79 ± 0.39	0.74
Maximum lumen diameter, mm	3.81 ± 0.84	3.51 ± 0.85	0.11
Mean lumen diameter, mm	2.68 ± 0.49	2.62 ± 0.46	0.60
Minimum stent area, mm^2	4.70 ± 1.83	4.31 ± 1.46	0.29
Maximum stent area, mm^2	8.86 ± 2.98	8.58 ± 2.75	0.65
Mean stent area, mm^2	6.61 ± 1.99	6.17 ± 1.66	0.28
Minimum stent diameter, mm	2.40 ± 0.44	2.31 ± 0.38	0.27
Maximum stent diameter, mm	3.31 ± 0.54	3.25 ± 0.52	0.62
Mean stent diameter, mm	2.85 ± 0.42	2.76 ± 0.37	0.29
Mean reference lumen area, mm^2	5.82 ± 2.61	5.22 ± 1.87	0.25
Distal reference lumen area, mm^2	4.80 ± 2.79	3.99 ± 1.55	0.12
Proximal reference lumen area, mm^2	7.11 ± 3.80	6.45 ± 3.00	0.39
Mean reference lumen diameter, mm	2.63 ± 0.54	2.50 ± 0.43	0.25
Distal reference lumen diameter, mm	2.39 ± 0.62	2.21 ± 0.42	0.13
Proximal reference lumen diameter, mm	2.91 ± 0.73	2.78 ± 0.64	0.40
Analyzed struts per lesion	299 ± 131	255 ± 113	0.11
Percentage of struts			
Covered struts, %	97.70 ± 3.17	95.97 ± 8.68	0.20
Adequate strut coverage, %	75.75 ± 16.08	77.06 ± 18.84	0.73
Uncovered apposed struts, %	1.29 ± 2.48	2.91 ± 7.72	0.16
Uncovered malapposed struts, %	1.01 ± 1.49	1.11 ± 1.33	0.76
Maximum malapposition distance, μm	492.43 ± 459.62	518.43 ± 532.57	0.81
Maximum neointimal thickness, μm	454.49 ± 201.20	470.20 ± 208.69	0.72
Mean neointimal thickness, μm	104.02 ± 42.84	120.42 ± 48.49	0.098
Neoatherosclerosis, n (%)	4 (11)	0 (0)	0.028

Data are presented as mean ± SD or n (%).
YP, yellow plaque.

laboratory data at 11-month follow-up, the value of high-density lipoprotein-cholesterol was significantly higher in the YP group, although other lipid-related parameters were comparable (Table 1).

OCT findings at 11 months

OCT findings at 11 months after PCI are shown in Table 3. Although the covered strut and adequate strut coverage rates were similar between the groups, mean neointimal thickness tended to be thinner in the YP group than Non-YP group (104 μm versus 120 μm, $p = 0.098$). On the other hand, the incidence of neoatherosclerosis was significantly higher in the YP group than Non-YP group (11 % versus 0 %, $p = 0.028$). Additional analysis showed that all 4 lesions with neoatherosclerosis contained lipid neointima, not calcified neointima. Furthermore, OCT images before stent implantation demonstrated that lipid plaques were originally present at the neoatherosclerosis sites of all 4 lesions.

CAS findings at 11 months

Evaluations by CAS could not be performed due to poor image quality for 6 lesions in the YP group and 4 lesions in the Non-YP group at 11 months (16 % vs. 8 %, $p = 0.31$). CAS findings at 11 months are shown in Fig. 2. While maximum NIC grade was not significantly different, dominant and minimum NIC grades were significantly lower in the YP group than Non-YP group ($p = 0.049$ and $p = 0.026$). There was no statistically significant difference in the heterogeneity index between the YP and Non-YP groups ($p = 0.33$). In addition, maximum yellow color grade was significantly higher in the YP group ($p < 0.001$) (Fig. 2).

Additional analysis

In this study, we additionally analyzed the interaction effect of stent type on the association of baseline YP with OCT and CAS findings at 11-month follow up. Although the interaction analysis showed the association of YP with the heterogeneity index varied significantly by stent

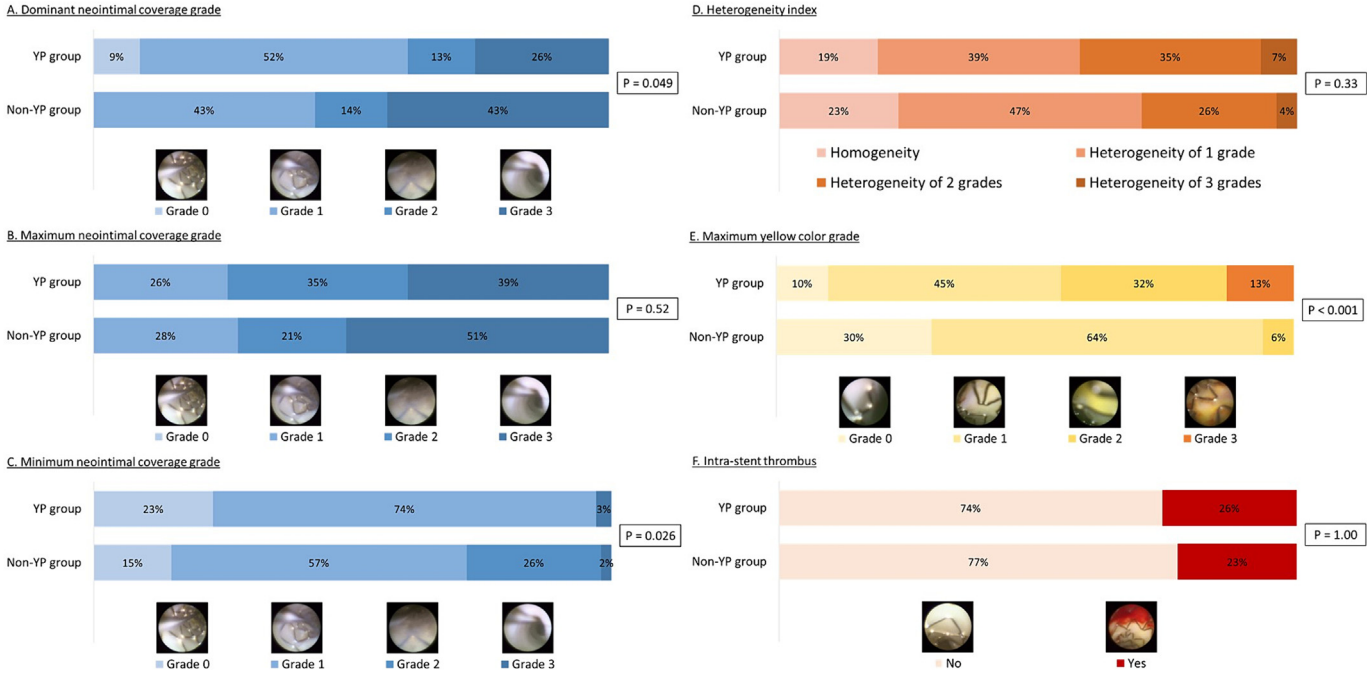

Fig. 2. Coronary Angioscopy Findings at 11-month Follow Up. **(A) Dominant neointimal coverage (NIC) grade.** Dominant NIC grade at 11-month follow up was significantly lower in the yellow plaque (YP) group than Non-YP group ($p = 0.049$). (**B) Maximum NIC grade.** Maximum NIC grade at 11-month follow up was similar between the YP and Non-YP groups ($p = 0.52$). (**C) Minimum NIC grade.** Minimum NIC grade at 11-month follow up was significantly lower in the YP group than Non-YP group ($p = 0.026$). (**D) Heterogeneity index.** Heterogeneity index at 11-month follow up was similar between the YP and Non-YP groups ($p = 0.33$). (**E) Maximum yellow color grade.** Maximum yellow color grade at 11-month follow up was significantly higher in the YP group than Non-YP group ($p < 0.001$). (**F) Intra-stent thrombus.** Intra-stent thrombus at 11-month follow up was similar between the YP and Non-YP groups ($p = 1.00$).

type ($p = 0.045$), there were no significant interaction effects of stent type on the association of baseline YP with other OCT and CAS findings at 11-month follow up (Online Table 1).

To evaluate the relationship between baseline YP and clinical outcomes, we conducted an additional analysis on 110 lesions from the staged PCI cohort (out of 118 lesions), excluding 8 lesions that could not be assessed due to poor CAS imaging immediately after stent implantation. The cumulative incidence of target lesion revascularization at 3 years after PCI was 2.3 % in the YP group and 7.1 % in the Non-YP group, with no statistically significant difference ($p = 0.32$) (Online Fig. 1A). Similarly, the cumulative incidence of target vessel revascularization at 3 years after PCI was 6.8 % in the YP group and 11.7 % in the Non-YP group, also without statistically significant difference ($p = 0.45$) (Online Fig. 1B). There were no occurrences of cardiac death or myocardial infarction observed in either group within the 3-year period.

Discussion

The main findings of the present study can be summarized as follows. 1) OCT findings at 11-month follow-up showed that mean neointimal thickness tended to be lower ($p = 0.098$) and the incidence of neoatherosclerosis was significantly higher in the YP group ($p = 0.028$). 2) CAS findings at 11-month follow-up revealed that dominant and minimum neointimal coverage grades were significantly lower ($p = 0.049$ and $p = 0.026$) and maximum yellow color grade was significantly higher in the YP group ($p < 0.001$).

A previous OCT study comparing the lesion morphologies after first-generation sirolimus-eluting stent implantation between patients with unstable angina pectoris and those with stable angina pectoris showed the lesions at baseline in unstable angina pectoris had higher incidence of lipid-rich plaque and thinner fibrous cap thickness than in those with stable angina pectoris. In addition, OCT findings at 9 months after stent implantation showed that the unstable angina pectoris group had significantly smaller percent volume of neointimal hyperplasia than the stable angina pectoris group [20]. A pathological report on acute myocardial infarction similarly showed that unstable lesions are prone to greater delay in vascular healing after DES implantation than stable lesions [21]. It is likely that drugs have high affinity for lipid-rich plaques and dwell there for longer periods because of greater strut penetration compared with strut penetration of more fibrotic types of plaque [21]. In addition, the lipid-rich plaques are more avascular compared with the more fibrous dominant regions of plaques and have fewer cells [21]. Therefore, these areas are less likely to be covered by migrating and proliferating cells from adjacent areas, which is thought to cause delayed vascular healing. There have been no reports investigating the relationship between baseline YP and mid-term vascular response in patients with CCS. Although the present study did not reach statistical significance, OCT findings at 11 months showed a trend toward thinner mean neointimal thickness in the YP group. In addition, minimal neointimal coverage grade assessed by CAS at 11 months was significantly lower in the YP group. The YP group was thought to have more lesions with lipid-rich plaques and thin-cap fibroatheroma, suggesting that such lesions may be more prone to delayed vessel healing after DES stenting even in CCS.

In the current study, the overall incidence of neoatherosclerosis was 4.5 %, and all lesions in which neoatherosclerosis occurred were detected in the YP group. Taking this result into account, the incidence of neoatherosclerosis was significantly higher in the YP group than the non-YP group. In the previous pathological study, underlying unstable plaque has been reported as one of the independent determinants of neoatherosclerosis [5]. The other report showed that thin-cap fibroatheroma identified by OCT was one of the predictors of neoatherosclerosis [22]. Therefore, it is reasonable to assume that the frequency of neoatherosclerosis was significantly higher in the YP group in the current study because it was possible that the YP group had more unstable lesions with lipid-rich plaque and thin-cap fibroatheroma. In a previous study evaluating OCT findings at 8 months after DES implantation, the incidence of neoatherosclerosis was 7.5 % in patients with CCS [23]. Compared to the incidence in the previous report, the incidence of neoatherosclerosis was lower in the current study. High LDL-cholesterol level was one of the risk factors for neoatherosclerosis 12 months after DES implantation [8]. Since the LDL-cholesterol levels were lower in the current study than the previous study, intensive lipid-lowering therapy may reduce the frequency of neoatherosclerosis. Although the mechanisms underlying the rapid development of neoatherosclerosis remain unknown, it is speculated that incompetent and dysfunctional endothelial coverage of the stented segment contributes to this process [3]. Stent implantation causes vascular injury with endothelial denudation [24]. Incomplete maturation of the regenerated endothelium (which is characterized by poor cell-to-cell junctions, reduced expression of anti-thrombotic molecules, and decreased nitric oxide production) is more frequently observed in DES than bare metal stent implantation because of the anti-proliferative effects of the eluted drugs [24–27]. Poorly formed cell junctions underlie impaired barrier function of the endothelium, which allows greater number of lipoproteins to enter the sub-endothelial space, leading to the development of neoatherosclerosis [3]. The frequency of neoatherosclerosis might have increased in the YP group because patients had more lipid-rich plaques and were more prone to delayed vascular healing. Pathologically, neoatherosclerosis within the stent is defined as: peri-strut foamy macrophage clusters with or without calcification, fibroatheromas, thin-cap fibroatheromas, and plaque ruptures with thrombosis as well as no communication with the underlying native atherosclerotic plaque [5]. However, OCT cannot determine whether the in-stent lesion communicates with the underlying native atherosclerotic plaque. In the current study, all neoatherosclerosis cases evaluated by OCT were found in the YP group, which suggests that OCT-defined neoatherosclerosis may include not only pathologically-defined neoatherosclerosis but also the underlying native atherosclerotic lesion.

The results of the current study suggested that baseline YP was associated with delayed vascular healing and increased neoatherosclerosis after DES implantation. On the other hand, it was reported that the lesions with neoatherosclerosis at 12-month follow-up had a significantly higher rate of target lesion revascularization than those without neoatherosclerosis [8]. In the multicenter in-stent restenosis registry, OCT findings demonstrated that neoatherosclerosis in in-stent restenosis lesions adversely affected the target lesion revascularization rate [7]. On the other hand, intensive lipid-lowering therapy induced a favorable change in plaque morphology with an increase in fibrous cap thickness, and decrease in both percentage plaque and lipid volume indexes [28,29]. Therefore, intensive lipid-lowering therapy before PCI may reduce lesions with YP and thus contribute to better vascular healing and clinical outcomes after stent implantation. Further investigation is needed to elucidate this issue.

Limitations

There are several limitations in the present study. First, this was a post-hoc analysis of the COLLABORATION-1 study [10], and the possibility of selection bias could not be ruled out because of the prospective observational design. Second, the sample size was relatively small. However, the sample size of this study was comparable to those of previous imaging studies. Third, the whole stented segment could not be completely evaluated on CAS in some cases because of limitations in the visual field, especially in angulated or tortuous lesions. However, in such cases, changing the guidewire sometimes improved the visual field. Fourth, morphological evaluation was impossible due to the poor quality of OCT or CAS images in some lesions. Fifth, baseline YP may include a lipid pool, which could impact the following vascular response. However, it was impossible to evaluate the relationship because OCT evaluation prior to stent implantation was not available for all lesions.

In addition, because coronary angioscopy was not performed before stent implantation in this study, the baseline yellow color grade was assessed by CAS images only immediately after stent implantation. The possibility that the yellow color grade changed from before to immediately after stent implantation could not be denied. Sixth, different types of CAS catheters were used during the study period according to their availability. We cannot completely rule out the possibility that this difference affected the angioscopic findings somewhat, although we carefully analyzed angioscopic images. Seventh, there were some stents that had a mixture of YP and non-YP sites within the same stented segment, and there may have been differences in the neointimal coverage. However, it is difficult to identify the YP site at the time of stent implantation by coronary angioscopy at the 11-month follow-up. Therefore, we could not assess the difference in neointimal coverage between the YP and non-YP sites within the same stent in this study. Eighth, two types of stents were enrolled in this study. Although stent type would have an impact on vessel healing, the interaction analysis showed there were no significant interaction effects of stent type on the association of baseline YP with OCT and CAS findings at 11-month follow-up, apart from the heterogeneity index. Finally, the supplementary analysis did not reveal any association between baseline YP and 3-year clinical outcomes. However, the limited sample size might have hindered the ability to fully assess these outcomes. A larger sample size may be necessary to provide a more definitive understanding of the association with clinical outcomes.

Conclusion

Baseline YP affected the incidence of neoatherosclerosis as well as poor neointimal coverage at 11 months after stent implantation.

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Declaration of competing interest

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