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ORIGINAL ARTICLE
Imaging

Early- and Middle-Phase Angioscopic Assessment of Arterial Healing Following Current Drug-Eluting Stent Implantation in Patients With Acute Coronary Syndrome

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Background: Drug-eluting stents (DESs) have been widely used for the treatment of acute coronary syndrome (ACS). However, there are few reports on early- and middle-phase arterial repair after DES implantation in ACS patients.

Methods and Results: Coronary angioscopy (CAS) findings covering the early and middle phases (mean [±SD] 4±1 and 10±2 months, respectively) of arterial healing after second- and later-generation DES placement between May 2009 and January 2020 were extracted from the Kansai Rosai Hospital Cardiovascular Center database. Neointimal coverage (NIC), yellow color intensity, and the incidence of thrombus adhesion were compared between ACS and chronic coronary syndrome (CCS) in the early (54 stents of 47 lesions, 38 ACS patients; 86 stents of 70 lesions, 52 CCS patients) and middle (179 stents of 154 lesions from 136 ACS patients; 459 stents of 374 lesions from 287 CCS patients) phases. In the early phase, NIC, the incidence of thrombus adhesion (ACS, 39.1%; CCS, 38.0%), and maximum yellow color grade were similar between the 2 groups. In the middle phase, although the maximum yellow color grade was significantly higher in the ACS group (P=0.013), NIC and the incidence of thrombus adhesion (ACS, 24.6%; CCS, 23.4%) were similar in the 2 groups.

Conclusions: Arterial healing assessment with CAS showed that NIC and the incidence of thrombus adhesion after DES implantation were similar between ACS and CCS patients.

Key Words: Acute coronary syndrome; Arterial healing; Coronary angioscopy

In the first-generation drug-eluting stent (DES) era, acute coronary syndrome (ACS) was associated with a higher incidence of stent thrombosis than chronic coronary syndrome (CCS).[1] The mechanism of late and very late stent thrombosis is thought to be delayed arterial healing and abnormal vascular responses, with a pathological study revealed that arterial healing was delayed in lesions with ACS compared with those with CCS.[2,3] Accordingly, the current guidelines recommend relatively long-term dual antiplatelet therapy (DAPT) in ACS patients because they are judged to be at higher thrombotic risk.[4,5]

Conversely, it has been reported that the risk of stent thrombosis is clearly lower for second- than first-generation DES, with some evidence supporting the use of a short DAPT strategy being published.[6–8] In the DAPT-STEMI trial, DAPT for 6 months was non-inferior to DAPT for 12 months in patients with ST-elevation myocardial infarction (STEMI) at 6 months after primary percutaneous coronary intervention (PCI) with second-generation DES.[9] In contrast, the SMART-DATE trial reported that short-term DAPT was non-inferior to long-term DAPT for major cardiovascular events, but the incidence of myocardial infarction was significantly higher following short-term DAPT.[10] Therefore, the safety of short-term DAPT for ACS remains uncertain.

In patients with ACS, early arterial healing after DES implantation is desirable to reduce the risk of stent thrombosis. Coronary angioscopy (CAS) can be used to observe intrastent status under direct and full-color vision, and can identify neointimal coverage (NIC) that cannot be seen

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Table 1. Patient and Lesion Characteristics

	Early phase			Middle phase		
	ACS	CCS	P value	ACS	CCS	P value
No. patients	38	52		136	287	
Male sex	27 (71)	47 (90)	0.018	115 (85)	239 (83)	0.74
Age (years)	68±10	71±8	0.086	67±12	70±10	0.016
Hypertension	37 (97)	44 (85)	0.046	110 (81)	210 (73)	0.084
Dyslipidemia	31 (82)	38 (73)	0.35	94 (69)	198 (69)	0.98
Diabetes	10 (26)	26 (50)	0.023	37 (27)	121 (42)	0.003
Smoking	10 (26)	18 (35)	0.40	48 (35)	59 (21)	0.001
Hemodialysis	3 (8)	2 (4)	0.65	0 (0)	8 (2.8)	0.059
Aspirin	37 (97)	52 (100)	0.42	126 (93)	271 (94)	0.48
$P2Y_{12}$ inhibitor	38 (100)	52 (100)	–	126 (93)	262 (91)	0.64
Statin	30 (79)	33 (64)	0.11	107 (79)	214 (75)	0.36
DOAC	1 (3)	0 (0)	0.42	4 (2.9)	15 (5.2)	0.29
No. lesions	47	70		154	374	
Target vessel			0.008			0.37
LAD	20 (43)	19 (27)		72 (47)	161 (43)	
LCx	3 (6.4)	20 (29)		26 (17)	88 (24)	
RCA	24 (51)	31 (44)		56 (36)	125 (34)	
Type B2/C lesions	40 (85)	47 (67)	0.029	132 (86)	274 (73)	0.002
Bifurcation	20 (43)	21 (30)	0.16	65 (42)	134 (36)	0.17
CTO	0 (0)	4 (5.7)	0.14	0 (0)	32 (8.6)	0.004
Calcification	5 (11)	12 (17)	0.33	11 (7.1)	71 (19)	0.001

Unless indicated otherwise, data are presented as the mean±SD or n (%). ACS, acute coronary syndrome; CCS, chronic coronary syndrome; CTO, chronic total occlusion; DOAC, direct oral anticoagulant; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery.

with other devices.[11–16] However, the early and mid-term arterial healing after implantation of second- and third-generation DES in patients with ACS has not been elucidated to date.

The purpose of this study was to comparatively investigate the early and middle-phase arterial healing following implantation of current DES in ACS and CCS lesions.

Methods

Patients

This was a single-center retrospective observational study. We extracted the CAS findings of second- and later-generation DES evaluated in the early phase (mean [±SD] 4±1 months after implantation; 140 stents in 117 lesions from 90 patients) or middle phase (10±2 months after implantation; 638 stents in 528 lesions from 423 patients) of arterial healing from the Kansai Rosai Hospital database for the period May 2009–January 2020. We then compared the CAS findings between ACS and CCS lesions in each phase: for the early phase, we evaluated 54 DES from 47 lesions in 38 ACS patients and 86 DES from 70 lesions in 52 CCS patients; for the middle phase, we evaluated 179 DES from 154 lesions in 136 ACS patients and 459 DES from 374 lesions in 287 CCS patients. All DES were implanted in de novo lesions in native coronary arteries. Patients who exhibited any event of earlier stent failure, such as in-stent restenosis, or who could not receive successful angioscopic evaluation were excluded from the study.

Although angioscopic evaluation at follow-up angiography as well as staged PCI for other lesions was recommended for all patients, this was not performed when informed consent could not be obtained or when a specialist for angioscopic evaluation was not available. The patients in this study 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 emergency patients, antiplatelet drugs (200 mg aspirin, 300 mg clopidogrel or 20 mg prasugrel) were loaded before PCI. Most patients continued to receive DAPT during the follow-up period.

This study was approved by the Medical Ethics Committee of Kansai Rosai Hospital and all patients provided written informed consent. This study was performed in accordance with the Declaration of Helsinki.

Angiographic and Angioscopic Follow-up

CAS was performed after the administration of unfractionated heparin (5,000 IU) into the radial or femoral artery via the inserted sheath and the administration of isosorbide dinitrate into the coronary artery. From May 2009 to September 2016, CAS was performed using a Fullview NEO angioscopic catheter (FiberTech, Tokyo, Japan). 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, smart-i angioscopic catheters (i Heart Medical, Tokyo, Japan) have been used because the Fullview NEO was discontinued. Using guide extension catheters such as GuideLiner (Japan Lifeline, Tokyo), Guidezilla (Boston Scientific, Natick, MA, USA) and guideplus (NIPRO, Osaka, Japan), blood flow was blocked by flushing with low molecular weight dextran. Both the Fullview NEO and smart-i angioscopic

Table 2. Procedural Characteristics

	Early phase			Middle phase		
	ACS	CCS	P value	ACS	CCS	P value
No. stents	54	86		179	459	
Follow-up duration (days)	115±33	126±30	0.039	314±66	308±70	0.34
Access site			0.16			0.30
Radial artery	38 (70)	64 (74)		117 (65)	272 (59)	
Femoral artery	16 (30)	18 (21)		55 (31)	160 (35)	
Brachial artery	0 (0)	4 (5)		7 (4)	27 (6)	
Guiding catheter size			0.050			0.004
6 Fr	48 (89)	65 (76)		139 (78)	309 (67)	
7 Fr	5 (9)	9 (11)		26 (15)	66 (14)	
8 Fr	1 (2)	12 (14)		14 (8)	84 (18)	
Type of stent			0.111			0.087
Second-generation DES	29 (54)	60 (70)		72 (40)	229 (50)	
Promus™	2 (3.7)	2 (2.3)		27 (15)	24 (5.2)	
Resolute™	23 (43)	19 (22)		8 (4.5)	55 (12)	
Xience™	4 (7.4)	39 (45)		37 (21)	150 (33)	
Third-generation DES	23 (43)	22 (26)		74 (41)	162 (35)	
Synergy™	15 (28)	15 (17)		53 (30)	127 (28)	
Ultimaster™	8 (15)	7 (8.1)		21 (12)	35 (7.6)	
Newer-generation DES	2 (3.7)	4 (4.7)		33 (18)	68 (15)	
Orsiro™	2 (3.7)	4 (4.7)		33 (18)	68 (15)	
Predilatation	28 (52)	65 (76)	0.006	115 (64)	389 (85)	<0.001
Predilatation balloon diameter (mm)	2.6±0.54	2.60±0.37	0.80	2.5±0.45	2.6±0.44	0.35
Predilatation balloon pressure (atm)	13±3.0	13±4	0.58	12±3.0	13±4.2	0.009
Stent diameter (mm)	3.2±0.40	2.96±0.40	0.005	3.1±0.54	3.0±0.48	0.005
Stent length (mm)	24±8.0	24±8.6	0.75	24±8.8	25±9.2	0.69
Stent implantation pressure (atm)	11±1.8	10.0±1.6	0.28	10±2.0	10±2.9	0.57
Post-dilatation	45 (83)	76 (88)	0.090	149 (83)	414 (90)	0.012
Post-dilatation balloon diameter (mm)	3.3±0.49	3.1±0.53	<0.001	3.4±0.53	3.2±0.52	<0.001
Post-dilatation balloon pressure (atm)	17±3.2	16±2.7	0.18	16±4.0	16±3.6	0.93

Unless indicated otherwise, data are presented as the mean±SD or n (%). ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DES, drug-eluting stent.

catheter images consisted of 3,000 pixels with full color and were digitally stored for off-line analysis. In addition, a forward-looking angioscopic catheter (OVALIS, Osaka, Japan) that can project images with 9,000 pixels and a smart-i 6K angioscopic catheter (Surgetech Corp.) that can project images with 6,000 pixels have been available since August 2018 and October 2018, respectively. These catheters were used in some cases.

Angioscopic Analysis

Angioscopic images were analyzed to determine the dominant degree of NIC over the stent, heterogeneity of NIC, the yellow color grade of the stented segment, and the presence of intrastent thrombus. NIC over the stent was classified into 4 grades, as described previously: 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; and Grade 3, stent struts fully embedded and invisible on angioscopy.[11]

Heterogeneity of NIC has been defined previously.[12] Briefly, NIC was evaluated throughout the 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. Stent edges were also excluded from the heterogeneity analysis. The yellow color was graded as follows: Grade 0, white; Grade 1, light yellow; Grade 2, yellow; and Grade 3, intense yellow.[13] A thrombus was defined as material adhering to the luminal surface or protruding into the lumen.[14]

As reported in a previous article, the estimated inter- and intra-observer κ coefficients were 0.84 and 0.95, respectively, for the dominant degree of NIC over the stent; 0.84 and 0.83, respectively, for heterogeneity of NIC; 0.82 and 0.86, respectively, for the yellow color grade of the stented segment; and 0.93 and 1.0, respectively, for the presence of intrastent thrombus.[13]

Statistical Analysis

Unless stated otherwise, data are presented as the mean±SD. Continuous variables with and without homogeneity of variance were analyzed by Student's t-test and Welch's t-test, respectively. Categorical variables were analyzed with Fisher's exact test for 2×2 comparisons. For comparisons of more than 2×2, the Mann-Whitney test was used. Multivariate analysis was performed using logistic regres-

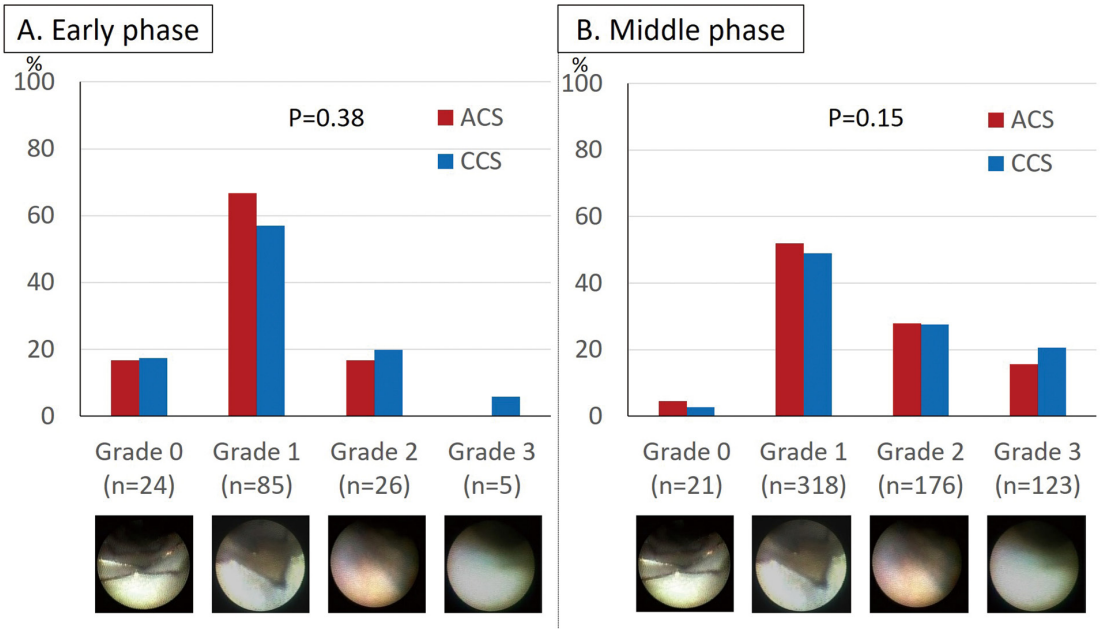

Figure 1. Dominant neointimal coverage (NIC) grade in acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) in the (**A**) early and (**B**) middle phases. (**A**) The dominant NIC grade in the early phase was similar (P=0.38) in the ACS (Grade 0, 16.7%; Grade 1, 66.7%; Grade 2, 16.7%; Grade 3, 0%) and CCS (Grade 0, 17.4%; Grade 1, 57%; Grade 2, 19.8%; Grade 3, 5.8%) groups. (**B**) The dominant NIC grade in the middle phase was also similar (P=0.15) in the ACS (Grade 0, 4.5%; Grade 1, 52.0%; Grade 2, 27.9%; Grade 3, 15.6%) and CCS (Grade 0, 2.8%; Grade 1, 49%; Grade 2, 27.5%; Grade 3, 20.7%) groups.

sion. Statistical significance was defined as 2-tailed P<0.05. All calculations were performed using IBM SPSS Statistics package version 27 (IBM Corp., Armonk, NY, USA).

Results

Patients

Patient, medication, lesion, and procedural characteristics are presented in **Table 1**. There were significantly more diabetic patients in the CCS group in both the early and middle phases. There were significantly more hypertensive patients in the ACS group in the early phase, and there were significantly more smokers in the ACS group in the middle phase. Lesion characteristics were similar except for the target vessels and Type B2/C lesions in the early phase, and chronic total occlusion, severe calcification, and Type B2/C lesions in the middle phase. In terms of procedural characteristics, predilatation was more frequently performed in the CCS group and stent size and post-dilation balloon size were significantly larger in the ACS group in both phases (**Table 2**).

Angioscopic Findings

The follow-up duration in the ACS and CCS groups was 115±33 and 126±30 days, respectively, in the early phase (P=0.039) and 314±66 and 308±70 days, respectively, in the middle phase (P=0.34). In the early phase, dominant NIC and NIC heterogeneity were similar between the ACS and CCS groups (**Figures 1A**,**2A**). The incidence of thrombus adhesion was also similar between the 2 groups (**Figure 3A**). Although the incidence of the stented segment with an intense yellow color in the ACS group was twice as high as in the CCS group, the yellow color grade was not significantly different between the 2 groups (**Figure 4A**). In the middle phase, dominant NIC grade and NIC heterogeneity were similar in the ACS and CCS groups (**Figures 1B**,**2B**). Although the maximum yellow color grade was significantly higher in the ACS group (**Figure 4B**), thrombus adhesion was similar between the ACS and CCS groups (**Figure 3B**).

Discussion

In the present study, through the evaluation of second- and later-generation DES, we determined that: (1) the dominant NIC grade, NIC heterogeneity, the incidence of thrombus adhesion, and the maximum yellow color grade were similar between ACS and CCS in the early phase; and (2) in the middle phase, the maximum yellow color grade was significantly higher in the ACS than CCS group, but the other CAS findings were similar between the 2 groups. To the best of our knowledge, this is the first report describing the intravascular status evaluated by CAS 4 or 10 months after current DES implantation for ACS lesions compared with CCS lesions.

Nishino et al reported CAS findings 6 months after implantation of a first-generation sirolimus-eluting stent.[15] In that study, a significantly higher percentage of patients in the sufficient coverage group had ACS lesions at the time of implantation than in the insufficient coverage group, and the presence of ACS at the time of implantation was an independent predictor of sufficient coverage.[15] Conversely, a previous optical coherence tomography (OCT) study demonstrated that exposed struts and exposed struts with malapposition were more frequent in patients with

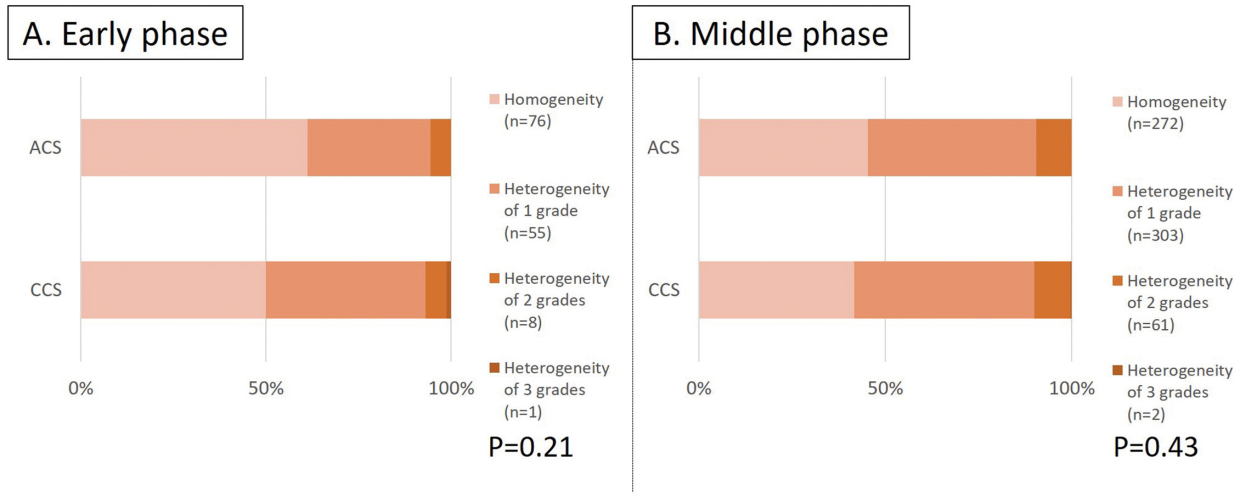

Figure 2. Heterogeneity of neointimal coverage (NIC) grade in acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) lesions in the (**A**) early and (**B**) middle phases. (**A**) The heterogeneity of NIC in the early phase was similar (P=0.21) in the ACS (homogeneity, 61.1%; heterogeneity of 1 grade, 33.3%; heterogeneity of 2 grades, 5.6%; heterogeneity of 3 grades, 0%) and CCS (homogeneity, 50.0%; heterogeneity of 1 grade, 43.0%; heterogeneity of 2 grades, 5.8%; heterogeneity of 3 grades, 1.2%) groups. (**B**) The heterogeneity of NIC in the middle phase was similar (P=0.43) in the ACS (homogeneity, 45.3%; heterogeneity of 1 grade, 45.3%; heterogeneity of 2 grades, 9.5%; heterogeneity of 3 grades, 0%) and CCS (homogeneity, 41.6%; heterogeneity of 1 grade, 48.4%; heterogeneity of 2 grades, 9.6%; heterogeneity of 3 grades, 0.4%) groups.

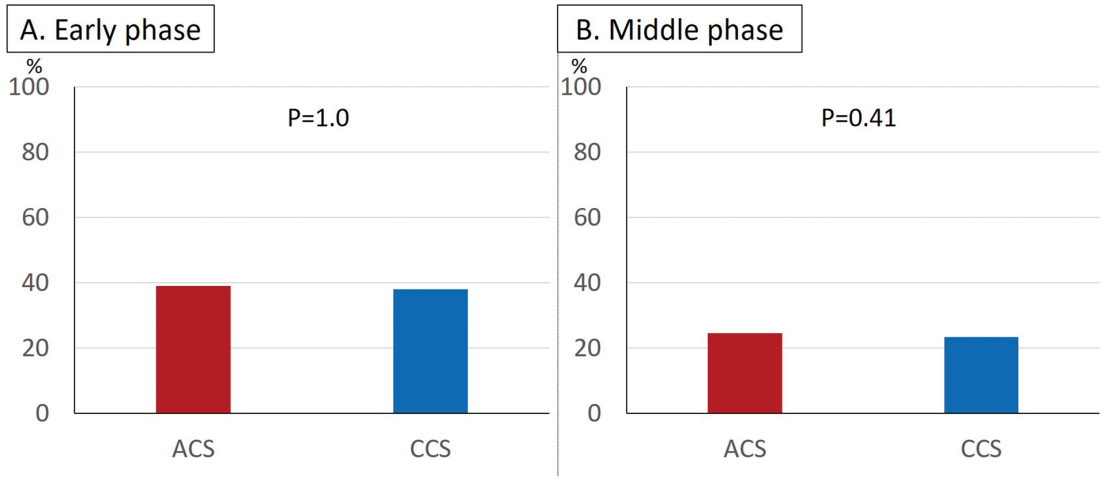

Figure 3. Incidence of thrombus adhesion in acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) lesions in the (**A**) early and (**B**) middle phases. The incidence of thrombus adhesion was similar between the ACS and CCS groups in both the early (**A**; 39.1% vs. 38.0%, respectively; P=1.0) and middle (**B**; 24.6% vs. 23.4%, respectively; P=0.41) phases.

ACS than in non-ACS patients 3 months after implantation of a first-generation DES.[16] Similarly, another study reported that the incidence of inadequately apposed stent and partially uncovered stent by neointima was significantly greater in patients with unstable than stable angina pectoris at 9 months.[17] In contrast, Mizoguchi et al evaluated OCT findings 12 months after second-generation DES implantation and found that the median neointimal thickness, frequency of uncovered struts, and percentage of stents fully covered by neointima were similar between STEMI patients and those with stable angina pectoris.[18] The results of the present study are similar to those of this previous OCT report in the middle phase after implantation of second- and later-generation DES. In addition, the CAS findings at 4 months were similar between the ACS and CCS groups. The second- and later-generation DES have thinner stent struts, more biocompatible polymers, and limus-type drugs for which there is reliable evidence in

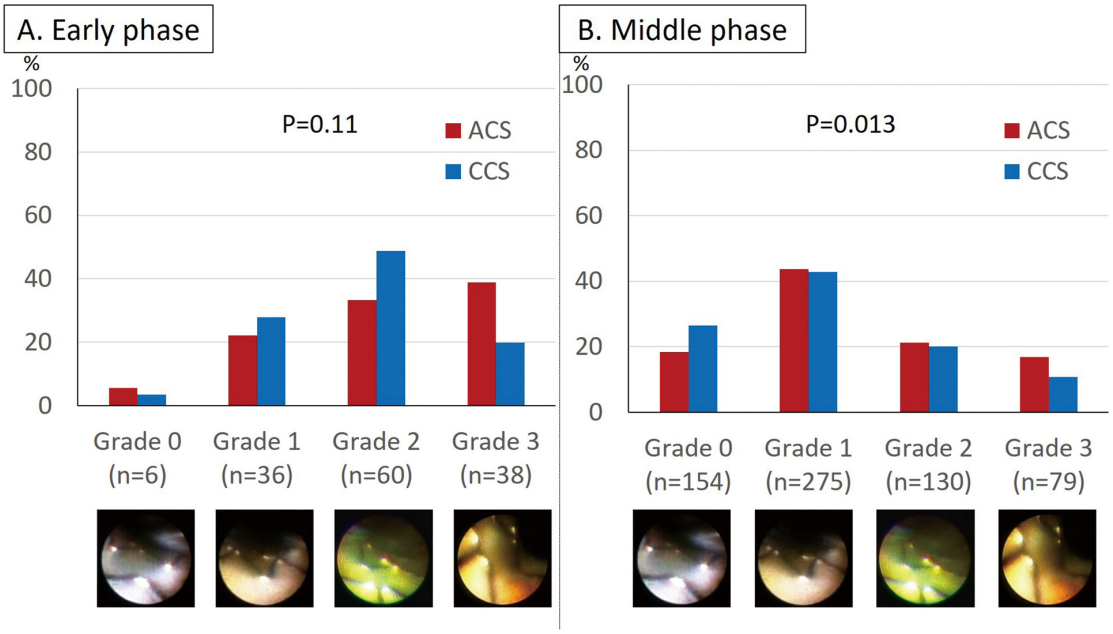

Figure 4. Maximum yellow color grade of the stented segment in acute coronary syndrome (ACS) lesions and chronic coronary syndrome (CCS) lesions in the (**A**) early and (**B**) middle phases. (**A**) The maximum yellow color grade of the stented segment in the early phase was similar (P=0.11) between the ACS (Grade 0, 5.6%; Grade 1, 22.2%; Grade 2, 33.3%; Grade 3, 38.9%) and CCS (Grade 0, 3.5%; Grade 1, 27.9%; Grade 2, 48.8%; Grade 3, 19.8%) groups. (**B**) The maximum yellow color grade of the stented segment in the middle phase was significantly (P=0.013) higher in the ACS (Grade 0, 18.4%; Grade 1, 43.6%; Grade 2, 21.2%; Grade 3, 16.8%) than CCS (Grade 0, 26.4%; Grade 1, 42.9%; Grade 2, 20.0%; Grade 3, 10.7%) group.

patients undergoing PCI.[19] These factors would contribute to the similar arterial healing between CCS and ACS lesions with vulnerable plaque.

A previous study demonstrated a significant relationship between the plaque color grade evaluated by CAS and the thickness of the fibrous cap estimated by OCT, with a high yellow intensity reflecting a thinner fibrous cap, a sign of more vulnerable plaque.[20] Other previous CAS studies reported that the yellow color intensity of plaque determined by CAS was strongly related to the prevalence of thrombus on the plaque, and that the number of yellow plaques was correlated with the development of ACS.[21,22] In the present study it appeared that the yellow color at 4 months after implantation represented the original yellow color of the vessel wall, although it is impossible to state this definitively because the color of the vessel wall was not evaluated at the time of stent implantation in our patients. Although the sample size was relatively small and there were no significant differences, the numerical frequency of Grade 3 yellow color in ACS was approximately twice that in CCS. It would be reasonable to expect that a higher yellow color grade corresponding to vulnerable plaque would be more frequently observed in ACS than CCS lesions. Indeed, we found that the yellow color grade was significantly higher in ACS than CCS lesions at 10 months. However, the frequency of Grade 3 lesions decreased to <20% of total ACS lesions at 10 months, suggesting that plaque stabilization was achieved. Whether neoatherosclerosis contributed to the higher yellow color intensity is unknown, and further investigations are needed to clarify this issue.

Although the current guidelines recommend shorter-term DAPT for patients with DES, relatively long-term DAPT is recommended in ACS patients because they are considered to be at higher thrombotic risk.[4,5,23] CAS has better detection power for thrombus than OCT,[24] and thrombus adhesion is an initial phase of arterial repair and does not occur where arterial repair is completed.[25,26] The present study demonstrated that the CAS findings of arterial healing were similar at 4 and 10 months after implantation of second- and later-generation DES, and, based on these findings, it may be possible to safely switch DAPT to single antiplatelet therapy (SAPT) from the early phase in ACS and CCS lesions. However, it has also been reported that plaque vulnerability in the non-stenting area is high in ACS patients, and DAPT has been shown to reduce adverse events such as acute myocardial infarction caused by non-culprit lesions.[27,28] Therefore, we should investigate the availability of SAPT while also considering the control of risk by lipid-lowering therapy and the optimal therapy for diabetes. Ongoing clinical trials may provide the answers.

Study Limitations

This study has several limitations. First, it was a single-center, non-randomized observational study. However, the sample size was sufficient to permit evaluation of the outcome and was comparable to previous CAS studies. Second, in some cases CAS could not completely evaluate the whole stented segment due to limitations in the CAS visual field, especially in angulated or tortuous lesions. However, in such cases, changing the guidewire sometimes improved the visual field. Third, the mechanism underlying ACS,

such as plaque rupture, plaque erosion, and calcified nodule, would affect arterial healing. However, we did not evaluate differences between these mechanisms because the use of OCT was only 8.5% in the early phase and 14.3% in the middle phase in the ACS group, and 22.9% in the early phase and 40.1% in the middle phase in CCS group. Fourth, because this study included patients who underwent coronary angioscopic procedures during follow-up coronary angiography, it is possible there was selection bias. Fifth, PCI procedures such as incomplete stent apposition would affect arterial healing. However, they were not evaluated because the use of OCT was limited in this study. Sixth, because 3 types of CAS were used in this study, the visibility and findings may differ between examinations. However, it was impossible to perform a validation study because it was difficult to use the multiple types of CAS on the same patient. Finally, some patient, lesion, and procedural background characteristics differed between the ACS and CCS groups, which could have affected CAS findings.

Conclusions

The dominant NIC grade and thrombus adhesion were similar between the 2 groups in the early and middle phase after the implantation of current DES. This similar arterial healing suggests that the short DAPT strategy may be appropriate not only for patients with CCS, but also those with ACS.

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Disclosures

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IRB Information

This study was approved by the Ethics Committee of Kansai Rosai Hospital (Reference no. 15D081 g).

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