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The impact of acute coronary syndrome on late drug-eluting stents restenosis

Insights from optical coherence tomography

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Abstract

The aim of the study was to investigate the optical coherence tomography (OCT)-identified difference of in-stent restenosis (ISR) tissue characteristics between patients with and without acute coronary syndrome (ACS) at index intervention.

The retrospective study included 80 patients with 85 drug-eluting stent (DES) restenosis lesions. Subjects were classified according to clinical presentation at the time of de-novo lesion intervention, namely ACS and non-ACS. OCT was performed at 5 years follow-up. The frequency of malapposition, neointimal characteristics, thrombus, and minimal stent area (MSA) were evaluated.

ACS group consisted of 48 (60%) patients. The mean duration from initial intervention to OCT study was 66.15 months. Malapposition was more frequent in the ACS group (25.5% vs 2.9%, $P = .006$), as well as a higher prevalence of thrombus in the ACS group (21.6% vs 0%, $P = .015$). MSA of ACS group was significantly less than that of non-ACS group (4.99 ± 1.80 vs 5.62 ± 2.08 mm^2, $P = .018$). Compared with non-ACS group, only MI group was related to smaller MSA (4.37 ± 1.39 vs $5.62 \pm 2.08\,mm^2$, $P = .048$); The unstable angina (UA) group was not associated with a decreased MSA. The occurrence of neoatherosclerosis tended to be higher in ACS group (60.8% vs 41.2%, $P = .076$).

In DES restenosis, an ACS presentation at initial intervention is associated with a higher incidence of malapposition, thrombus, and smaller MSA.

Abbreviations: ACS = acute coronary syndrome, DES = drug-eluting stent, ISR = in-stent restenosis, MI = myocardial infarction, MSA = minimal stent area, NA = neoatherosclerosis, OCT = optical coherence tomography.

Keywords: acute coronary syndrome, drug-eluting stent, in-stent restenosis, optical coherence tomography

1. Introduction

In-stent restenosis (ISR) is the leading cause of late device failure, unplanned and repeat revascularization in the drug-eluting stent (DES) era.[1] DES is widely applied in clinical practice, yet a number of studies have reported its restenosis rates higher than 10%.[2,3] Besides, it is generally known that patients with acute coronary syndrome (ACS) have higher risk of recurrent revascularization and worse long-term prognosis after percutaneous coronary intervention compared with those who have stable angina.[4,5] Optical coherence tomography (OCT) is a valuable intravascular imaging modality to assess restenosis.[6] Previous study has uncovered that the initial presentation of ACS was associated with more frequent heterogeneous neointima findings, which was related with deteriorated clinical outcomes.[7] Such findings indicated that the postintervention vascular response might be different between patients who initially presented with and without ACS. However, whether ISR neointimal characteristics evaluated by OCT depend on initial de novo ACS is still unknown.

Therefore, we sought to further explore the impact of ACS on DES restenotic neointimal characteristics and potential mechanisms with high-resolution OCT in the present study.

2. Methods

2.1. Study population

From January 2014 to October 2016, we retrospectively identified 111 patients with 120 DES angiographic restenosis lesions who underwent preprocedural OCT at Anzhen hospital. Angiographic restenosis was defined as a diameter stenosis >50% on angiography and further classified as Mehran types.[8] Inclusion criteria were: with ISR after DES implantation on angiography; and amenable for OCT examination. Exclusion

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criteria were: bypass graft lesion; cardiogenic shock; left ventricular ejection fraction <40%; serum creatinine >2 mg/dL; and poor image quality. The following exclusions were made: 10 patients with poor OCT image quality, 13 patients implanted with bare-metal stents (BMS), and 8 patients with incomplete data. Finally, a total of 80 patients with 85 lesions were included in the analysis.

The clinical presentations at the time of index intervention were divided into 2 groups: ACS or non-ACS, ACS was further categorized as unstable angina (UA) and myocardial infarction (MI, including ST segment elevated MI and non-ST segment elevated MI).[9] Non-ACS included stable angina and silent ischemia. This study was approved by the Institutional Ethics Committee of Anzhen Hospital.

2.2. OCT images acquisition

OCT image acquisition was performed using commercially available frequency domain OCT systems (C7-XR OCT Intravascular Imaging System; St. Jude Medical Inc., St. Paul, MN). The intracoronary OCT imaging technique has been previously described.[10] OCT images were generated at 100 frames/sec, whereas the catheter was pulled back at 20 mm/sec. A contrast medium was continuously flushed through a guiding catheter at a rate of 4 to 5 mL/s for 3 to 4 seconds. Continuous images were acquired and stored digitally for analysis.

2.3. OCT imaging analysis

The quantitative and qualitative analysis of OCT images was performed using off-line OCT proprietary software (LightLab Imaging Inc., Westford, MA). The region of interests (ROI) was defined as in stent segment and 5 mm proximal and distal segments. Cross-sectional OCT images of in-stent segments were analyzed every 1 mm by 2 independent investigators (SJW and WL) who were blinded to clinical and laboratory data. When there was discordance between the 2 observers, a consensus reading was acquired from a 3rd investigator (YHG).

The pattern of restenotic tissue structure in the cross-sectional images at every 1 mm interval was categorized into 3 types: homogeneous, heterogeneous, and layered pattern.[6] OCT assessment was made on the basis of definitions reported in expert consensus document:[11] malapposition was defined as separation of stent struts from the vessel wall with a strut-vessel lumen distance > 200 μm. Thrombus was defined as signal-rich, low-backscattering protrusions (white thrombus), or high-backscattering protrusions (red thrombus) inside the lumen with signal-free shadowing. Neoatherosclerosis (NA) was defined as the presence of lipid-laden intima and/or calcification inside the stent. Thin-cap fibroatheroma-like neointimal was defined as the presence of an area with signal attenuation and a diffused border, and fibrous cap thickness at the thinnest part ≤65 μm. The site of NA was classified as proximal section (PS), middle section (MS), and distal section (DS) of the stent body.[12] Microvessel was defined as small tubular or vesicular structures with a diameter <200 μm.

Quantitative analysis of OCT images were performed at minimal lumen area sites. The minimum lumen area and stent area were manually traced, and mean neointimal thickness was automatically calculated.

2.4. Statistical analysis

The data are expressed as means ± SD, n (%), or median (interquartile range [IQR]). Intergroup comparison was done with the χ^2 independence test or Fisher exact probability test, and difference in mean values was tested by Student *t* test, at a critical level of 5% or lower. Comparison of continuous variables between the 3 groups was done by one-way ANOVA test. Inter- and intraobserver variability in diagnosis of NA presence and tissue properties were evaluated by Cohen coefficient kappa. All data were analyzed using SPSS software (version 21, IBM Inc., IL).

3. Results

3.1. Clinical and angiographic characteristics

The study comprised 80 patients with 85 ISR lesions. The ACS cohort included 48 patients, whereas the non-ACS group comprised 32 patients. Patients profile are summarized in Table 1. There were no significant differences between groups for any item.

Table 1

Patient characteristics.

	Overall (n = 80)	ACS group (n = 48)	non-ACS group (n = 32)	Univariate *P*-value
Sex, M n, %	59 (68.6)	37 (77.1)	22 (68.8)	.407
Age, y	58.49 ± 11.17	60.13 ± 12.21	56.03 ± 9.02	.109
Hypertension, n, %	55 (64.0)	32 (66.7)	23 (71.9)	.622
Diabetes mellitus, n, %	34 (39.5)	18 (37.5)	16 (50.0)	.268
Hyperlipidemia, n, %	30 (34.9)	15 (31.3)	15 (46.9)	.157
Smoking history, n, %	41 (47.7)	25 (52.1)	16 (50.0)	.855
ISR clinical presentation				.449
Non-ACS, n, %	27 (31.4)	15 (31.3)	12 (37.5)	
Unstable angina, n, %	46 (53.5)	30 (62.5)	16 (50.0)	
Myocardial infarction, n, %	7 (8.1)	3 (6.3)	4 (12.5)	
Lab findings				
Total cholesterol, mmol/L	3.81 ± 1.00	3.75 ± 0.94	3.91 ± 1.09	.478
Triglyceride, mmol/L	1.78 ± 1.26	1.66 ± 1.20	1.96 ± 1.35	.317
HDL-C, mmol/L	1.01 ± 0.20	1.02 ± 0.21	1.00 ± 0.18	.636
LDL-C, mmol/L	2.16 ± 0.78	2.13 ± 0.76	2.22 ± 0.80	.592
Fasting glucose, mmol/L	7.18 ± 3.71	6.76 ± 3.30	7.81 ± 4.22	.214
HbA1c, %	6.56 ± 1.60	6.30 ± 1.68	6.96 ± 1.41	.094

Values are mean ± SD or n (%). ACS = acute coronary syndrome, HDL = high-density lipoprotein, ISR = in-stent restenosis, LDL = low-density lipoprotein, SD = standard deviation.

Table 2

Lesion characteristics.

	Overall (n = 85)	ACS group (n = 51)	non-ACS group (n = 34)	Univariate *P*-value
Time from PCI to OCT study, mo	66.15 ± 42.84	70.10 ± 41.04	60.24 ± 45.38	.301
Lesion location				.782
LAD, n, %	41 (48.2)	23 (45.1)	18 (52.9)	
LCX, n, %	22 (25.9)	14 (27.5)	8 (23.5)	
RCA, n, %	21 (24.7)	13 (25.5)	8 (23.5)	
Total stent length, mm	30.76 ± 9.80	30.75 ± 9.30	30.79 ± 10.66	.985
Stent type				.203
1st-generation DES	52 (61.2)	34 (66.7)	18 (52.9)	
2nd-generation DES	33 (38.8)	17 (33.3)	16 (47.1)	
Mehran classification				.341
Focal:I n, %	35 (41.2)	23 (45.1)	12 (35.3)	
Diffuse:II/III/IV n, %	22 (25.9)	10 (19.6)	12 (35.3)	
III, n, %	11 (12.9)	6 (11.8)	5 (14.7)	
IV, n, %	17 (20.0)	12 (23.5)	5 (14.7)	
Treatment				.317
DES, n, %	32 (37.6)	16 (31.4)	16 (47.1)	
DCB, n, %	41 (48.2)	27 (52.9)	14 (41.2)	
PLB, n, %	6 (7.1)	3 (5.9)	3 (8.8)	

ACS = acute coronary syndrome, DCB = drug-coated balloon, DES = drug-eluting stent, LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, PLB = plain balloon.

Table 2 shows the angiographic characteristics of ISR lesions according to clinical presentation at initial intervention. Overall, angiographic ISR types were similar in all groups. The mean duration from PCI to follow-up was 70.10 ± 41.04 months for ACS group and 60.24 ± 45.38 months for non-ACS group. There were no significant differences in stent location and total stent length between groups. Most of the lesions were treated with either DESs or drug-eluting balloons.

3.2. OCT findings

The OCT findings of ISR lesions are shown in Table 3. The restenotic tissue patterns were similar among groups. Compared with the non-ACS group, malapposition was more frequently observed in patients of ACS group (27.5% vs 2.9%, $P = .004$). Thrombus also occurred more frequently in the ACS group (21.6% vs 0%, $P = .015$). We divided the ACS group into UA and MI subgroups and analyzed the frequencies of malapposition and thrombus among 3 groups (Fig. 1). Although not statistically significant, NA was more frequently found in the ACS group (60.8% vs 41.2%, $P = .076$). Notably, the minimal stent area (MSA) was significantly smaller in the ACS group (4.99 ± 1.80 vs 5.62 ± 2.08 mm^2, $P = .018$). Moreover, only MI group was related to smaller MSA compared with non-ACS group (4.37 ± 1.39 vs 5.62 ± 2.08 mm^2, $P = .048$); the UA group was not associated with a decreased MSA (5.75 ± 1.98 vs 5.62 ± 2.08 mm^2, $P = .970$). As the severity of index presentation grew, the value of MSA decreased (Fig. 2). The representative angiographic and OCT images of patients initially treated for ACS are shown in Fig. 3.

The inter-/intraobserver variability (kappa values) of OCT measurement was as follows: 0.90/0.94 for malapposition, 0.93/0.95 for thrombus, and 0.90/0.92 for NA presence.

Table 3

Distribution of optical coherence tomography variables according to initial clinical presentation.

	Overall (n = 85)	ACS group (n = 51)	non-ACS group (n = 34)	Univariate *P*-value
Restenotic tissue structure				.703
Homogeneous, n, %	32 (37.6)	19 (37.3)	13 (38.2)	
Heterogeneous, n, %	41 (48.2)	26 (51.0)	15 (44.1)	
Layered, n, %	12 (14.1)	6 (11.8)	6 (17.6)	
MLA site				
Minimal lumen area, mm^2	1.84 ± 1.02	1.95 ± 1.04	1.67 ± 0.97	.220
Stent area, mm^2	6.59 ± 2.27	6.61 ± 2.12	6.56 ± 2.52	.920
Neointimal thickness, mm	0.71 ± 0.25	0.69 ± 0.22	0.74 ± 0.30	.384
Neoatherosclerosis, n, %	45 (52.9)	31 (60.8)	14 (41.2)	.076
TCFA-like neointima, n, %	12 (14.1)	8 (15.7)	4 (11.8)	.611
Calcified neointimal, n, %	4 (4.7)	3 (5.9)	1 (2.9)	.530
NA site, PS/MS/DS, n, %	18/5/22 (21.2/5.9/25.9)	14/3/14 (27.5/5.9/27.5)	4/2/8 (11.8/5.9/23.5)	.245
MSA, mm^2	5.24 ± 1.93	4.99 ± 1.80	5.62 ± 2.08	.018
Malapposition, n, %	15 (17.6)	14 (27.5)	1 (2.9)	.004
Thrombus, n, %	11 (12.9)	11 (21.6)	0 (0)	.015
Microvessels, n, %	26 (30.6)	16 (31.4)	10 (29.4)	.848

ACS = acute coronary syndrome, DS = distal segment, MLA = minimal lumen area, MS = middle segment, MSA = minimal stent area, NA = neoatherosclerosis, PS = proximal segment, TCFA = thin-cap fibroatheroma.

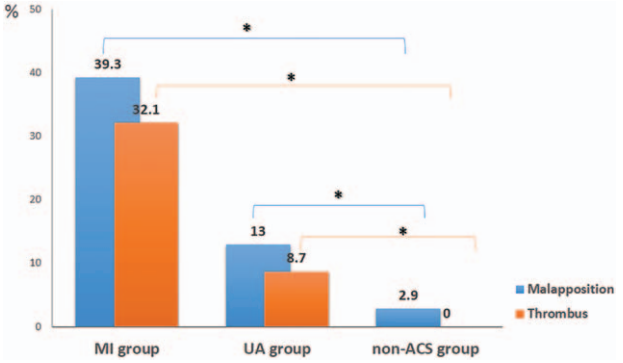

Figure 1. Incidence of malapposition and thrombus according to initial clinical presentation. Percentage of lesions with malapposition and thrombus in MI group, UA group, and non-ACS group. *Indicates $P < .01$ compared with non-ACS group. ACS = acute coronary syndrome, MI = myocardial infarction, UA = unstable angina.

4. Discussion

The main findings of our study are: thrombus and malapposition in ISR patients were more frequent in those with de novo ACS; less MSA was observed among ACS patients; and in-stent NA was more likely to occur in ACS patients.

4.1. The role of thrombus, malapposition in ISR

The findings of our study corroborates the fact that restenotic and thrombotic processes coexist in ISR patients. In our study, 21.6% of patients initially presented as ACS had thrombus at ISR lesions. The data were not unexpected: thrombus was reported in 80% of symptomatic DES ISR lesions.[13,14] Oikawa et al[15] also found that white thrombus existed in 46.2% of sirolimus-eluting stent restenotic lesions. Our study endorses these results and broadens the previous experience by assessing the role of initial clinical presentation. Our data suggest that post-DES neointimal hyperplasia mechanisms of de novo ACS lesions differ from that of non-ACS lesions.

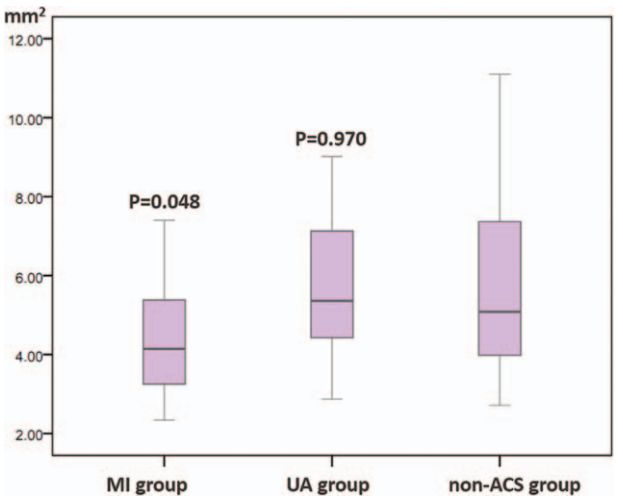

Figure 2. Comparison of minimal stent area according to initial clinical presentation. Values of minimal stent area in MI group, UA group, and non-ACS group. ACS = acute coronary syndrome, MI = myocardial infarction, UA = unstable angina.

Thrombus formation is a multifactorial process and malapposition is one of the predisposing factors. Malapposition is very common accompanying late and very late stent thrombosis.[16] In patients with ACS who underwent DES deployment, the incidence of late malapposition was 37.5%.[17] Likewise, Räber et al found that clusters of malapposed/protruding struts were more frequent in culprit lesions of ACS compared with non-ACS patients late after DES implantation.[18] In line with previous researches, our study discovered that malapposition was more frequent among ACS group. Delayed endothelialization and positive remodeling poststenting are potential contributing factors. However, the present study was not able to distinguish late-persistent from late-acquired malapposition at one single time point OCT. Our interpretation of results are therefore limited.

Our findings are supportive of the "thromborestenosis phenomenon" theory which indicated that both restenosis and stent thrombosis can simultaneously develop as the result of impaired vascular healing.[15] Previous pathology and intravascular imaging studies have confirmed that adverse arterial healing pattern exists in culprit lesions of patients with ACS after DES implantation.[18,19] A vicious cycle of infiltrative and extensive lesions, escalating and persistent inflammatory reactions increasing the restenosis and thrombus propensity could be a possible explanation of even worse vascular repair in ACS patients. In addition, the more severe atherosclerotic culprit lesions of ACS patients could even accelerate the NA progression, which is a critical substrate for late stent failure including restenosis and related thrombosis.

4.2. Minimal stent area and ISR

Stent underexpansion has been identified as a mechanical factor contributing to ISR after DES implantation.[20] Intravascular ultrasound studies concerning DES have suggested MSA thresholds to prevent angiographic ISR.[21,22] In our study, the MSA of MI group was significantly smaller than that of UA group and non-ACS group. It is reasonable to speculate that these patients had more significant plaque/thrombus burden during the index intervention. Thus, fully expansion of stents may be hampered by the residual plaque/thrombus protrusion. In fact, poststenting underexpansion has been documented in 42% of NSTEMI patients.[23] Patients with MI (including STEMI and NSTEMI) undergoing percutaneous coronary intervention are more susceptible to suboptimal stent implantation, which is associated with device-oriented adverse outcomes.[24] Hence, our observation has added value to the importance of more precise stent deployment for ACS patients. These patients could benefit from early detection and correction of underexpansion during initial PCI, potentially by using intravascular imaging.

4.3. Neoatherosclerosis and ISR

DESs are associated with accelerated development of in-stent NA.[25] Autopsy studies reported its prevalence as high as 51% in DES implanted for more than 1 year, which is comparable with our finding.[26] Meanwhile, our study showed the occurrence of NA tended to be higher in the ACS group. It is conceivable that ACS patients had more severe atherosclerosis at culprit lesions along with increased risk of atherosclerosis formation within stented segments.[27] Neoatheroslerosis may play a role in the neointimal hyperplasia process among ACS patients.

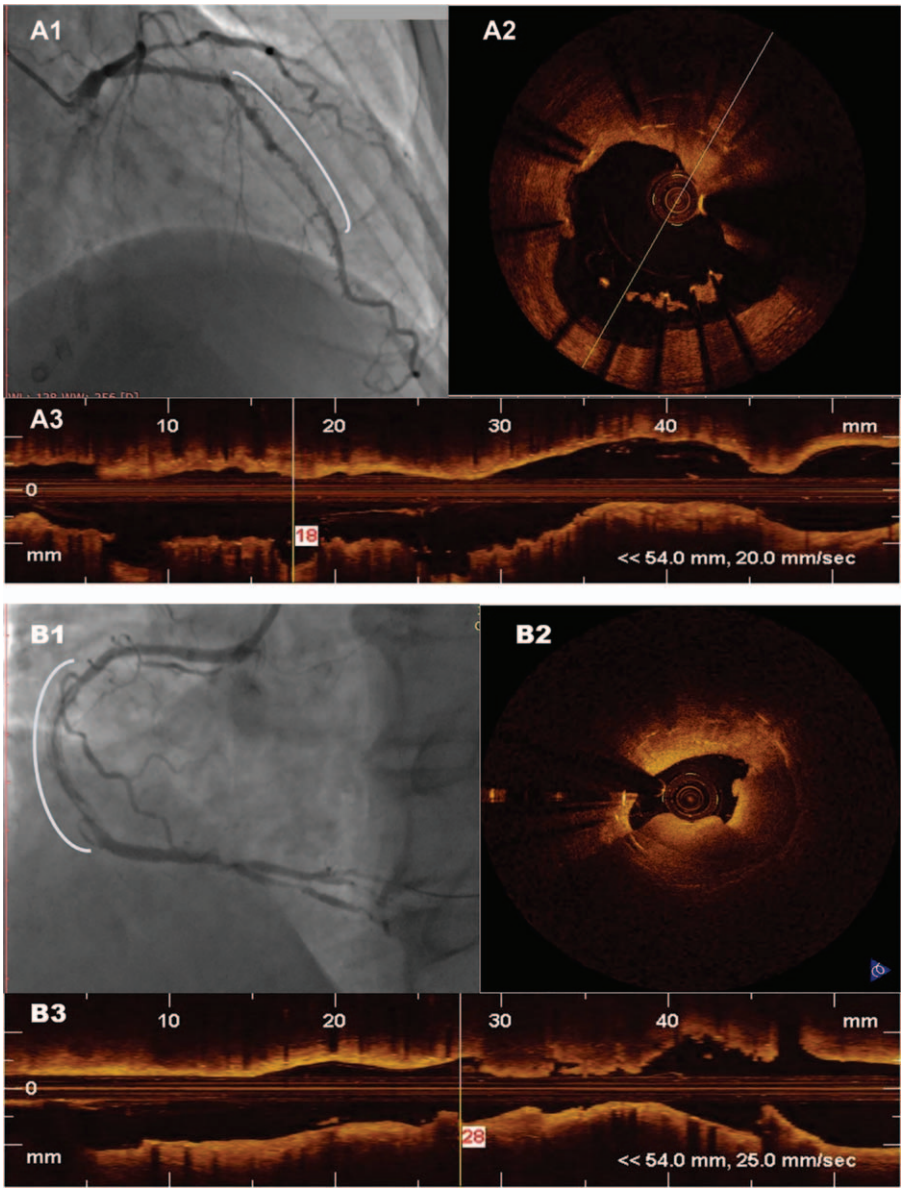

Figure 3. DES restenosis lesion characteristics in patients initially treated for acute coronary syndrome. (A) Example of white thrombus associated with malapposition at restenosis lesion: DES placement for UA 60 months ago. Both OCT cross-section and longitudinal images (A2 and A3) of the restenosis lesion shows struts malapposition and coupled white thrombus. (B) Example of red thrombus at restenosis lesion: DES implantation for NSTEMI 72 months ago. An OCT cross-sectional image in the restenosis region (B2) shows red thrombus. The OCT longitudinal reconstruction (B3) demonstrates the thrombus is located at the lumen with extensive neointimal growth. DES = drug-eluting stent, OCT = optical coherence tomography, UA = unstable angina.

4.4. Limitations

The study has several limitations: first, this is a retrospective study. The majority of our patients had symptomatic restenotic lesions and underwent repeated revascularization. Given the potential selection bias, our results could not be applied to general populations with variable degree of ISR. Second, OCT data immediately after initial stenting were not available. Third, the sample size of the present study was not sufficient to elucidate different ISR properties among different DES types. Fourth, details of index procedure (ie, postdilatation and maximum inflation pressure) and the cardiac adverse events during postindex procedure period were not analyzed in the present study. Because many patients were referred to our center and came with incomplete medical records, we could not get full access of such information. However, these data do not affect results of the current study.

5. Conclusions

In summary, our study suggests that late DES restenotic characteristics vary with the initial clinical presentation. Thrombus, malapposition, and smaller MSA are more frequently observed at ISR lesions among patients with ACS for stenting.

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