Clinical Characteristics of In-stent Neoatherosclerosis Causing Late Stent Failure

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Background: In-stent neoatherosclerosis (NA) is a cause of late stent failure. Late stent failure remains a challenging issue after stenting, and its causal mechanism has not been elucidated. Objectives: The aim of this study was to investigate the clinical characteristics of late stent failure with or without NA by optical coherence tomography (OCT). Methods and results: Among 179 patients who had undergone coronary stent implantation (bare metal stent and drug-eluting stent), 22 patients experienced late stent failure with and without NA identified by OCT. The presence of lipid-laden plaque or calcification inside the stent was defined as NA. The 22 patients were divided into two groups according to OCT images: 13 patients with NA (NA group) and 9 patients without NA (non-NA group). OCT analysis also showed that thrombus was more frequently observed and maximum intimal thickness was significantly larger in the NA than in the non-NA group (35.7% vs 0.0% and 1.26 mm vs 0.98 mm, p<0.05, respectively). In terms of characteristics, in-stent restenosis lesions and use of oral anticoagulants occurred at a lower frequency, and the minimal lumen diameter was significantly smaller in the NA group than in the non-NA group (7.7% vs 44.4%, 0.0% vs 66.7%, and 0.33 mm vs 0.83 mm, p<0.05, respectively). Conclusion: In-stent restenosis and use of anticoagulants may be associated with the mechanism of in-stent neoatherosclerosis. KEY WORDS: in-stent neoatherosclerosis, optical coherence tomography, late stent failure, anticoagulant therapy

I. Introduction

Drug-eluting stents (DES) significantly reduce the rate of restenosis and the need for target lesion revascularization compared to bare metal stents (BMS). However, late adverse events including very late stent thrombosis and late stent restenosis termed “late catch-up (LCU)” phenomenon are still major issues even with DES. Recently, it has been reported that in-stent neoatherosclerosis (NA) plays an important role in the mechanism of LCU phenomenon. The development of optical coherence tomography (OCT) has enabled us to identify in-stent NA, which is characterized by vulnerable plaque features such as lipid laden plaque, thin-cap fibroatheromas (TCFA), and luminal thrombus and therefore, patients with NA have often unstable coronary disease. Previous reports have suggested that elapsed time after stent implantation, smoking, and chronic kidney disease (CKD) are predictors of NA after stent implantation; however, the precise mechanism of NA has not been elucidated.

In the present study, we investigated patients who had LCU with or without in-stent NA to understand the characteristics and mechanism of NA after stent implantation.

II. Method

Study populations

The present study included 22 consecutive patients who had late stent failure and OCT images obtained between April 2008 and March 2013 in this center. The previous stents that caused late stent failure included either BMS or DES (10 BMSs and 12 DESs). The only type of DES that was used was the sirolimus-eluting stent. The study included patients with stenting not only for the native artery but also for in-stent restenosis (ISR) lesions. Late stent failure was defined as the occurrence of ISR or stent thrombosis beyond 1 year after stent implantation. All patients had documented any ischemic events, were amenable to coronary angiography and had been treated with PCI for stent failure.

Coronary angiography and analysis

Following intracoronary administration of nitrates (0.2 mg), coronary standardized quantitative coronary angiography (QCA) was performed in more than two orthogonal views of major coronary vessels using validated QCA software (CCIP-310/W, Ca-
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Table 1 Baseline clinical characteristics at the incidence of NA

| NA(+) n=13 | NA(-) n=9 | P  |
|-----------|-----------|----|
| Age, y    | 68.7±3.3  | 64.6±3.3  | 0.41 |
| Male, n (%)| 10 (76.9) | 8 (88.9)  | 0.47 |
| Diabetes mellitus | 7 (53.8) | 6 (66.7)  | 0.54 |
| Hypertension | 11 (84.6) | 8 (88.9)  | 0.77 |
| Dyslipidemia | 8 (61.5) | 5 (55.6)  | 0.77 |
| Hemodialysis | 1 (7.7)  | 0 (0.0)    | 0.39 |
| History of smoking | 8 (61.5) | 6 (66.7)  | 0.80 |
| Previous PCI |
| Urgent | 7 (53.8) | 2 (22.2)  | 0.13 |
| ISR    | 1 (7.6)  | 4 (44.4)  | 0.04 |
| Blood examination |
| CKD (eGFR<60ml/min), n (%) | 6 (46.2) | 4 (44.4)  | 0.93 |
| Cr, mg/dl | 0.95±0.1 | 0.95±0.1  | 0.94 |
| LDL-cholesterol | 98.2±7.2 | 91.4±5.8  | 0.50 |
| HDL-cholesterol | 59.7±7.9 | 51.8±6.2  | 0.50 |
| Triglyceride | 191±27 | 158±49    | 0.53 |
| HbA1c, % | 6.7±0.5 | 6.2±0.3   | 0.41 |
| Medication |
| Insulin, n (%) | 2 (15.4) | 1 (11.1)  | 0.77 |
| Statin | 8 (61.5) | 8 (88.9)  | 0.15 |
| ACEi /ARB | 10 (76.9) | 9 (100.0) | 0.12 |
| Dual antiplatelet therapy | 9 (69.2) | 5 (55.6)  | 0.51 |
| Anticoagulant therapy | 0 (0.0)  | 6 (66.7)  | 0.005 |

NA: neoatherosclerosis, PCI: percutaneous coronary intervention, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, Cr: creatinine, LDL: low-density lipoprotein, HDL: high-density lipoprotein, ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensinII receptor blocker.

Fig. 1 Representative OCT images of NA. (A) Lipid rich neointima, appearing as a signal-poor region with diffuse borders (asterisks). White arrow indicates OCT-defined macrophage accumulation; bright spot with high OCT backscattering attenuation. (B) Neointimal hyperplasia without NA. High signal and homogeneous neointima pattern is all around observed. Scale bar = 1 mm.

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thex, Tokyo, Japan). Lesions were classified according to the modified American College of Cardiology/American Heart Association (ACC/AHA) criteria. Angiographic binary restenosis was defined as greater than 50% stenosis. ISR pattern was defined by angiographic findings according to a previous report.12) OCT imaging and plaque characteristics

OCT images acquired were either time-domain OCT images, acquired using an M3 Cardiology Imaging System (Light Lab
Imaging, Inc., Westford, USA), or frequency-domain OCT images (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, USA). Briefly, the imaging wire was automatically pulled back from a distal to proximal position and lactate Ringer’s solution was continuously infused from the tip of the occlusion balloon in the M3 system and contrast media was continuously infused in the C7 system to displace blood.\(^{13,14}\) Quantitative and qualitative analysis of OCT images were performed. Lipid laden plaque was defined as a diffusely bordered signal-poor region with rapid signal attenuation, and calcification was defined as a clearly delineated signal-poor region with low backscatter.\(^{15}\) Thin-cap fibroatheroma (TCFA) was characterized as a plaque with lipid content in >1 quadrant with a thin fibrous cap (<65 μm).\(^{16}\) Thrombus was defined as a protruding mass attached to the luminal surface or floating within the lumen. Macrophage accumulation was seen as a bright spot with high OCT backscattering attenuation.\(^{17}\) Neovascularization was defined as a small vesicular or tubular structure with a diameter 200μm.\(^{18}\)

The presence of lipid-laden plaques or calcification inside the stent identified by OCT was defined as NA. Calcified intrastent tissue was not observed in this study (Fig. 1). The patients were divided into two groups according to the presence of NA: 13 patients with NA (NA group) and 9 patients without NA (non-NA group). Cross-sectional OCT images were analyzed by 2 independent observers (K.I. and A.M.) who were blinded to the clinical and procedural characteristics.

### III. Statistical analysis

Continuous variables are expressed as mean ± standard deviation and were evaluated by means of a Student’s \(t\)-test. Categorical variables are expressed as frequencies and were evaluated using chi-square test or Fisher’s exact test as appropriate. Values of \(p<0.05\) were considered statistically significant. Multiple logistic regression analysis were performed to determine the independent predictors for NA.

### IV. Results

Comparisons of baseline clinical characteristics in the event of

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| Target lesion, n (%) | NA(+) | NA(−) | \(P\) |
|----------------------|-------|-------|----|
| LMT, n (%)           | 0 (0.0) | 0 (0.0) | 0.22 |
| RCA                  | 5 (38.4) | 6 (50.0) |
| LAD                  | 5 (38.4) | 3 (50.0) |
| LCX                  | 3 (23.0) | 0 (0.0) |
| Lesion type          |       |       |   |
| Type B2/C            | 10 (76.9) | 5 (55.6) | 0.29 |
| Eccentricity         | 9 (69.2) | 4 (44.4) | 0.24 |
| Calcification        | 3 (23.1) | 2 (22.2) | 0.96 |
| Bifurcation          | 5 (38.5) | 2 (22.2) | 0.42 |
| Thrombus             | 2 (15.4) | 0 (0.0) | 0.22 |
| Angle>45             | 2 (15.4) | 0 (0.0) | 0.22 |
| CTO                  | 3 (23.1) | 1 (11.1) | 0.47 |
| Ostial               | 0 (0.0) | 0 (0.0) | 1.00 |
| Pre procedure        |       |       |   |
| Stenosis, %          | 86.4±3.8 | 76.3±7.2 | 0.09 |
| MLD, mm              | 0.33±0.1 | 0.83±0.1 | 0.01 |
| RVD                  | 2.44±0.2 | 2.68±0.1 | 0.48 |
| Length               | 28.7±8.5 | 18.3±1.8 | 0.25 |
| Post procedure       |       |       |   |
| Stenosis, %          | 10.1±2.8 | 4.76±2.8 | 0.25 |
| MLD, mm              | 2.79±0.1 | 2.35±0.1 | 0.09 |
| Acute gain           | 2.39±0.1 | 1.66±0.3 | 0.05 |

QCA; quantitative coronary angiography, LMT; left main trunk, RCA; right coronary artery, LAD; left anterior descending artery, LCX; left circumflex artery, CTO; chronic total occlusion. %DS percentage of diameter stenosis, RVD; reference vessel diameter, MLD; minimum lumen diameter.
In terms of OCT findings, the maximal intimal thickness was significantly larger in the NA group than in the non-NA group (1.26 mm vs 0.98 mm, \( p=0.04 \)). There was a greater tendency toward higher frequency of thrombus in the NA group than in the non-NA group (38.5% vs 0.0%, \( p=0.05 \)) (Table 5). In multivariate analysis, ISR lesions remained an independent predictor for NA (odds ratio, 0.04; [95% CI, 0.00-0.97]; \( p=0.04 \)).

V. Discussion

In the present study, we investigated the differences between patients who experienced LCU with and without in-stent NA defined by OCT. Our primary findings were that in patients with NA compared to those without NA: the proportion of ISR lesions and anticoagulant therapy was significantly lower; the MLD derived by QCA before stenting causing LCU was significantly smaller; and the maximum intimal thickness derived by OCT at the time of the incidence of LCU was significantly larger. Late stent failure including both late restenosis and late stent thrombosis are major problems after stent implantation. \(^4, 5\) Results of five-year follow up from SIRIUS, j-Cypher Registry have shown that very late stent thrombosis and late target lesion revascularization are continuous hazards, lasting at least up to five years after implantation of sirolimus-eluting stents \(^19, 20\). Recent reports have suggested NA as a possible pathway for late stent failure, in which NA was defined as lipid laden plaque or calcification inside the stent, and these atherosclerotic plaques often includes vulnerable characteristics such as TCFA, intimal rupture, and thrombus \(^7, 8\). This recent knowledge of outcomes after stent implantation can be attributed to the introduction and progression of intracoronary imaging technology such as OCT. The advent of this technology has enabled us to share and utilize knowledge in every day practice, and in doing so we determined that not all patients with LCU restenosis had in-stent NA. There-

### Table 3 PCI procedure

| NA(+) | NA(−) | P |
|-------|-------|---|
| DES use, n (%) | 10 (76.9) | 4 (44.4) | 0.31 |
| Stent diameter, mm | 3.05±0.1 | 2.95±0.1 | 0.51 |
| Number of stent | 1.42±0.1 | 1.37±0.2 | 0.86 |
| Total stent length, mm | 31.4±4.1 | 31.7±7.6 | 0.96 |
| Multiple stent, n (%) | 5 (38.5) | 2 (22.2) | 0.60 |
| Direct stent | 2 (15.4) | 1 (11.1) | 0.89 |
| Max pressure, atm | 18±0.8 | 16±1.3 | 0.22 |

DES; drug-eluting stent.

### Table 4 Angiographical data at late stent failure

| NA(+) | NA(−) | P |
|-------|-------|---|
| Duration, day | 1,964±279 | 2,591±400 | 0.20 |
| ACS, n (%) | 5 (38.5) | 2 (22.2) | 0.60 |
| ISR type | 0.54 |
| Focal | 10 (76.9) | 4 (55.6) |
| Diffuse (in-stent) | 1 (7.7) | 2 (22.2) |
| Diffuse (proliferative) | 1 (7.7) | 1 (11.1) |
| Occlusion | 1 (7.7) | 1 (11.1) |
| QCA |
| Stenosis, % | 63.4±5.0 | 68.5±7.9 | 0.57 |
| MLD, mm | 1.07±0.1 | 0.71±0.1 | 0.15 |
| Length | 16.5±1.9 | 16.8±3.5 | 0.92 |

ACS; acute coronary syndrome, ISR; in-stent restenosis.

### Table 5 OCT analysis at late stent failure

| NA(+) | NA(−) | P |
|-------|-------|---|
| MLA, mm\(^2\) | 1.71±0.2 | 1.19±0.13 | 0.10 |
| MLD, mm | 1.22±0.1 | 1.13±0.04 | 0.34 |
| Lesion length | 14.7±3.2 | 12.1±3.33 | 0.61 |
| Lipid arc, ° | 211 | - |
| Minimal FC, μm | 139 | - |
| Max intimal thickness, mm | 1.26±0.8 | 0.98±0.8 | 0.04 |
| TCFA, n (%) | 3 (23.1) | 0 (0.0) | 0.15 |
| Disruption | 6 (46.2) | 1 (11.1) | 0.15 |
| Thrombus | 5 (38.5) | 0 (0.0) | 0.05 |
| Macrophage | 3 (23.1) | 0 (0.0) | 0.16 |
| Neovascularization | 6 (46.2) | 4 (44.4) | 0.75 |
| Malapposition | 2 (15.4) | 2 (22.2) | 0.53 |

MLA; minimum lumen area, FC; Fibrous cap, TCFA; thin cap fibroatheroma.

NA between the NA group and non-NA groups are shown in Table 1. There were no significant differences between the groups except for with ISR lesions and anticoagulant therapy: the proportion of in-stent lesions and anticoagulant therapy was significantly lower in the NA group than in the non-NA group (7.7% vs 44.4%, \( p=0.04 \), and 0.0% vs 66.7%, \( p=0.005 \), respectively). The reason why anticoagulant agents were administered was that all the patients had atrial fibrillation.

Angiographic features and QCA data before stent implantation causing LCU are summarized in Table 2. Preprocedural minimum lumen diameter (MLD) before LCU-causing stent implantation was significantly smaller in the NA group than in the non-NA group (0.33 mm vs 0.83 mm, \( p=0.01 \)), while preprocedural percent diameter stenosis (% DS), postprocedural MLD, and acute gain tended to be greater in the NA group (86.4% vs 76.3%, \( p=0.09 \), 2.79 mm vs 2.35 mm, \( p=0.09 \), and 2.39 mm vs 1.66mm, \( p=0.05 \), respectively). PCI procedure including use of DES was almost similar between the two groups (Table 3). When late stent failure occurred, there were no significant difference in the duration from stent implantation or the rate of acute coronary syndrome (1,964 days vs 2,591 days, \( p=0.20 \), and 38.5% vs 22.2%, \( p=0.60 \), respectively) (Table 4).
fore, we investigated the differences between patients with and without in-stent NA more than one year after stent implantation, which to the best of our knowledge has not previously been investigated. Recently, several clinical factors have been reported as predictors of NA including, stent duration, smoking, CKD, DES use, and angiotensin converting enzyme inhibitor/angiotensin II receptor blocker use. However, these predictive factors were not observed in the present study. The following are some possible reasons why the predictors of NA differed from those that were previously reported: the sample size of the present study was small; the difference in the distribution of coronary risk factors from that in the previous study; patients with early restenosis were excluded in the present study because we highlighted late stent failure; and the study included patients with stenting for not only the native artery but also for ISR lesions. As a result, we obtained two novel findings associated with NA in the present study.

In-stent restenotic lesions and NA:
The occurrence of ISR lesions was significant lower in patients with NA than those without NA in the present study. We consider this a novel finding. The restenotic lesions were recurrent ISR where DES was implanted for early restenotic lesion of BMS, which was considered to be fibrous plaque not containing lipid plaque or inflammatory cells, that is to say, neither atherosclerotic nor vulnerable plaque. Moreover, the present study determined that the plaque volume of ISR lesions could be smaller than native artery lesions as it was observed that preprocedural MLD before late catch-up stent implantation was significantly smaller in NA patients than in non-NA patients, providing the evidence that early ISR plaques are less vulnerable. Conversely, a pathological study reported that underlying unstable plaques were identified as one of the independent risk factors for NA. We infer that the components of in-stent intimal hyperplasia plaques do not include atheroma, and that it is not likely that inflammatory cells penetrate into the plaque via vasa vasorum and that in-stent plaques develop into atheroma including necrotic core.

Anticoagulant therapy and NA:
We found that the use of anticoagulant therapy was less frequent in patients with NA than in those without NA. In this study, all patients using anticoagulant therapy received the vitamin K antagonist (VKA), warfarin. However, there have been no reports suggesting that VKA has a negative effect on atherosclerosis. On the contrary, a recent report suggested that VKA accelerates vascular atherosclerotic change. However, it emphasized that VKA treatment promoted artery calcification including coronary arteries, but not atheroma including lipid causing plaque vulnerability. Besides, in the present study, thrombus formation occurred more frequently in patients with NA than in those without NA. Furthermore, the aforementioned study reported that thrombus was often seen in late stent failure caused by NA. According to the classification of atherosclerotic lesions by Stary, type VI lesions are characterized by histology including surface defect, hematoma, and thrombosis, and fatal outcomes are most often associated with type VI atherosclerotic lesions. Immature in-stent neointima are characterized by marginalized subendothelial leukocytes amorphous fibrin, and peri-strut hemorrhage hemosiderin deposits.

In the progression of atherosclerosis, thrombus formation occurs without event and heals repeatedly leading to increasing plaque volume. We considered that warfarin might suppress the development of atherosclerosis through this process by inhibiting thrombus formation and reducing thrombus volume, leading to healing of the plaque without necrotic core.

VI. Limitation
This retrospective, observational, single-center study had several limitations. First, the sample size was very small. Second, the study population was different from those in previous studies with regards the definition of stent failure as previously discussed, which explains why previously described predictors of NA were not observed in our study. Third, the duration of each medication was unknown, which may have affected the incidence of LCU. Fourth, OCT images were not performed at stent implantation causing LCU.

VII. Conclusion
We investigated the clinical characteristics of patients with late stent failure with or without NA. In our study, anticoagulant therapy and recurrent ISR were strongly associated with in-stent NA. This small, single-center study could provide useful clues to the cause of NA after stent implantation, although further investigations are required.

Disclosures
The authors have no financial conflicts of interest to disclose.

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