Incidence and Predictors of Neoatherosclerosis in Patients with Early In-Stent Restenosis Determined Using Optical Coherence Tomography

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Summary

In-stent restenosis (ISR) still exists after drug-eluting stent (DES) implantation, even up to one year. The incidence and risk factors for neoatherosclerosis in patients with early ISR have not yet been elucidated. Here, we used optical coherence tomography (OCT) to evaluate the incidence and predictors of neoatherosclerosis in patients with early ISRs.

OCT was performed on ISR lesions in 185 patients in order to detect neoatherosclerosis. The median follow-up was 180 days, and neoatherosclerosis was detected in 37% of early ISR lesions. According to the presence of neoatherosclerosis, patients with ISR were divided into two groups: neoatherosclerosis (group A, \( n = 69 \)) and non-neoatherosclerosis (group B, \( n = 116 \)) groups.

The risk factors were similar, except for hypercholesterolemia. Moreover, the tissue characteristics were not significantly different between patients with and without neoatherosclerosis. Follow-up low-density lipoprotein-cholesterol (LDL-C) levels were divided into three grades (LDL < 70 mg/dL, 70 mg/dL \( \leq \) LDL < 100 mg/dL, and LDL \( \geq \) 100 mg/dL). The incidence of neoatherosclerosis was significantly lower (23% versus 57%, \( P < 0.0001 \)) in the LDL < 70 mg/dL group. There was no significant difference in the incidence of neoatherosclerosis in patients with lipid levels between 70 and 100 mg/dL (\( P = 0.53 \)). However, neoatherosclerosis was significantly more common in patients with a follow-up LDL-C level > 100 mg/dL (45% versus 15%, \( P < 0.0001 \)).

In patients with early ISR lesions, the LDL-C levels may be related to the formation and progression of early neoatherosclerosis, and poor LDL-C control may be a risk factor for the occurrence of early-stage neoatherosclerosis following DES implantation.

Key words: Percutaneous coronary intervention, Drug-eluting stent, LDL-C

Atherosclerotic cardiovascular diseases remain the major cause of mortality worldwide. Drug-eluting stents (DESs) have dramatically reduced in-stent restenosis (ISR), which has been the major limitation of bare-metal stents. However, stent failure remains a concern, particularly in some patients in which early ISR occurs within one year. Previous pathological studies have frequently observed neoatherosclerosis in patients with DESs, and neoatherosclerosis occurs earlier than in patients with bare-metal stent (BMS). No association has been observed between the lesion within the neointima and the underlying native atherosclerosis. Native atherosclerosis is a chronic, complex, and progressive pathological process. Neoatherosclerosis, which is an important ISR mechanism, is a relatively rapid process. The phenomenon of neoatherosclerosis, which causes ISR and acute thrombotic occlusions, is now emerging as a new atherosclerosis-related problem.

In-stent neoatherosclerosis has been recognized as an important mechanism of DES failure, particularly late after implantation, regardless of its generation. According to Otsuka, et al., neoatherosclerosis occurs more frequently and earlier in patients with first-generation DES than in patients with BMS. However, the neoatherosclerotic changes in patients with second-generation DES were not significantly different from patients with first-generation DES. But, researchers have not clearly determined whether the incidence of early ISR is caused by
Figure 1. Representative images of neoatherosclerosis in patients with early ISR. A: The diagnostic angiogram revealed an incomplete occlusion in the left anterior descending artery (LAD), and the patient underwent DES implantation (B, white arrow). C: Angiogram showing ISR at six months of follow-up (white arrow). D: Cross-sectional OCT images of the lesion show the neointimal tissue and neoatherosclerosis (white asterisk).

neoatherosclerosis.

Optical coherence tomography (OCT) accurately determines the strut coverage and characterizes the neointima following stent implantation. OCT has become the imaging modality of choice for the in vivo assessment of stent failures, including neoatherosclerosis and very late stent thrombosis.

This study aimed to investigate the possible effect of neoatherosclerosis-induced early ISR lesions and to elucidate the mechanism by which neoatherosclerosis effectively prevents early neoatherosclerosis-related clinical events following DES implantation.

Methods

Study population: From October 2016 to September 2018, 185 patients with previously implanted stents, including sirolimus-eluting stents, paclitaxel-eluting stents, and everolimus-eluting stents, who were diagnosed with ISR were included in this study. ISR was defined as a stenosis diameter ≥ 50% occurring in the segment inside the stent or 5 mm proximal or distal to the stent in follow-up angiography. The use of OCT before performing percutaneous coronary intervention (PCI) was recommended in all patients. The exclusion criteria were hemodynamic instability, inability of the OCT imaging wire to cross the ISR lesion into the distal vessel due to tight stenosis or severe vessel tortuosity, left main or saphenous vein graft lesions, or the presence of angiographically visible thrombus. The study conformed to the Declaration of Helsinki. The present study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Harbin Medical University, China. All patients signed an informed consent form. Representative images of neoatherosclerosis in patients with early in-stent restenosis are presented in Figure 1.

OCT data acquisition: Patients were pretreated with 300 mg of aspirin, 300 mg of clopidogrel, and 100 U/kg of heparin. Coronary angiography was performed with the radial or femoral approach using 6-F to 7-F guide catheters following the intracoronary administration of 100-200 mg of nitroglycerine. OCT was performed using a commercially available frequency-domain OCT C7-XR™ and a Dragonfly catheter (LightLab Imaging/St. Jude Medical), as previously reported. The OCT images were automatically recorded for analysis. Representative OCT images are presented in Figure 2.

Quantitative analysis of OCT images: OCT images were analyzed by two experienced reviewers who were blinded to the clinical information using a previously re-
Figure 2. Representative images of OCT findings. A: Fibroplaque. B: Lipid-laden neointima. C: Neointima rupture. D: Calcified neointima.

Results

Clinical characteristics and laboratory results: A total of 185 patients with 185 early ISRs were included in the present study. The clinical characteristics of the patients are summarized in Table I. The median follow-up time was 180 days (interquartile range: 150 to 360 days). Patients were divided into two groups according to the presence of neoatherosclerosis: neoatherosclerosis (group A, n = 69) and non-neoatherosclerosis (group B, n = 116) groups. The risk factors were similar between the two groups, except for hypercholesterolemia (62% versus 40%, P = 0.03); group A included more patients diagnosed with hypercholesterolemia. All patients received statin therapy after stenting, including atorvastatin and rosuvastatin, and no significant difference was observed between the two groups. Baseline laboratory results, including serum levels of cholesterol and its lipoprotein carriers (low-density lipoprotein-cholesterol [LDL-C], and high-density lipoprotein-cholesterol [HDL-C]), creatinine, urea, CK-MB, and high-sensitivity C-reactive protein (hs-CRP), were not significantly different between the two groups (Table I). Higher CK levels were observed in group B.
Based on these results, different basic diagnoses were not significantly different between the two groups (P = 0.68, P = 0.74, P = 0.28, and P = 0.25, respectively). A few patients (group A, n = 9, group B, n = 6) exhibited poor intimal healing and incomplete stent coverage, but there was no significant difference in the formation of neoatherosclerotic plaques in the stent between the two groups. The percentages of covered struts and uncovered struts and maximal length of uncovered segments were not significantly different between the two groups (P = 0.06, P = 0.06, and P = 0.11, respectively). Based on these results, different basic diagnoses and locations of target vessel lesions exert little effect on the formation of neoatherosclerosis.

**Follow-up laboratory results:** The serum levels of cholesterol and its lipoprotein carriers (LDL-C, very low-density lipoprotein cholesterol [VLDL-C], and HDL-C) are known to be associated with atherosclerotic cardiovascular disease. LDL-C is the dominant form of atherogenic cholesterol. In the present study, patients with neoatherosclerosis more frequently presented with poor lipid control levels during follow-up, particularly total cholesterol (179.09 ± 57.45 versus 141.79 ± 45.67, P < 0.0001) and LDL-C levels (104.96 ± 47.94 versus 72.04 ± 35.82, P < 0.0001), than patients without neoatherosclerosis (Table III). We compared the follow-up LDL-C levels at different grades (Grade I, LDL-C < 70 mg/dL; Grade II, 70 mg/dL ≤ LDL-C < 100 mg/dL; and Grade III, LDL-C ≥ 100 mg/dL), and the results are presented in Table III (P < 0.0001). In patients with lower lipid control levels (LDL-C < 70 mg/dL), the incidence of in-stent neoatherosclerosis was significantly reduced (23% versus 57%, P < 0.0001). There was no significant difference in the incidence of in-stent neoatherosclerosis in patients with lipid levels ranging from 70 to 100 mg/dL (32% versus 28%, P = 0.53). However, patients with lipid levels > 100 mg/dL exhibited a significantly greater incidence of in-stent neoatherosclerosis (45% versus 15%, P < 0.0001). No significant differences were observed in other variables, including urea, creatinine, creatine kinase, creatine kinase-MB, and high-sensitivity C-reactive protein (hs-CRP) levels. Thus, follow-up LDL-C levels play a significant role in the modification of early neoatherosclerosis pathogene-

| Age (years), mean ± SD | Neatherosclerosis (n = 69) | Non-neatherosclerosis (n = 116) | P-value |
|------------------------|---------------------------|-------------------------------|---------|
| Men, n (%)             | 62.6 ± 8.5                | 61.4 ± 11.6                   | 0.43    |
| Current smoker, n (%)  | 50 (72)                   | 78 (67)                       | 0.46    |
| Hypertension, n (%)    | 32 (46)                   | 50 (43)                       | 0.70    |
| Hypercholesterolemia, n (%) | 27 (39)       | 52 (45)                       | 0.42    |
| Diabetes mellitus, n (%) | 43 (62)       | 46 (40)                       | 0.003   |
| Statin type, Atorvastatin, n (%) | 22 (32)     | 41 (35)                       | 0.60    |
| Aspirin, n (%)         | 69 (100)                  | 116 (100)                     | 1.00    |
| Clonidogrel, n (%)     | 48 (70)                   | 72 (62)                       | 0.30    |
| Ticagrelor, n (%)      | 21 (30)                   | 44 (38)                       | 0.30    |
| β-Receptor blocker, n (%) | 30 (43)       | 51 (44)                       | 0.95    |
| ACEI or ARB, n (%)     | 29 (42)                   | 48 (41)                       | 0.97    |
| Calcium channel blocker, n (%) | 16 (23)      | 26 (22)                       | 0.93    |
| Number of days of follow-up, median (25%, 75%) | 180 (150, 360) | 180 (150, 360) | 0.99   |

**ACEI** indicates angiotensin-converting enzyme inhibitor; **ARB** angiotensin receptor blocker; **HDL-C** high-density lipoprotein cholesterol; **hs-CRP** high-sensitivity C-reactive protein; and **LDL-C** low-density lipoprotein cholesterol.
Table II. Angiographic and OCT Findings

|                         | Neoatherosclerosis (n = 69) | Non-neoatherosclerosis (n = 116) | P-value |
|-------------------------|-----------------------------|---------------------------------|---------|
| Indication for index PCI, n (%) | 0 (0)                        | 3 (3)                           | 0.18    |
| Stable angina           | 22 (32)                     | 52 (45)                         |         |
| Unstable angina         | 10 (14)                     | 11 (9)                          |         |
| STEMI                   | 37 (54)                     | 50 (43)                         |         |
| Culprit vessel, n (%)   |                             |                                 | 0.33    |
| Left anterior descending (LAD) | 36 (52)                     | 74 (64)                         |         |
| Left circumflex (LCX)   | 6 (9)                       | 12 (10)                         |         |
| Right coronary artery (RCA) | 27 (39)                     | 30 (26)                         |         |
| Procedural characteristics |                             |                                 |         |
| Mean reference vessel diameter (mm), mean ± SD | 3.8 ± 0.8                   | 3.9 ± 0.6                       | 0.51    |
| Type of stent           |                             |                                 | 0.89    |
| Sirolimus-eluting stent | 25 (36)                     | 43 (37)                         | 0.78    |
| Paclitaxel-eluting stent| 18 (26)                     | 28 (24)                         | 0.47    |
| Everolimus-eluting stent| 26 (38)                     | 45 (39)                         | 0.81    |
| Total stent length (mm), mean ± SD | 27.5 ± 10.5               | 28.5 ± 12.1                     | 0.53    |
| Stent diameter (mm), mean ± SD | 3.1 ± 0.5                  | 3.16 ± 0.7                      | 0.24    |
| Maximal inflation pressure (atm), mean ± SD | 14.5 ± 8.0                | 14.9 ± 8.7                      | 0.75    |

OCT characteristic

|                         | Neoatherosclerosis (n = 69) | Non-neoatherosclerosis (n = 116) | P-value |
|-------------------------|-----------------------------|---------------------------------|---------|
| Minimal stent area (mm²), mean ± SD | 6.1 ± 2.0                   | 6.3 ± 2.0                       | 0.68    |
| Minimal stent diameter (mm), mean ± SD | 2.8 ± 0.4                  | 2.8 ± 0.5                       | 0.74    |
| Mean stent area (mm²), mean ± SD | 7.5 ± 2.1                   | 7.8 ± 2.1                       | 0.28    |
| Mean stent diameter (mm), mean ± SD | 3.1 ± 0.5                   | 3.2 ± 0.7                       | 0.24    |
| Minimal lumen area (mm²), mean ± SD | 1.8 ± 0.9                   | 1.8 ± 0.9                       | 0.98    |
| Covered struts, n (%) | 60 (87)                     | 110 (95)                        | 0.06    |
| Uncovered struts, n (%) | 9 (13)                      | 6 (5)                           | 0.06    |
| Maximum length of the uncovered segment (mm), mean ± SD | 0.3 ± 1.1                   | 0.1 ± 0.5                       | 0.11    |

NSTEMI indicates non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Table III. Follow-Up Laboratory Results

|                          | Neoatherosclerosis (n = 69) | Non-neoatherosclerosis (n = 116) | P-value |
|--------------------------|-----------------------------|---------------------------------|---------|
| Total cholesterol (mg/dL), mean ± SD | 179.1 ± 57.5               | 141.8 ± 45.7                    | < 0.0001|
| LDL-C (mg/dL), mean ± SD | 104.9 ± 47.9               | 72.0 ± 35.8                     | < 0.0001|
| HDL-C (mg/dL), mean ± SD | 47.6 ± 9.3                 | 47.5 ± 15.8                     | 0.97    |
| Triglycerides (mg/dL), mean ± SD | 177.8 ± 97.8              | 169.2 ± 159.2                   | 0.69    |
| LDL-C grade              |                             |                                 |         |
| Grade I (LDL-C < 70 mg/dL), n (%) | 16 (23)                    | 66 (57)                         | < 0.0001|
| Grade II (70 mg/dL ≤ LDL-C < 100 mg/dL), n (%) | 22 (32)                    | 33 (28)                         | 0.53    |
| Grade III (LDL-C ≥ 100 mg/dL), n (%) | 31 (45)                    | 17 (15)                         | < 0.0001|
| Urea (μmol/L), mean ± SD | 16.3 ± 83.5                | 6.2 ± 2.4                       | 0.33    |
| Cre (μmol/L), mean ± SD | 87.2 ± 45.6                | 91.5 ± 91.0                     | 0.72    |
| Creatine kinase (U/L), mean ± SD | 343.5 ± 820.1             | 274.1 ± 513.1                   | 0.49    |
| Creatine kinase-MB (μg/L), mean ± SD | 31.5 ± 89.4               | 20.0 ± 53.8                     | 0.32    |
| hs-CRP (mg/L), mean ± SD | 3.3 ± 4.1                  | 10.0 ± 71.9                     | 0.46    |

HDL-C indicates high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

Discussion

In the present study, neoatherosclerosis was detected in 37% of patients with early restenotic lesions at a median of 180 days following DES implantation. In patients with early ISR lesions, follow-up LDL-C levels play a significant role in the modification of early neoatherosclerosis pathogenesis, and poor LDL-C control may be a risk factor for the occurrence of early-stage neoatherosclerosis following DES implantation.

Despite the reduction in late thrombotic events with newer-generation DESs, late stent failure remains a con-
cern following stent placement.\textsuperscript{20} ISR is a common complication following coronary stenting. The terminal inflammatory response to vessel wall injury during PCI plays a central role in ISR after stenting, with vessel wall inflammation driving fibroblast growth and smooth muscle cell hyperplasia. The mechanistic factors contributing to ISR after vascular intervention include acute or subacute prolapase of the disrupted plaque, elastic recoil of the vessel wall, constructive remodeling, neointimal hyperplasia, and de novo in-stent atherosclerosis (neoatherosclerosis).\textsuperscript{6}

Based on emerging evidence, chronic inflammation or incompetent endothelial function induces de novo neoatherosclerosis, which may be an important mechanism of the ISR or thrombosis.\textsuperscript{3,12,14}

In-stent neoatherosclerosis is histologically characterized by an accumulation of lipid-laden foamy macrophages with or without necrotic core formation and/or calcification within the neointima.\textsuperscript{11} No association has been observed between the lesion within the neointima and the underlying native atherosclerosis. According to Nakazawa, et al.,\textsuperscript{13} in addition to uncovered struts as markers of incomplete endothelialization as the primary cause of DES thrombosis, advanced neoatherosclerosis with neointimal rupture also represents another factor that potentially contributes to very late thrombotic events. The incidence of neoatherosclerosis was greater in patients with DES lesions (31%), and the prevalence of neoatherosclerosis was greater than 52%\textsuperscript{5} in patients with ISR lesions. In our study, the prevalence of neoatherosclerosis was 37% in patients with early ISR lesions, and the data suggest that neoatherosclerosis is correlated with poor long-term clinical outcomes. The mechanisms of neoatherosclerotic development in patients with DES remain unknown.

The mechanisms and processes contributing to the development of atherosclerosis inside the stents differ from those in the native coronary arteries. Our data delineated the risk factors for in-stent neoatherosclerosis. The traditional clinical risk factors for atherosclerosis in native coronary arteries, such as age, sex, smoking, hypertension, and diabetes mellitus, were not associated with neoatherosclerosis. Neoatherosclerosis may develop in months to years following stent placement, whereas atherosclerosis in native coronary arteries develops over decades.\textsuperscript{4} The earliest development of neoatherosclerosis is characterized by foamy macrophage infiltration beginning at four months, and the earliest necrotic core formation begins at nine months following the implantation of sirolimus-eluting stents.\textsuperscript{22} As shown in the study by Otsuba, et al.,\textsuperscript{14} the prevalence of neoatherosclerosis was similar for patients with first-generation and second-generation DES but greater than for patients with a bare-metal stent at ≤ 1 year after implantation. Our study also revealed a consistent prevalence of neoatherosclerosis between the two groups at follow-up within one year.

Previous pathological studies have described the potential mechanisms underlying the development of neoatherosclerosis.\textsuperscript{14} Incompetent and dysfunctional endothelial coverage following stent placement, particularly in DESs characterized by poorly formed cell-to-cell junctions, allows greater entry of lipoproteins into the subendothelial space. The disturbance in local blood flow following stent placement also contributes to the continued activation of the regenerating endothelial cells toward a pro-inflammatory phenotype, resulting in the adhesion and migration of monocytes into the subendothelial space where they differentiate into foamy macrophages residing in either the subluminal or peri-strut regions. The accumulation of proteoglycans within the neointima, particularly following DES implantation, is associated with greater retention of lipoproteins to promote the development of neoatherosclerosis. The accumulation of foamy macrophages and their persistent apoptosis likely result in the development of the necrotic core to form a fibroatheroma. Further enlargement of the necrotic core over time results in the formation of a thin-cap fibroatheroma, which may eventually lead to in-stent plaque rupture.

A major etiological factor explaining the rapid neoatherosclerotic transition is that stents releasing anti-proliferative drugs cause delayed endothelialization of the luminal stent surface in the DES, resulting in “delayed arterial healing.” This leaky endothelial layer might facilitate the migration of inflammatory cells and lipoproteins from the blood into the neointima, resulting in the development of new atherosclerotic lesions. The cholesterol uptake capacity is an independent risk factor for neoatherosclerosis and target lesion revascularization following stent implantation. Based on this finding, the functional evaluation of HDL-C levels is important for the risk stratification of patients treated with coronary stents.\textsuperscript{30} LDL-C and hs-CRP levels are also independently associated with neoatherosclerosis following stent placement.\textsuperscript{19} A substantial reduction in LDL-C levels (reduction in LDL-C levels of 50% or an LDL-C level ≤ 70 mg/dL) prevents nonhomogeneous changes in the neointima, such as heterogeneous, layered, or neoatherosclerotic patterns.\textsuperscript{19} In the present study, although patients were prescribed lipid-lowering agents, many did not achieve acceptable LDL-C levels. In patients with better lipid control (LDL-C < 70 mg/dL), the incidence of in-stent neoatherosclerosis was significantly reduced at earlier time points during follow-up (6-12 months). However, a significant number of patients with lipid levels > 100 mg/dL progressed to in-stent neoatherosclerosis. Thus, persistent hypercholesterolemia in patients undergoing statin therapy might have altered the neoatherosclerosis pathogenesis. Therefore, intensive LDL-C control therapy might play a significant role in maintaining a favorable neointimal pattern and preventing in-stent neoatherosclerosis. Compared with conventional statin treatment in DES-treated patients, intensive LDL-C control within one year after stenting effectively reduces the prevalence of neoatherosclerosis and decreases late and very late stent-related major events. Based on the rapid progression of neoatherosclerosis in DES, early intervention for neoatherosclerosis may be beneficial to improve the long-term outcomes and clinical prognosis of patients with DES implants. Limitations: Several limitations of this study should be acknowledged. First, this study used a retrospective design with selective bias, and the findings must be confirmed in a prospective study. Second, the sample size of this study is relatively small, and the prevalence of early ISR is relatively low in patients following stent implantation, al-
though we required a long time to collect the data. Third, although OCT has a high resolution, it is unable to identify either the absence of the endothelium or abnormal endothelial functional integrity following DES implantation. Further studies are required to elucidate the molecular mechanism underlying the development of neatherosclerosis. Finally, we have not yet determined whether genes, proteins, or metabolites may alter the development of neatherosclerosis in patients with ISR lesions. Further studies are required to elucidate the mechanisms underlying our findings.

Conclusions

In this study, we used OCT to evaluate the incidence and predictors of neatherosclerosis in patients with early ISRs. Neatherosclerosis was detected in 37% of patients with early restenotic lesions at a median of 180 days following DES implantation. In patients with early ISR lesions, follow-up LDL-C levels play a significant role in the modification of the early neatherosclerosis pathogenesis, and intensive LDL-C control therapy may be an effective approach to prevent early-stage neatherosclerosis following DES implantation.

Disclosure

Conflicts of interest: None.

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