Reviews in Cardiovascular Medicine

Original Research

Relationship between non-culprit lesion plaque characteristics changes and in-stent neoatherosclerosis formation: 1-year follow-up optical coherence tomography study

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DOI:10.31083/j.rcm2204177

Submitted: 18 August 2021 Revised: 26 October 2021 Accepted: 8 November 2021 Published: 22 December 2021

The relationship between the in-stent neoatherosclerosis (ISNA) formation and the plaque's characteristic changes in the non-culprit lesion is unclear. We aim to investigate the plaque characteristics changes at non-culprit lesions between patients with ISNA and without ISNA formation at 1-year follow-up. We retrospectively enrolled patients who had DES implantation in de novo lesion and underwent immediately after stenting and 1-year follow-up optical coherence tomography (OCT) examination. OCT-defined ISNA was defined as the presence of lipid-laden neointima or calcification within the culprit stent with a longitudinal extension of $\geq$1 mm. Non-culprit lesions were divided into two groups: ISNA group (with ISNA) and non-ISNA group (without ISNA). Plaque characteristics of non-culprit lesions were evaluated at baseline and 1-year follow-up. In total, 89 patients with 89 non-culprit lesions (ISNA: n = 37; non-ISNA: n = 52) were included in the analyses. The lesions in the ISNA group show a smaller minimum lumen area compared to the non-ISNA group at 1-year follow-up (2.57 $\pm$ 1.08 mm^2 versus 3.20 $\pm$ 1.62 mm^2, p = 0.044). The lesions of the ISNA group show a significant decrease in minimum lumen area changes percent (–7.25% versus 6.46%, p = 0.039). And there are more lesions with minimum lumen area (64.9% versus 38.5%, p = 0.014) and minimum lumen diameter (64.9% versus 40.4%, p = 0.023) decrease in the ISNA group. Furthermore, the lesions in ISNA group have more plaques with lipid core length increase (25.0% versus 10.0%, p = 0.040), more plaques with FCT decrease (50.0% versus 74.0%, p = 0.027) and less TCFA change to non-TCFA (33.3% versus 87.5%, p = 0.010). The plaque characteristic changes in non-culprit lesions are closely related to ISNA formation. The ISNA formation may accompany by a tardier plaque stabilization process in non-culprit lesions.

Keywords

Optical coherence tomography; Neoatherosclerosis; Non-culprit lesion

1. Introduction

Drug-eluting stent (DES) use has successfully reduced the risk of repeat revascularization compared with bare-metal stents (BMSs) [1]. However, late-phase clinical events, such as late stent thrombosis (LST) and in-stent restenosis (ISR), may still occur [2–4]. In-stent neoatherosclerosis (ISNA) defined as the development of atherosclerotic changes in the nascent neointimal tissue within previously implanted stents has been identified as the culprit for delayed in-stent-restenosis or stent thrombosis [5–7]. Previous studies have demonstrated that ISNA occurs more frequently and earlier in DES than in bare-metal stent (BMS) [8, 9]. The mechanisms of ISNA have not been fully clarified [10]. A recent study has shown ISNA is more common among patients with angiographic and clinical evidence of native atherosclerosis progression suggesting similar pathophysiological mechanisms [11]. However, it is not very clear whether the ISNA formation would be accompanied by the plaque's characteristic changes in the non-culprit lesion. According to the histological similarities between native atherosclerosis and ISNA, we hypothesized that the ISNA formation would affect the progression of plaques at non-culprit lesions. Therefore, we sought to investigate the plaque characteristics changes at non-culprit lesions between patients with ISNA and without ISNA formation at 1-year follow-up by optical coherence tomography (OCT).

2. Methods

2.1 Patient population

Our OCT registry is one of the multicenter registries of patients who underwent OCT of the coronary arteries which involves 20 sites across 6 Countries (The Massachusetts General Hospital OCT Registry, registered on ClinicalTrials.gov, NCT01110538). Study subjects were collected from our OCT registry database (single-center). In our center, patients with stent implantation and OCT imaging were usually told to back for coronary angiography examination and OCT imaging 1 year after discharge, even without any symptoms. We retrospectively enrolled acute coronary syndrome (ACS) patients who had DES implantation in de novo lesion and underwent immediately after stenting and 1-year follow-up OCT examination. All patients received statins and antiplatelet therapy during the follow-up period. The

subjects with poor OCT image quality were excluded. The detailed demographic, clinical, and hematologic data were collected from all subjects. According to the result of 1-year follow-up OCT, the patients were divided into 2 groups: ISNA group, defined as patients with OCT-defined ISNA at 1-year follow-up; non-ISNA group, defined as patients without OCT-defined ISNA at 1-year follow-up. A detailed patient flow is shown in Fig. 1.

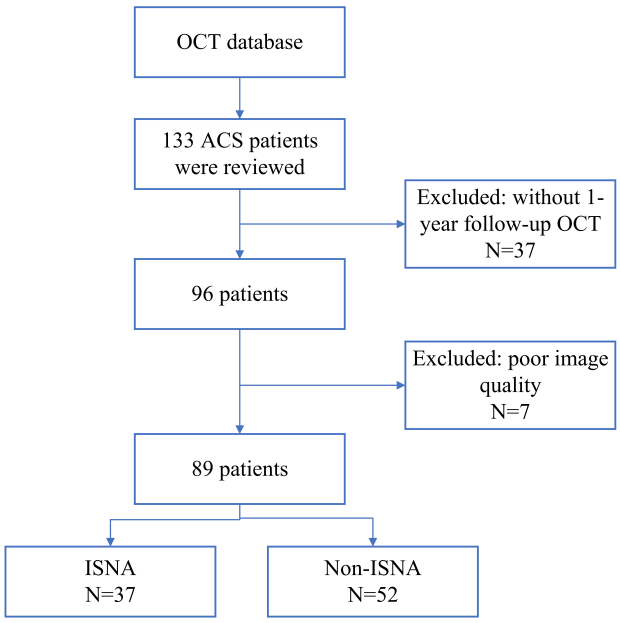

Fig. 1. Study population. 133 ACS patients in our OCT database were reviewed. We excluded patients without 1-year follow-up OCT images (N = 37) and with poor image quality (N = 7). There were finally 89 patients enrolled in this study (ISNA group, N = 37; Non-ISNA group, N = 52).

2.2 Optical coherence tomography examination and images analysis

Optical coherence tomography was performed with time-domain M2/M3 system (LightLab Imaging, Westford, Massachusetts, USA) or frequency-domain OCT systems (C7-XR OCT Intravascular Imaging System; St Jude Medical, St Paul, Minnesota, USA) as described previously [12]. OCT images were digitally archived to a database and analyzed in the imaging core lab by two experienced investigators who were blinded to clinical information using proprietary software (OPTISTM Off-line Review Workstation, version: E.4.1, St. Jude Medical. Inc, Minnesota, USA). When there was discordance between the readers, a consensus reading was obtained from a third independent investigator. Cross-sectional OCT images were analyzed at 1-mm intervals along with the pullbacks. All cross-sectional images were initially screened for quality assessment. If any portion of the image was out of the screen, a side branch occupied $>45^\circ$ of the cross-section, or the image had poor quality caused by residual blood, sew-up artifact, or reverberation were excluded from the analysis [13].

ISNA was defined as the presence of lipid-laden neointima or calcification within the culprit stent with a longitudinal extension of $\geq$1 mm [14]. Plaques of non-culprit lesions were classified into 2 categories: (1) fibrous, defined as a homogeneous high signal region, or (2) lipid plaque, defined as a low signal region with diffuse border. Lipid length and lipid arc were measured on the longitudinal reconstructed view and the cross-sectional image, respectively. The maximum lipid arc was recorded. Lipid-rich plaque (LRP) was defined as lipid plaque with a lipid arc $>90^\circ$ in any cross-section assessed by OCT [15]. Minimal fibrous cap thickness was measured 3 times at the thinnest part, and the average value was calculated. Thin-cap fibroatheroma (TCFA) was defined as the thinnest fibrous cap thickness $\leq$ of 0.65 mm (65 μm) in LRP on a cross-sectional image [15]. Plaque rupture was identified by the presence of a disrupted fibrous cap.

Changes percentage of lipid length (ΔLL %), minimum lumen area (ΔMLA %) and minimum lumen diameter (ΔMLD %) were calculated as follows:

$$\frac{value\ at\ 1\ year\ follow\ up - \ value\ at\ base\ line}{value\ at\ base\ line} \times 100\%$$

For lipid plaques at baseline, the lipid length changes level and lipid arc changes level at 1-year were defined. According to the value of ΔLL %, the lipid length changes level was defined as no changes ($-10\% \leq \Delta LL\ \% \leq 10\%$), decrease ($\Delta LL\ \% < 10\%$) and increase ($\Delta LL\ \% > 10\% \times$ value of baseline); According to the difference value (D-value = value at 1-year follow up minus value at baseline) of maximum lipid arc between baseline and 1-year follow-up, lipid arc changes level was also defined as no changes ($-10^\circ \leq$ D-value $\leq 10^\circ$), decrease (D-value $< -10^\circ$) and increase (D-value $> 10^\circ$). If the lipid plaque was changed to the fibrous plaque at 1-year follow-up also considered as a decrease in lipid length and arc.

3. Statistics

All statistical analysis was performed by an independent statistician. Categorical data are presented as n (%). Continuous variables are presented as mean $\pm$ standard deviations for normally distributed variables and median (interquartile range) for abnormally distributed variables. Kolmogorov-Smirnov test was used to test the normality of variables. The significances of variables in 2 groups were conducted using the Student's *t*-test for normally distributed continuous variables and the Mann Whitney U test for abnormally distributed continuous variables. Categorical variables were compared using the Chi-square test or the Fisher exact test. The inter-and intra-observer agreement was evaluated by Bland-Altman analysis for the continuous variable (such as fibrous cap thickness, lipid arc, and length) and by Kappa analysis for categorical variables (such as TCFA, macrophage). All analysis was performed using IBM SPSS Statistics (V.23, IBM Corp, Armonk, New York, USA), a p-value < 0.05 was considered to represent a statistically significant result.

Table 1. Clinical characteristics in different groups.

Characteristics	ISNA	non-ISNA	*p*-value
Patients No.	37	52	-
Male, n (%)	29 (78.4%)	39 (75.0%)	0.711
Age, year	52.1 ± 11.3	56.3 ± 8.74	0.086
Hypertension, n (%)	24 (64.9%)	38 (73.1%)	0.406
Hyperlipidemia, n (%)	10 (37.0%)	11 (20.8%)	0.118
Diabetes, n (%)	19 (51.4%)	24 (46.2%)	0.629
History of smoke, n (%)	23 (62.2%)	27 (51.9%)	0.337
History of MI, n (%)	8 (21.6%)	9 (17.3%)	0.610
Metabolic profiles at baseline			
Total cholesterol	4.62 ± 1.49	4.81 ± 1.17	0.551
Triacylglycerol	2.32 ± 1.97	2.19 ± 1.25	0.736
HDL	1.15 ± 0.37	1.30 ± 0.34	0.076
LDL	2.45 ± 1.03	2.58 ± 0.89	0.568
H1Abc	6.16 ± 1.00	6.58 ± 1.60	0.234
Metabolic profiles at 1-year follow-up			
Total cholesterol	3.65 ± 0.81	3.41 ± 0.68	0.194
Triacylglycerol	1.71 ± 0.98	1.56 ± 0.67	0.454
HDL	1.11 ± 0.28	1.09 ± 0.27	0.718
LDL	1.93 ± 0.75	1.75 ± 0.53	0.243
H1Abc	6.41 ± 1.05	6.58 ± 1.38	0.691
Statin			
Atorvastatin (20 mg), n (%)	21 (56.8%)	35 (67.3%)	0.592
Rosuvastatin (10 mg), n (%)	6 (16.2%)	6 (11.5%)	
Others, n (%)	10 (27.0%)	11 (21.2%)	
Clinical presentation			
Unstable angina pectoris, n (%)	18 (48.6%)	30 (57.7%)	0.654
NSTEMI, n (%)	11 (29.7%)	14 (26.9%)	
STEMI, n (%)	8 (21.6%)	8 (15.4%)	
Location of Non-culprit lesion			
LAD, n (%)	18 (48.6%)	29 (55.8%)	0.584
LCX, n (%)	6 (16.2%)	10 (19.2%)	
RCA, n (%)	13 (35.1%)	13 (25.0%)	
Non-culprit lesion located in the same vessel with stent, n (%)	28 (75.7%)	35 (67.3%)	0.392
Stent type			
Sirolimus eluting stent, n (%)	16 (43.2%)	23 (44.2%)	0.795
Paclitaxel eluting stent, n (%)	9 (24.3%)	15 (28.8%)	
Zotarolimus eluting stent, n (%)	7 (18.9%)	6 (11.5%)	
Everolimus eluting stent, n (%)	5 (13.5%)	8 (15.4%)	
Stent length	26.07 ± 7.57	30.16 ± 11.73	0.113
Stent diameter, mm	3.11 ± 0.44	3.09 ± 0.44	0.853
Stent malapposition	8 (21.6%)	12 (23.1%)	0.871
In-stent tissue prolapse	6 (16.2%)	7 (13.5)	0.717

HDL, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; H1Abc, Hemoglobin A1c; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 2. The difference of lesion characteristics between different groups at different time.

	ISNA (n = 37)	non-ISNA (n = 52)	*p*-value
Baseline			
Minimum lumen area, mm^2	2.76 ± 1.31	3.04 ± 1.52	0.368
Minimum lumen diameter, mm	1.62 ± 0.50	1.70 ± 0.51	0.492
Lipid plaque, n (%)	32 (86.5%)	50 (96.2%)	0.122*
Lipid rich plaque, n (%)	32 (100.0%)	50 (100.0%)	-
Lipid core length, mm	6.96 ± 3.85	7.00 ± 5.12	0.978
Lipid arc	233.79 ± 73.22	244.28 ± 84.23	0.596
Minimal fibrous cap thickness, μm	90.0 (60.0, 185.0)	110.0 (57.50, 170.0)	0.905
thin-cap fibroatheroma, n (%)	9 (28.1%)	16 (32.0%)	0.710
Plaque rupture, n (%)	1 (2.7%)	4 (7.7%)	0.314
Macrophage	22 (59.5%)	32 (61.5%)	0.843
1-year follow-up			
Minimum lumen area, mm^2	2.57 ± 1.08	3.20 ± 1.62	0.044
Minimum lumen diameter, mm	1.58 ± 0.41	1.97 ± 1.62	0.165
Lipid plaque, n (%)	30 (81.1%)	43 (82.7%)	0.845
Lipid rich plaque, n (%)	29 (96.7%)	40 (93.0%)	0.501
Lipid core length, mm	6.20 ± 3.48	7.02 ± 5.23	0.502
Lipid arc	215.52 ± 75.40	230.16 ± 93.85	0.522
Minimal fibrous cap thickness, μm	115.0 (60.0, 292.5)	140.0 (100.0, 230.0)	0.351
thin-cap fibroatheroma, n (%)	6 (19.4%)	2 (4.7%)	0.062*
Plaque rupture, n (%)	0	1 (1.9%)	1.000*
Macrophage	20 (54.1%)	26 (50.0%)	0.706

* Fisher exact test.

4. Results

4.1 Clinical characteristics

We have retrospectively reviewed 133 patients in our OCT Registry database, 44 were excluded due to without 1-year follow-up OCT (n = 37) and poor image quality (n = 7). In total, 89 patients with 89 non-culprit lesions were included in the analyses. ISNA was observed in 37 out of 89 patients (41.6%) without related clinical symptoms. Baseline clinical characteristics are summarized in Table 1. Following the baseline study, no differences were observed between the two groups.

4.2 Lesion characteristics at baseline

There is no significant difference in minimum lumen area and minimum lumen diameter in analytical lesion between ISNA and non-ISNA at baseline. The plaques of most lesions are lipid plaques (82 of 89 in total patients, 32 of 37 in ISNA group, and 50 of 52 in non-ISNA group), and there are no differences in plaques type between ISNA and non-ISNA at baseline (p = 0.122). All lipid plaques represent lipid-rich plaque. For the lipid plaques analysis (n = 82), there are no significant differences in lipid core length, lipid arc, and minimal fibrous cap thickness between the two groups. The occurrence of TCFA also has no significant difference in different groups. Although there were plaques rupture found in both groups with no significant difference, no relevant clinical presentations were found. The detailed data were shown in Table 2.

4.3 Lesion characteristics at 1-year follow-up

The lesions in the ISNA group show smaller minimum lumen area compared to the non-ISNA group at 1-year follow-up (2.57 ± 1.08 mm^2 versus 3.20 ± 1.62 mm^2, p = 0.044), while the minimum lumen diameter still has no significant difference between two groups. The characteristics of plaques presented as plaque type, the lipid core length, lipid arc, and minimal fibrous cap thickness are no significant differences between ISNA and non-ISNA at 1-year follow-up (Table 2). However, the plaques in the ISNA group seem to have a more frequent occurrence of TCFA compared to the non-ISNA group (19.4% versus 4.7%, p = 0.062). Most plaque ruptures have healed except 1 in the non-ISNA group. The detailed data were also shown in Table 2.

4.4 1-year follow-up versus baseline lesions progression

As shown in Table 3, all lesions become more stable at 1-year follow-up, which are presented as fewer lipid plaques (92.1% versus 82.0%, p = 0.044) and TCFA (30.5% versus 12.2%, p = 0.006), thicker minimal fibrous cap thickness [100.0 (60.0, 170.0) μm versus 130 (90.0, 250.0) μm, p = 0.003]. There are no significant changes of minimum lumen area, minimum lumen diameter, the lipid core length, and lipid arc at 1-year follow-up ($p > 0.05$, Table 3).

The lesions of ISNA group show a significant decrease in minimum lumen area changes percent (–7.25% versus 6.46%, p = 0.039) compared non-ISNA group. And there are more lesions with minimum lumen area (64.9% versus 38.5%, p = 0.014) and minimum lumen diameter (64.9% versus 40.4%, p

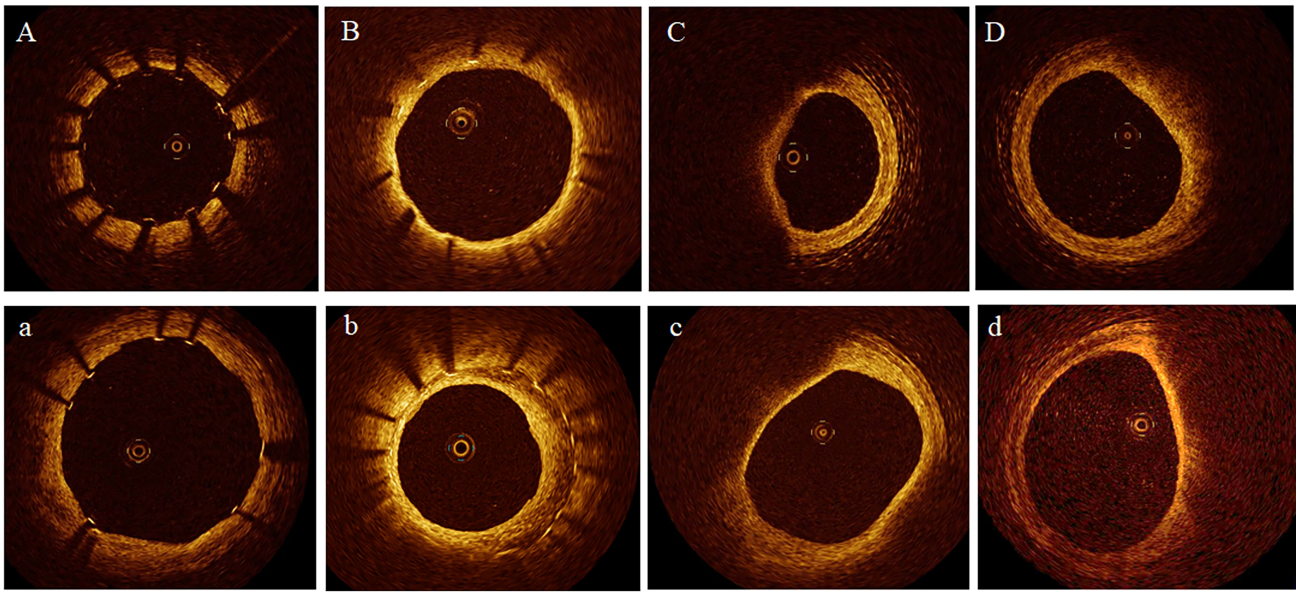

Fig. 2. The representative OCT images. (A–D) represents the OCT images of the non-ISNA group. (A) stent implantation at baseline. (B) neointimal coverage of stent at 1-year follow-up. (C) lipid-rich plaque at baseline. (D) same plaque with image C at 1 year-follow-up, showing thicker FCT and smaller lipid arc. (a–d) represents the OCT images of the ISNA group. (a) stent implantation at baseline. (b) ISNA formation 1-year follow-up. (c) lipid-rich plaque (TCFA) at baseline. (d) same plaque with image c at 1 year-follow-up, showing thicker FCT and smaller lipid arc, but still is TCFA.

Table 3. The difference of lesion characteristics at different times in total patients.

	Baseline	1-year follow-up	*p*-value
	(n = 89)	(n = 89)	
Minimum lumen area, mm^2	2.92 ± 1.44	2.93 ± 1.45	0.952
Minimum lumen diameter, mm	1.67 ± 0.50	1.81 ± 1.27	0.331
Lipid plaque, n (%)	82 (92.1%)	73 (82.0%)	0.044
Lipid rich plaque, n (%)	82 (100.0%)	69 (94.5%)	0.032
Lipid core length, mm	6.98 ± 4.64	6.34 ± 4.48	0.978
Lipid arc	233.37 ± 79.6	219.49 ± 84.31	0.596
Minimal fibrous cap thickness, μm	100.0 (60.0, 170.0)	130 (90.0, 250.0)	0.003
thin-cap fibroatheroma, n (%)	25 (30.5%)	9 (12.2%)	0.006
Plaque rupture, n (%)	5 (5.6%)	1 (1.1%)	0.211

= 0.023) decrease in the ISNA group compared to non-ISNA. Although there are no significant differences in lipid plaques morphology, the lipid plaques of ISNA group showed significant changes at 1-year follow-up compared to the non-ISNA group: more plaques with lipid core length increase (25.0% versus 10.0%, p = 0.040), more plaques with FCT decrease (50.0% versus 74.0%, p = 0.027) and less TCFA change to non-TCFA (33.3% versus 87.5%, p = 0.010). The lesions' progressions are summarized in Table 4 and the representative OCT images were shown in Fig. 2.

5. Discussion

In this study, we have evaluated the progression of non-culprit lesions in patients with or without ISNA formation after stent implantation at 1-year follow-up. The principal findings of the present study were as follows: ISNA was observed in 37 out of 89 patients (41.6%) without related clinical symptoms; compared to patients with non-ISNA: non-culprit lesion in patients with ISNA have smaller minimum lumen size and high incidence of TCFA at 1-year follow-up; the minimum lumen area and minimum lumen diameter of the non-culprit lesion in patients with ISNA decreased more significantly at 1-year follow-up; less TCFA of non-culprit lesions in patients with ISNA turn to non-TCFA at 1-year follow-up.

A growing number of studies have reported the presence of ISNA in DES [10, 16]. ISNA may represent an accelerated and possibly more unstable manifestation of atherosclerosis [17, 18]. And the ISNA with neointimal rupture and thrombosis is the culprit for definite very late stent thrombosis and is also associated with a high frequency of ST-segment elevation myocardial infarction [19, 20]. There are limited data regarding the association between ISNA formation and the progression of the non-culprit lesion. This is the first study

Table 4. The different progression of lesion characteristics between ISNA and non-ISNA group at 1-year follow-up.

	ISNA (n = 37)	non-ISNA (n = 52)	*p*-value
MLA changes, mm^2	–0.23 (–0.60, 0.37)	0.190 (–0.42, 0.67)	0.062
MLA changes percent, %	–7.25 (–23.53, 14.20)	6.46 (–13.61, 27.69)	0.039
Lesion with MLA decrease, n (%)	24 (64.9%)	20 (38.5%)	0.014
MLD changes, mm	–0.070 (–0.27, 0.15)	0.045 (–0.18, 0.27)	0.113
MLD changes percent, %	–4.90 (–16.83, 8.46)	1.91 (–9.79, 21.81)	0.099
Lesion with MLD decrease, n (%)	24 (64.9%)	21 (40.4%)	0.023
Lipid plaque analyze			
Lipid plaque at baseline, n	32	50	
Lipid core length changes level at 1Y	-	-	0.040
no changes, n (%)	4 (12.5%)	17 (34.0%)	
decrease, n (%)	20 (62.5%)	28 (56.0%)	
increase, n (%)	8 (25.0%)	5 (10.0%)	
Lipid arc changes level at 1Y	-	-	0.541
no changes, n (%)	7 (21.9%)	10 (20.0%)	
decrease, n (%)	17 (53.1%)	32 (64.0%)	
increase, n (%)	8 (25.0%)	8 (16.0%)	
FCT increase, μm	0.00 (–10.0, 90.0)	50 (10.0, –80.0)	0.124
Lesion with FCT increase, n (%)	16 (50.0%)	37 (74.0%)	0.027
Lipid plaques change to fibrous plaque, n (%)	5 (15.6%)	7 (14.0%)	0.839
TCFA at baseline, n	9	16	
TCFA change to non-TCFA	3 (33.3%)	14 (87.5%)	0.010*

* Fisher exact test.

MLA, minimal lumen area; MLD, minimum lumen diameter; FCT, fibrous cap thickness; TCFA, thin-cap fibroatheroma.

to show the significant association between the presence of OCT-defined ISNA and the progression of non-culprit lesions evaluated by OCT.

The mechanism of ISNA is poorly understood and it is believed to be a pathological process involving multiple factors and mechanisms. The histological characteristics of ISNA are similar to native atherosclerosis, which is characterized by the accumulation of lipid-laden foamy macrophages within the neointima with the presence or absence of necrotic core formation and/or calcification inside previously implanted stents [18]. Based on the above theory, it inferred that there should be a close relationship between the progression of native atherosclerosis and the development of ISNA. In the study of Masanori Taniwaki *et al.* [11], they found that ISNA was more likely to develop in patients with a progressive native atherosclerosis phenotype confirmed by angiographic and clinical evidence during 5 years follow-up. Our results are partly in line with this study. However, our study provides more detailed plaque characteristics changes of native atherosclerosis using OCT imaging. We found the different progression of the non-culprit lesions between patients with and without ISNA formation. Although there is no significant difference in plaque characteristics at 1-year follow-up between ISNA and non-ISNA group, the native atherosclerosis of non-culprit lesions in patients with ISNA formation has shown more lesions with lipid core length increase, fewer lesions with FCT increase, and fewer TCFA changes to non-TCFA. That means non-culprit lesions in patients with ISNA formation have more significant progression compared to those without ISNA formation. The underlying mechanism of stability changes of non-culprit lesions is complex, such as aggressive lipid lowering therapy by statin treatment or using a PCSK9 inhibitor [21, 22], chronic kidney disease [23], and the metabolic profiles of patients. The findings in this study were based on the relatively consistent of baseline clinical characteristics of patients, which suggesting that there may be other underlying atherosclerotic factors related to the progression of non-culprit lesions in the ISNA group.

Local hemodynamic forces change induced by ISNA formation may be one of potential factor involved in this progress. Low endothelial shear stress, tangential stress caused by blood flow friction on the endothelial surface, is a focal proinflammatory stimulus associated with the development and progression of coronary atherosclerosis [24, 25]. A recent study also found that low endothelial shear stress has an important role in ISNA formation [26]. Therefore, another reasonable hypothesis is that the in-stent lumen area reduced by ISNA formation induces the change of endothelial shear stress out stent, as most of the lesions included in this study were located in the same vessels with stents (75.7% and 67.3%). The local hemodynamic forces in vessels with ISNA formation may be atherogenic which results in ISNA

formation and progression of out stent native atherosclerosis. Furthermore, the ISNA formation results in lumen loss and turbulent flow (low endothelial shear stress) may also exacerbate the progression of native atherosclerosis out stent.

There are no significant differences in non-culprit lesion related outcomes between patients with and without ISNA. Of note, the previous study has shown that the cumulative incidence of non-culprit lesion revascularization was almost three times higher than culprit lesions revascularization at longtime follow up [27]. Therefore, the lumen loss and fewer lesions turn to stabilization in the non-culprit lesions of patients with ISNA may increase the incidence of non-culprit lesions revascularization, which will turn these patients into patients with a high risk of cardiovascular events.

OCT work as an important role in evaluated the de novo coronary lesions and also ISNA with the excellent resolution at the expense of poor imaging depth that often precludes assessment of the atheroma burden and remodelling pattern. Recently, several dual-probe catheters have been introduced including combined near infrared spectroscopy-intravascular ultrasound (NIRS-IVUS), IVUS-OCT, the OCT-NIRS, the OCT-near infrared fluorescence (NIRF) molecular imaging, IVUS-NIRF, IVUS intravascular photoacoustic imaging and combined fluorescence lifetime-IVUS imaging [28]. These multimodal approaches appear able to overcome limitations of standalone imaging and provide comprehensive visualization of de novo coronary lesions and ISNA [28, 29].

6. Study limitations

The results of our study need to be interpreted in light of some limitations. First, this study is a retrospective study, the subjects included in this study are from a single center and the sample number is relatively small. There is a patient selection bias in this retrospective study and the incidence of ISNA may be overestimated. Second, the follow-up time is not long enough. The clinical outcome of ISNA formation and non-culprit lesions progression need a more long time follow-up to be evaluated. Third, the most of DES used in this study were the early generation that was rarely used in clinical practice. However, the previous histological study has found that new generation everolimus-eluting stents have a similar propensity to develop ISNA as early-generation DES [30]. Therefore, our findings should also apply to new-generation DES.

7. Conclusions

The plaque characteristic changes in non-culprit lesions are closely related to ISNA formation. Patients with ISNA formation present a tardier plaque stabilization process non-culprit lesions compared to patients without ISNA formation. The underlying mechanism of this phenomenon is still needed further discussion.

Author contributions

Conceptualization, XH and JH; Methodology, YZ, CF and LX; Investigation, YZ, XF, XW, QL, LF, DL and MY; Writing – Original Draft, XH and CF; Writing –Review & Editing, JH, LX and XH; Funding Acquisition, XH; Resources, XH, JH and LX; Supervision, XH; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

This protocol was approved by the Harbin Medical University Ethics Committee (Approval number: KY2018-225) and informed consent was obtained from all patients.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This work was funded by the National Natural Science Foundation of China (Grant Number: 81801803), China Postdoctoral Science Foundation (Grant Number: 2018M640310), and Heilongjiang Postdo Methodology ctoral Science Foundation (Grant Number: LBH-Z19032). This work was also supported by the Fund of Key Laboratory of Myocardial Ischemia, Ministry of Education.

Conflict of interest

The authors declare no conflict of interest.

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