

# Evolution of nonculprit coronary atherosclerotic plaques assessed by serial virtual histology intravascular ultrasound in patients with ST-segment elevation myocardial infarction and chronic total occlusion

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**Objective** The pathophysiology and natural course of coronary nonculprit plaques remain unclear. We investigated whether the short-term natural course of nonculprit plaques differs between ST-segment elevation myocardial infarction (STEMI) and chronic total occlusion (CTO) patients.

**Methods** We performed serial virtual histology intravascular ultrasound on nonculprit plaques in 26 STEMI and 11 CTO lesions at baseline and the 6-month follow-up.

**Results** At baseline, more lesions in the STEMI group were virtual histology intravascular ultrasound-derived thin-cap fibroatheromas (TCFA; 76.9 vs. 18.1%,  $P = 0.002$ ). During the follow-up period, the plaque composition changed dynamically in the STEMI group (fibrofatty:  $9.8 \pm 1.9$  to  $17.3 \pm 2.9\%$ ,  $P = 0.030$ ; dense calcium:  $12.7 \pm 1.8$  to  $8.1 \pm 1.7\%$ ,  $P = 0.026$ ; necrotic core:  $21.1 \pm 1.8$  to  $15.4 \pm 2.2\%$ ,  $P = 0.052$ ), with a consistent plaque size. In the CTO group, the plaque composition and plaque size remained consistent without a significant change. Also, more lesions in the STEMI group remained as or progressed to TCFA, compared with the CTO group (67 vs. 11%,  $P = 0.089$ ). Factors associated with a persistent TCFA or with a new development of TCFA were a large necrotic core volume index and the diagnosis of STEMI, whereas new statin usage was a protective factor.

## Introduction

ST-segment elevation myocardial infarction (STEMI) and chronic total occlusion (CTO) are both associated with atheromatous disease and subsequent occlusion of the coronary artery. However, these two lesions have a different pathophysiology. In STEMI lesions, plaque rupture and acute thrombus formation are the main mechanisms [1], whereas CTO lesions also arise from thrombotic occlusion, but are usually associated with long-standing ischemia, followed by thrombus organization and tissue aging [2]. Although previous intravascular

**Conclusion** Nonculprit lesions in STEMI patients were more unstable at the baseline compared with those in CTO patients. During follow-up, nonculprit lesions in STEMI and CTO patients showed a distinct pattern of change; the former were stabilized in plaque composition, whereas the latter remained consistent. The diagnosis of STEMI and a large necrotic core volume were predictors of evolution to a TCFA, and new statin usage was a protective factor. *Coron Artery Dis* 27:650–657 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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ultrasound (IVUS) studies in STEMI or CTO patients have evaluated the plaque of culprit lesions [3,4], it remains uncertain whether the pathophysiology and natural course of coronary nonculprit plaques differ between STEMI and CTO patients. The analysis and comparison of the nonculprit plaques of two distinct diagnoses, that is, STEMI and CTO, may provide a better understanding of the plaques. Especially nonculprit proximal plaques of CTO lesions showed a similar plaque composition to the CTO lesion [5], which was a distinct characteristic compared with that of stable non-occlusive coronary diseases [6].

For nonculprit plaques, the management of non-infarct-related lesions has been a topic of controversy recently. Although some reports have shown that percutaneous

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coronary intervention (PCI) on significant non-infarct-related arteries may reduce the risk of a future cardiac event [7,8], a counterargument has been raised focusing on the potential risks of preventive PCI and potential benefits of medical therapy. For further understanding of the nature of non-infarct-related lesions, more sophisticated lesion analysis, such as virtual histology intravascular ultrasound (VH-IVUS), could be used.

In the present study, we used serial VH-IVUS to assess and compare the dynamic nature of nonculprit coronary artery plaques in patients with STEMI and CTO.

## Methods

### Study population

Our study population included STEMI and CTO patients who received successful PCI for the culprit lesion, and those with a follow-up angiography and IVUS analysis. Patients received follow-up angiogram at 6–9 months after the index PCI according to our center's clinical practice protocol. The demographic and clinical characteristic data of the study population were confirmed by a retrospective hospital chart review. STEMI was defined as new ST elevation at the J point in two contiguous leads with the cutoff point more than 0.1 mV in all leads other than leads V2–V3, where the following cutoff points were applied: greater than 0.2 mV in men aged older than 40 years, greater than 0.25 mV in men aged younger than 40 years, or greater than 0.15 mV in women and angiographically confirmed acute thrombotic occlusion of the native coronary artery [9]. CTO was defined as luminal compromise in a native coronary artery resulting in the complete interruption of antegrade flow as assessed by coronary arteriography with an occlusion duration more than 3 months [10]. Lesions that were proximal to the culprit lesion were analyzed.

### IVUS analysis

After successful stent deployment at the culprit lesion, a phased-array, 20 MHz, 3.2 Fr IVUS catheter (Eagle Eye; Volcano Corporation, Rancho Cordova, California, USA) was placed at the proximal edge of the stented lesion and withdrawn using a motorized automatic transducer pull-back system at 0.5 mm/s. We analyzed lesions without thrombus, which was confirmed by angiography and by gray-scale IVUS. The gray-scale IVUS images and captured radiofrequency data were recorded onto digital media for offline analysis. Gray-scale and VH-IVUS analyses were carried out using offline pcVH2.1 software (Volcano Corporation). Measurements for lesion characteristics were performed for each frame (median measurement interval, 0.40 mm). The images were reviewed by independent experienced observers. Corresponding images of baseline and follow-up IVUS examinations were identified by the distance from two fiducial landmarks such as side branches and stent edges. Gray-scale IVUS measurements of the lumen, external elastic

membrane (EEM) cross-sectional area (CSA), plaque and media (P&M) CSA (defined as EEM CSA minus lumen CSA), and plaque burden (defined as P&M CSA divided by EEM CSA) were performed for each recorded frame. The plaque components were classified by color-coded pixels as fibrofatty tissue (FF: light green), fibrotic tissue (FT: dark green), dense calcium (DC: white), and necrotic core (NC: red).

### Definition of lesion and plaque classification

A nonculprit lesion was defined as having a plaque burden more than 40% in at least three consecutive frames (>1.5 mm in length) and more than 5 mm proximal to stented lesions to minimize the possible influence of angioplasty procedure. Lesions were considered separated if there was a greater than or equal to 5-mm-long segment with less than 40% plaque burden between them. Plaque classification was defined on the basis of the plaque composition and geometrical analysis by VH-IVUS as follows: (a) thin-cap fibroatheroma (TCFA), (b) thick-cap fibroatheroma (ThCFA), (c) pathological intimal thickening (PIT), (d) fibrotic plaque, and (e) fibrocalcific plaque (FC) [11,12]. VH-IVUS defined fibroatheroma as having a confluent NC more than 10% of the total plaque volume in mainly fibrous and/or FF tissue. In fibroatheroma, a plaque without virtual histology evidence of a fibrous cap and with more than 30° of NC abutting the lumen in three consecutive frames was defined as TCFA. ThCFA was defined as a fibroatheroma with a definable fibrous cap. PIT comprised primarily FF and FT with 10% or less NC and 10% or less DC. A fibrotic plaque contained predominantly FT with less than 10% NC, less than 15% FF, and less than 10% DC, whereas a FC plaque predominantly contained FT with greater than 10% DC but less than 10% NC. A lesion could contain more than one fibroatheroma. The following hierarchy was used: a TCFA took precedence over ThCFA and any fibroatheroma took precedence over any nonfibroatheroma [13,14]. It was also used as the sequence of evolution. The concept 'evolution to a TCFA' was defined as new development of TCFA from a non-TCFA, along with a persistent TCFA.

### Statistical analysis

Continuous variables were presented as mean ± SE and were compared using the Mann–Whitney *U*-test. Categorical variables were presented as proportions and the  $\chi^2$ -test was used to compare differences between groups. A comparison of baseline and follow-up values of the IVUS scale was analyzed using McNemar's test, as appropriate. Multiple logistic generalized estimating equation (GEE) modeling using the independence structure was performed to analyze the longitudinal changes on IVUS and clinical parameters as independent variables versus the evolution to TCFA as the binary dependent variable. GEE is a general statistical approach to fit a marginal model for longitudinal data analysis.

This method, an extension of the quasi-likelihood approach, incorporates within-patient and between-patient variations into model fitting to improve the efficiency of the estimation and the power [15].

Two-sided *P* values less than 0.05 were considered statistically significant for all tests. All statistical analyses were carried out using SPSS (version 20.0; IBM Corp., Armonk, New York, USA).

## Results

### Baseline patient characteristics and gray-scale IVUS and VH-IVUS data

After successful revascularization, serial VH-IVUS was performed in 26 lesions (24 patients) in the STEMI group and 11 lesions (11 patients presented with stable angina) in the CTO group at baseline and at the 6-month follow-up [median follow-up duration 218 days (interquartile range, 186–245 days)]. The median age of the patients was  $59.8 \pm 9.7$  years, with men comprising 85.7% of the population, and other baseline characteristics are listed in Table 1. The proportion of patients with hypertension and dyslipidemia was higher in the CTO group; there were more current smokers in the STEMI group. Laboratory data showed similar data at baseline, whereas the change in the lipid profile was more dynamic in the STEMI group, with marginal statistical significance. Discharge medication, including statin, was similar between the two groups, and there were significantly more new statin users in the STEMI group compared with the CTO group (92.3 vs. 36.4%,  $P < 0.001$ ).

In terms of lesion characteristics, at baseline, the values measured with the gray-scale IVUS were similar between groups (Table 2). In the total study population, the nonculprit lesions had a plaque burden of  $50.4 \pm 7.7\%$ . The plaque characteristics measured with VH-IVUS were not significantly different between groups. However, the proportion of TCFA was significantly higher in the STEMI group than in the CTO group [76.9% (20 lesions) vs. 18.1% (2 lesions),  $P = 0.002$ ; Fig. 1].

### Plaque evolution

When comparing plaque composition at baseline, the plaque composition (i.e. FT, FF, DC, NC volume index) and plaque size were similar between the STEMI and the CTO groups. Also, at the 6-month follow-up, there was no difference in values between the two groups (Table 2).

However, we could find a change in plaque composition by a paired comparison within the STEMI group. The proportion of FF increased ( $9.8 \pm 1.9$  to  $17.3 \pm 2.9\%$ ,  $P = 0.030$ ), whereas the proportion of DC decreased significantly ( $12.7 \pm 1.8$  to  $8.1 \pm 1.7\%$ ,  $P = 0.026$ ) and that of NC decreased with marginal significance ( $21.1 \pm 1.8$  to

**Table 1 Patient characteristics at baseline and follow-up**

	STEMI (n = 24)	CTO (n = 11)	<i>P</i> value
<b>Demographic data</b>			
Age (years)	59.8 ± 2.0	59.6 ± 3.1	0.879
Sex: male	20 (83.3)	10 (90.9)	0.491
BMI (kg/m <sup>2</sup> )	24.0 ± 0.5	25.6 ± 1.0	0.199
Hypertension	8 (33.3)	9 (81.8)	0.027
Diabetes mellitus	5 (20.8)	5 (45.5)	0.227
Dyslipidemia	5 (20.8)	6 (54.5)	0.041
Current smoker	14 (58.3)	1 (9.1)	0.021
Smoking at follow-up	5 (20.8)	1 (9.1)	0.392
<b>Angiographic data</b>			
Culprit artery			0.434
Left anterior descending artery	11 (45.8)	4 (36.4)	
Left circumflex artery	4 (16.7)	4 (36.4)	
Right coronary artery	9 (37.5)	3 (27.3)	
Disease extent			0.202
One-vessel disease	10 (41.7)	2 (18.2)	
Two-vessel disease	8 (33.3)	7 (63.6)	
Three-vessel disease	6 (25.0)	2 (18.2)	
<b>Laboratory data</b>			
LVEF (%)	52.5 ± 1.9	60.2 ± 2.7	0.027
Hemoglobin (g/dl)	15.1 ± 0.3	14.0 ± 0.6	0.052
hs-CRP (mg/l)	1.91 ± 0.75	1.26 ± 0.99	0.930
Serum creatinine (mg/dl)	1.04 ± 0.03	1.10 ± 0.06	0.852
eGFR (ml/min/1.73 m <sup>2</sup> ) <sup>a</sup>	69.1 ± 4.4	71.4 ± 5.4	0.756
Total cholesterol at baseline (mg/dl)	180.8 ± 9.9	172.7 ± 8.5	0.986
Total cholesterol at follow-up (mg/dl)	143.1 ± 5.8	153.1 ± 5.0	0.311
Δ Total cholesterol (mg/dl) <sup>b</sup>	−43.1 ± 7.5	−19.6 ± 6.6	0.071
Triglyceride at baseline (mg/dl)	119.4 ± 19.0	194.2 ± 49.3	0.056
Triglyceride at follow-up (mg/dl)	117.6 ± 16.2	130.4 ± 15.9	0.106
Δ Triglyceride (mg/dl) <sup>b</sup>	−4.8 ± 13.6	−63.8 ± 34.5	0.160
HDL-cholesterol at baseline (mg/dl)	43.1 ± 1.7	39.0 ± 3.7	0.051
HDL-cholesterol at follow-up (mg/dl)	44.5 ± 2.5	40.1 ± 4.1	0.302
Δ HDL-cholesterol (mg/dl) <sup>b</sup>	2.5 ± 2.0	1.1 ± 2.2	0.918
LDL-cholesterol at baseline (mg/dl)	96.8 ± 9.7	90.6 ± 6.7	0.658
LDL-cholesterol at follow-up (mg/dl)	66.6 ± 3.6	76.8 ± 4.1	0.030
Δ LDL-cholesterol (mg/dl) <sup>b</sup>	−34.4 ± 7.1	−13.8 ± 6.1	0.057
<b>Discharge medication</b>			
Aspirin	26 (100)	11 (100)	NA
Clopidogrel	26 (100)	11 (100)	NA
β-Blocker	18 (69.2)	8 (72.7)	0.832
ACEI or ARB	22 (84.6)	7 (63.6)	0.157
Statin	24 (92.3)	10 (90.9)	0.887
Statin new-users	24 (92.3)	4 (36.4)	< 0.001
High-intensity statin <sup>c</sup>	8 (33.3)	1 (9.1)	0.126

Values presented as *n* (%) or mean ± SE.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NA, not available; STEMI, ST-segment elevation myocardial infarction.

<sup>a</sup>eGFR was calculated using the Modification of Diet in Renal disease formula:  $175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$  ( $\times 0.742$  for women).

<sup>b</sup>Δ values were calculated as 'level at follow-up − baseline level'.

<sup>c</sup>High-intensity statin was defined as statins that lower LDL-cholesterol by  $\sim \geq 50\%$ , including atorvastatin 40–80 mg daily and rosuvastatin 20–40 mg daily.

$15.4 \pm 2.2\%$ ,  $P = 0.052$ ). This trend was similar in the volume index (mm<sup>3</sup>/mm) of the FF, NC, and DC. Especially, the reduction in NC was observed in the decrease in the mean NC CSA and maximal NC values. The total plaque size, measured on the basis of plaque burden, and mean plaque CSA, remained consistent throughout the follow-up period. However, in the CTO group, no significant change in plaque composition or plaque size (i.e. plaque burden and mean plaque CSA) was observed. Collectively, in the STEMI group, the plaque size was consistent with a dynamic change in plaque composition, whereas in the CTO group, the

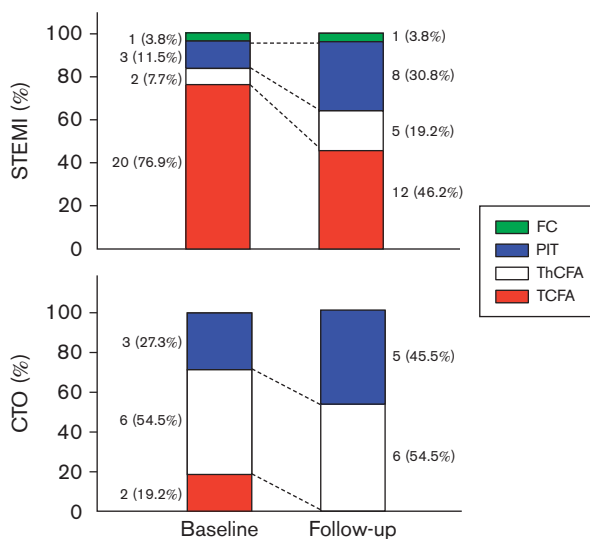
**Table 2 Lesion characteristics at baseline and follow-up for the STEMI and CTO groups.**

	STEMI (n = 26)			CTO (n = 11)			P value of STEMI vs. CTO	
	Baseline	Follow-up	P value	Baseline	Follow-up	P value	Baseline	Follow-up
<b>Gray-scale IVUS</b>								
Study lesion length (mm)	6.0±0.7	–	–	3.7±0.8	–	–	0.281	–
Distance from coronary ostium (mm)	24.5±4.0	–	–	16.8±6.0	–	–	0.291	–
Mean EEM CSA (mm <sup>2</sup> )	20.7±1.1	20.7±1.2	0.845	18.1±1.3	18.1±1.3	0.999	0.172	0.200
Minimal lumen CSA (mm <sup>2</sup> )	8.74±0.57	8.94±0.60	0.485	8.15±0.69	9.13±0.95	0.362	0.555	0.866
Mean lumen CSA (mm <sup>2</sup> )	10.25±0.60	10.62±0.78	0.356	8.87±0.72	9.96±0.90	0.291	0.193	0.623
Mean plaque CSA (mm <sup>2</sup> )	10.6±0.6	10.8±1.2	0.810	9.2±0.9	7.7±0.9	0.044	0.241	0.108
Plaque burden (%)	50.3±1.5	48.8±2.1	0.280	51.2±2.2	44.7±3.2	0.062	0.954	0.144
Plaque volume index (mm <sup>3</sup> /mm)	10.1±0.6	10.5±0.9	0.532	9.1±0.9	8.3±1.0	0.167	0.386	0.166
<b>VH-IVUS</b>								
FT (%)	56.4±2.2	59.0±2.7	0.477	55.5±3.4	61.2±3.6	0.228	0.821	0.652
FF (%)	9.8±1.9	17.3±2.9	0.030	17.1±4.4	19.4±3.6	0.676	0.084	0.685
DC (%)	12.7±1.8	8.1±1.7	0.026	9.5±2.7	7.0±2.4	0.180	0.329	0.717
NC (%)	21.1±1.8	15.4±2.2	0.052	18.2±2.9	12.3±3.1	0.089	0.391	0.443
FT volume index (mm <sup>3</sup> /mm)	3.6±0.4	3.8±0.5	0.616	2.9±0.4	2.6±0.6	0.493	0.325	0.153
FF volume index (mm <sup>3</sup> /mm)	0.65±0.12	1.1±0.2	0.026	1.0±0.4	0.82±0.22	0.596	0.240	0.361
DC volume index (mm <sup>3</sup> /mm)	0.81±0.14	0.43±0.08	0.007	0.47±0.14	0.27±0.09	0.077	0.243	0.305
NC volume index (mm <sup>3</sup> /mm)	1.5±0.2	0.93±0.16	0.023	1.0±0.2	0.64±0.16	0.104	0.164	0.257
NC at maximal NC site (%)	29.0±2.1	22.2±2.7	0.047	25.0±3.6	18.8±3.5	0.080	0.321	0.483
Mean NC CSA (mm <sup>2</sup> )	1.46±0.20	0.94±0.15	0.018	0.98±0.21	0.60±0.14	0.073	0.104	0.103

Values presented as mean ± SE.

CSA, cross-sectional area; CTO, chronic total occlusion; DC, dense calcium; EEM, external elastic membrane; FF, fibrofatty tissue; FT, fibrotic tissue; IVUS, intravascular ultrasound; NC, necrotic core; STEMI, ST-segment elevation myocardial infarction; VH-IVUS, virtual histology intravascular ultrasound.

**Fig. 1**



Changes in nonculprit lesion plaque type during follow-up in STEMI and CTO patients. CTO, chronic total occlusion; FC, fibrocalcific plaque; PIT, pathological intimal thickening; STEMI, ST-segment elevation myocardial infarction; ThCFA, thick-cap fibroatheroma; TCFA, thin-cap fibroatheroma.

plaque size and composition were consistent. Representative images of the two groups are shown in Fig. 2.

In terms of plaque classification, among the 20 baseline TCFA lesions in the STEMI group, three regressed to ThCFAs, six to PITs, and one to a fibrotic plaque, whereas the other 10 TCFA lesions remained consistent during

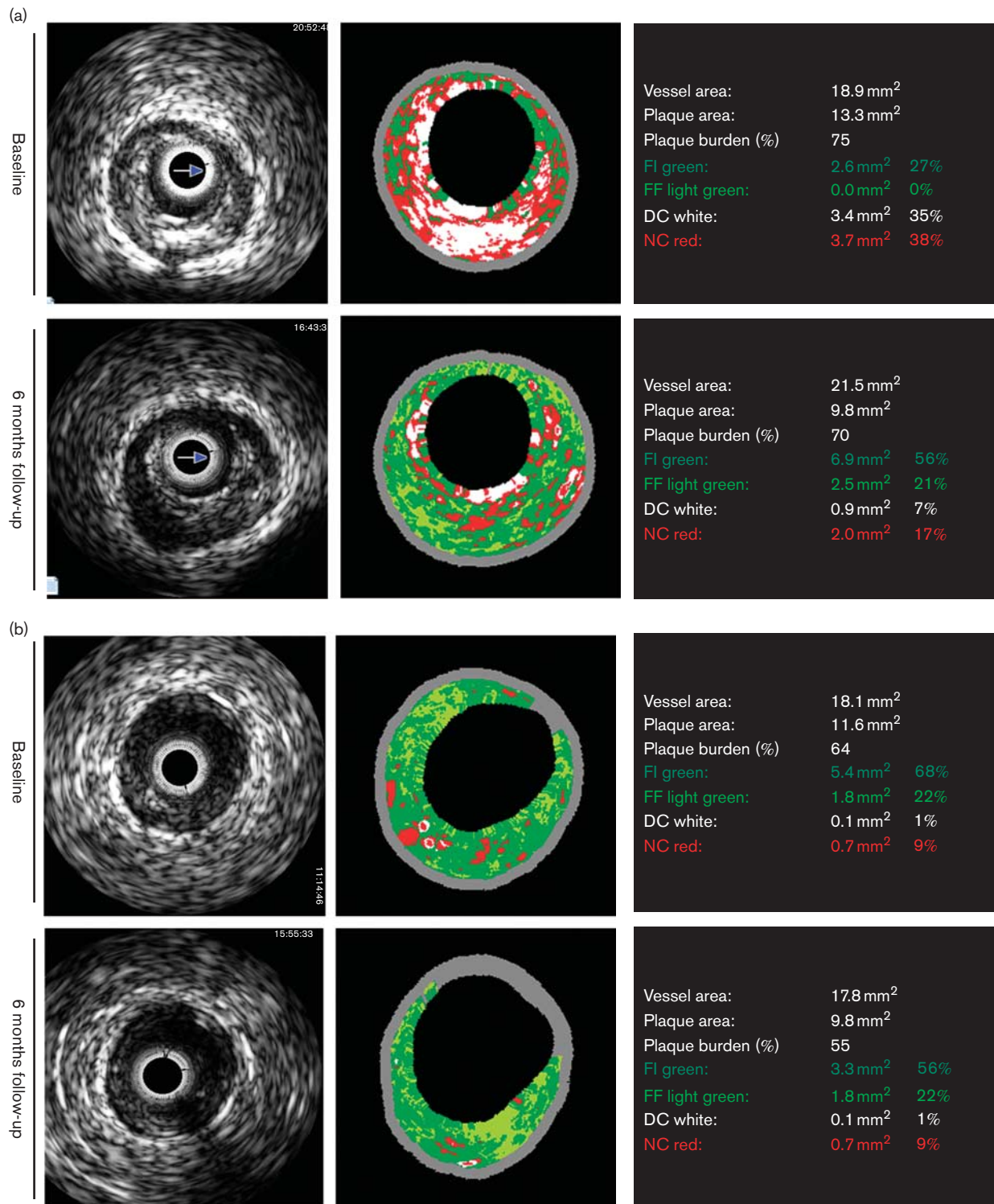
the 6-month follow-up period. Two TCFA lesions newly developed from a ThCFA and a PIT, respectively (Table 3). Among the six non-TCFA lesions, four (67%) lesions progressed to more advanced plaques (one ThCFA to TCFA, one PIT to TCFA, one PIT to ThCFA, and one FC plaque to PIT).

In the CTO group, every TCFA lesion regressed into PIT lesions, whereas there were no newly developed TCFA lesions during the follow-up period. Only one of nine non-TCFA lesions (11%) progressed (one PIT to ThCFA). The difference in the proportion of progressed lesions between the STEMI and CTO groups was marginally significant (67 vs. 11%,  $P=0.089$ ).

**Factors related to the evolution of the lesion to a TCFA**

Using the GEE model for repeated measures, we estimated factors associated with evolution to TCFA. After univariate analysis, clinical variables such as the diagnosis (STEMI vs. CTO), older age (>65 years old), new statin users, and lesion variables such as the plaque burden (>50%), lesion location (distance from the coronary ostium), and NC volume index were added to the multivariate analysis model. As a result, the diagnosis of STEMI [odds ratio (OR) 134.96, 95% confidence interval (CI) 6.57–2776.65,  $P=0.001$ ] and baseline NC volume index (OR 27.06, 95% CI 5.16–141.88 per 1 mm<sup>3</sup>/mm,  $P<0.001$ ) were significant predictors of persistent or new development of TCFA at follow-up, whereas statin new usage (OR 0.14, 95% CI 0.027–0.74,  $P=0.021$ ) exerted a protective effect on evolution to a TCFA. Other factors had no predictive value in TCFA evolution (Table 4).

Fig. 2



Representative figures of the natural course of lesions in the STEMI and CTO groups. In the STEMI group (a), the plaque size was consistent with a dynamic change in plaque composition (increase in fibrotic tissue and fibrofatty tissue, decrease in dense calcium and necrotic core), whereas in the CTO group (b), the plaque size and composition remained consistent. CTO, chronic total occlusion; DC, dense calcium; FF, fibrofatty tissue; NC, necrotic core; STEMI, ST-segment elevation myocardial infarction.

**Table 3** Changes in lesion plaque type during follow-up

	Baseline [n (%)]	Follow-up			
		TCFA	ThCFA	PIT	Fibrotic
<b>STEMI group</b>					
TCFA	20 (76.9)	10	3	6	1
ThCFA	2 (7.7)	1	1	0	0
PIT	3 (11.5)	1	1	1	0
FC	1 (3.8)	0	0	1	0
Total	26	12 (46.2)	5 (19.2)	8 (30.8)	1 (3.8)
<b>CTO group</b>					
TCFA	2 (18.2)	0	0	2	0
ThCFA	6 (54.5)	0	5	1	0
PIT	3 (27.3)	0	1	2	0
FC	0 (0.0)	0	0	0	0
Total	11	0 (0.0)	6 (54.5)	5 (45.5)	0 (0.0)

CTO, chronic total occlusion; FC, fibrocalcific; PIT, pathological intimal thickening; STEMI, ST-segment elevation myocardial infarction; TCFA, thin-cap fibroatheroma; ThCFA, thick-cap fibroatheroma.

**Table 4** Predictors of TCFA evolution

Factors	Odds ratio	95% confidence interval	P value
<b>Clinical factors</b>			
Diagnosis of STEMI	134.96	6.57–2776.65	0.001
Old age (≥65 years old)	6.25	0.83–47.18	0.075
Statin new users	0.14	0.027–0.74	0.021
<b>Lesion factors</b>			
Distance from coronary ostium (>20 mm)	1.53	0.25–9.28	0.641
Plaque burden (>50%)	1.68	0.27–10.30	0.573
Necrotic core volume index (1 mm <sup>3</sup> /mm)	27.06	5.16–141.88	<0.001

STEMI, ST-segment elevation myocardial infarction; TCFA, thin-cap fibroatheroma.

**Plaque with clinical events**

At the 6-month follow-up, one patient in the STEMI group underwent revascularization for the nonculprit lesion 177 days after the initial PCI. The lesion was at the proximal right coronary artery and the plaque was a TCFA both at baseline and at follow-up. The plaque burden increased from 55 to 59% and the mean plaque CSA increased from 15 to 18 mm<sup>2</sup> in this patient. In terms of plaque composition, FT and FF tissue increased (FT: 54–58%; FF: 6–16%) and DC and NC decreased (DC: 11–6%; NC: 29–20%).

**Discussion**

In the present study, we showed the difference in the short-term natural history of nonculprit plaques. Unlike previous studies, we carried out a comparative analysis of serial baseline and follow-up IVUS images from two distinct patient groups: STEMI patients versus CTO patients. The results of our study can be summarized as follows. (a) In STEMI patients, more than three-quarters of nonculprit coronary lesions were TCFA at baseline, whereas most of the plaques in CTO patients were stable. (b) In terms of plaque composition and size, STEMI lesions and CTO lesions showed different evolution patterns. The plaque composition was stabilized in

the STEMI lesions, without a significant change in the plaque size, whereas both the plaque size and composition were consistent in the CTO lesions. (c) During the 6-month follow-up, the change in the plaque type was more dynamic in STEMI patients. (d) From the total population, the factors associated with TCFA evolution were a diagnosis of STEMI and a large NC volume index, whereas statin new usage was a protective factor. Collectively, our study showed a hypothesis-generating result on the different course of nonculprit lesions between STEMI and CTO.

**Difference in nonculprit plaques between the STEMI and CTO groups**

Recently, VH-IVUS studies of coronary atherosclerotic plaques showed the histopathologic features of lesions in a diverse spectrum of coronary artery diseases [16]. In these studies, it was generally accepted that TCFA with abundant NC was inclined to be ruptured, a so-called vulnerable plaque. Hong *et al.* [17] and Cascon-Perez *et al.* [18] reported that TCFA was more frequent in patients with acute coronary syndrome (ACS) than in those with stable angina, and the culprit lesions of ACS had greater amounts of NC and smaller amounts of FF compared with the target lesion of stable angina. Nakamura *et al.* [19] analyzed the nonculprit lesion between stable and unstable angina patients, where unstable angina patients presented with a higher prevalence of VH-TCFA than stable angina patients. Meanwhile, Guo *et al.* [20] reported that the NC in plaques of CTO lesions were not different from those of nonocclusive stenotic lesions. In our study, we found that TCFA were more frequently observed in nonculprit lesions of STEMI patients than in those of CTO patients.

**The pathophysiology of STEMI and CTO lesions**

The coronary artery plaques of STEMI and CTO lesions differ in their pathophysiology. The difference in the plaque characteristics results from the distinct inflammatory activity of the atherosclerotic disease process. Bogaty *et al.* [21] reported that inflammatory activity was systemic, and widespread in the arterial wall in both nonculprit and culprit coronary arteries in ACS patients compared with long-standing stable angina patients. This inflammation is triggered by tissue injury; it mediates wound healing and scar formation [22]. In terms of calcification, the subintimal lipid deposition, atherogenic, and inflammatory cytokines induce the osteogenic changes in the arterial wall, which leads to the development of calcification, which in turn leads to plaque vulnerability as well as atheroma progression [23]. From our study, we found that calcification was more abundant at baseline in the STEMI group.

However, most coronary artery plaques in CTOs have undergone extended periods of inflammation, comprising intracellular and extracellular lipids, smooth muscle cells, an extracellular matrix, and calcium. As the

antegrade blood flow is blocked for an extended period of time, the vessel undergoes negative remodeling, decreasing the dimension of the EEM [24]. The distinct inflammatory process of an atherosclerotic lesion is a systemic response and could be related to the different plaque characteristics and natural course in STEMI and CTO lesions, both culprit and nonculprit.

### The natural course of plaques in STEMI and CTO

The natural course of coronary atherosclerotic plaques has been reported in a few recent studies. From a population including ACS patients, Kubo *et al.* [25] showed that 75% of TCFAs healed during a 12-month follow-up and that new TCFAs also developed in non-culprit coronary artery plaques. Zhao *et al.* [14] reported the dynamic nature of nonculprit lesions in STEMI patients, who frequently have TCFA morphology that does not change during the 13-month follow-up and is accompanied by a decrease in MLA and an increase in NC. In the current study, interestingly, the plaque composition changed to a more stable phenotype with no size reduction in the STEMI group. In the CTO group, the phenotype and the plaque size were consistent. Also, in terms of plaque classification, more lesions progressed to TCFA lesions or remained as TCFA lesions in the STEMI group.

The degree of change in plaque composition in this study showed discrepancies compared with other previous studies. Zhao *et al.* [14] reported that NC and DC increased, whereas FF and FT decreased in STEMI patients, and Kashiyama *et al.* [26] showed that lipid volume of coronary plaque increased despite statin treatment in moderate to advanced renal disease. Also, Raber *et al.* [27] reported that DC increased and FT decreased with the use of high-intensity statin in acute myocardial infarction patients. In contrast, Hong *et al.* [17] reported that NC decreased and FF increased during a 1-year statin treatment in patients with coronary artery disease and Taguchi *et al.* [28] reported that the FF increased, NC decreased, and DC remained unchanged in coronary artery disease patients without plaque regression.

This discrepancy may be partially explained as follows: first, our study population comprised only Asians compared with Caucasians in the studies of Raber *et al.* [27] and Zhao *et al.* [14]. The BMI of our population was lower than those of Raber and colleagues ( $27.5 \pm 3.8 \text{ kg/m}^2$ ) and Zhao and colleagues ( $27.0 \pm 2.4 \text{ kg/m}^2$ ). A relationship between high BMI and plaque progression has been reported [29,30]. Second, 90% of patients in the STEMI group were new statin users. This high rate of statin-naïve patients could have influenced our result as well. Third, the high smoking cessation rate could have affected the change in plaque composition because smoking was associated independently with a larger NC and calcium in the coronary plaque [31,32]. Taken together, the difference in ethnicity, low BMI, initiation of statin therapy,

and high rate of smoking cessation could have influenced the change in plaque composition in our study.

### Plaque stabilization and related factors

TCFAs are the likely precursors of the majority of fatal coronary plaque ruptures [33]. Therefore, predictors of plaque evolution to a TCFA may be important with respect to clinical significance. We used the GEE model to analyze the dependent outcomes of repeated measures for each lesion. Among clinical factors, the diagnosis of STEMI was a factor with a high risk of evolution to TCFA, whereas statin new usage exerted a protective effect on TCFA evolution. As discussed above, the systemic inflammatory activity in STEMI patients could have influenced the plaque characteristics in nonculprit lesions. Also, 92% of STEMI patients were new statin users and had a larger decrease in the follow-up LDL-cholesterol level. Statin therapy has been known to cause plaque stabilization in previous studies [34], which was consistent with our results. Among lesion factors, a large NC volume was a predictor of TCFA evolution. Previous reports also showed that TCFAs with a large NC are vulnerable plaques that may lead to major adverse cardiovascular events [33,35] and culprit lesions of fatal myocardial infarction had a large NC with extensive inflammatory cell infiltrate [36]. Moreover, TCFAs associated with a large NC and a thin cap with inflammation are known to be vulnerable to rupture, the so-called rupture-prone, high-risk TCFAs [33,37].

### Study limitations

Several limitations of this study should be noted. First, the small sample size could have yielded a large false-negative rate (so-called  $\beta$  error) and could have affected the reliability of our GEE model. Also, because of the small sample size, the results from our study are not conclusive, but are rather hypothesis generating. Second, we only evaluated proximal nonculprit lesions of the culprit artery, not all major coronary arteries (including the nonculprit arteries), which might be less influenced by the angioplasty procedure. Therefore, conclusions on the additional arteries cannot be made. Third, some aspects of our study are prone to selection bias. The retrospective study design using medical records and the VH-IVUS procedure itself (high cost and invasive nature) could have acted as a selection bias. Fourth, the follow-up period was short; thus, clinical events could not be detected effectively. Whether the characteristics of nonculprit lesions affect the occurrence of clinical events and have clinical significance is an important subject that could not be evaluated. Because of the above-mentioned reasons, we define our study as a hypothesis-generating research, which should be confirmed in further studies.

### Conclusion

Nonculprit coronary artery atherosclerotic plaques in STEMI patients and CTO patients had distinct

characteristics. At baseline, the plaques of STEMI patients were more vulnerable. During the follow-up period, the STEMI group stabilized in plaque composition, whereas the CTO group showed decreased plaque size. The diagnosis of STEMI and large NC volume index were predictors of an evolution to a TCFA lesion, whereas statin new usage exerted a protective effect on TCFA evolution.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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