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Prevalence and Characteristics of TCFA and Degree of Coronary Artery Stenosis

An OCT, IVUS, and Angiographic Study

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ABSTRACT

BACKGROUND The relationship between features of vulnerable plaque and angiographic coronary stenosis is unknown.

OBJECTIVES The purpose of this study was to systematically investigate the absolute number, relative prevalence, and characteristics of thin-cap fibroatheroma (TCFA) at different degrees of stenosis using optical coherence tomography (OCT), intravascular ultrasound, and coronary angiography.

METHODS We identified 643 plaques from 255 subjects who underwent OCT imaging in all 3 coronary arteries. They were divided into 3 groups on the basis of angiographic diameter stenosis: Group A (30% to 49%, n = 325), Group B (50% to 69%, n = 227), and Group C (>70%, n = 91).

RESULTS OCT showed that the absolute number of TCFA was greatest in Group A (n = 58), followed by Groups B (n = 40) and C (n = 33). However, the relative prevalence of TCFA was higher in Group C (36%) than in Groups A (18%) or B (18%) ($p = 0.003$ and $p = 0.002$, respectively). Fibrous cap of TCFA was thinner in Group C than in Groups A ($p < 0.001$) or B ($p = 0.001$). intravascular ultrasound showed that the plaque burden of TCFA was largest in Group C (80.1 ± 7.4%), compared with Groups B (67.5 ± 9.4%) and A (58.1 ± 8.4%). TCFA in Group C had a higher remodeling index than those in Group A ($p = 0.002$).

CONCLUSIONS The absolute number of TCFA is 3 times greater in nonsevere stenosis than in severe stenosis. It is, however, twice as likely for a lesion to be TCFA in cases of severe stenosis than in nonsevere stenosis. Moreover, TCFA in severely-stenotic areas had more features of plaque vulnerability. (J Am Coll Cardiol 2014;64:672–80) © 2014 by the American College of Cardiology Foundation.

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Thin-cap fibroatheroma (TCFA) is recognized as a precursor for plaque rupture, which is responsible for the majority of cases of acute coronary syndromes (ACS) and sudden cardiac death. Pathologically, TCFA is characterized as a large lipid pool with overlying thin fibrous cap (<65 μm) (1). Clinical investigations have shown that TCFA is a significant predictor for rapid progression of angiographic stenosis (2) and a strong predictor for future clinical adverse events (3,4). Coronary angiogram is routinely used to make a diagnosis of coronary artery disease and to determine the extent of luminal compromise. It had been widely believed that vulnerable plaque is most often present in areas of mild luminal stenosis (5). However, the absolute number and relative prevalence of TCFA in relation to angiographic stenosis severity has not been reported.

SEE PAGE 681

Intracoronary optical coherence tomography (OCT) is a novel intracoronary diagnostic technique that offers a resolution of approximately 10 to 20 μm. It has the capability to measure the fibrous cap thickness and to detect lipid content, and can therefore be used to identify in vivo TCFA and to determine the plaque vulnerability (6). In the clinical setting, intravascular ultrasound (IVUS) is another imaging modality that has been used to measure lumen area, plaque burden, and vascular remodeling (3,7). IVUS-derived parameters, including plaque burden and positive remodeling, are important for identification of high-risk TCFA during follow-up (3,4). However, the relationship between OCT- and IVUS-derived characteristics of TCFA, as well as the angiographic stenosis severity, has not been reported.

In this study, we aimed to systematically investigate the relationship between the absolute number and relative prevalence and characteristics of TCFA, as well as the angiographic stenosis severity, using OCT, IVUS, and coronary angiography. In particular, we were interested in testing the hypothesis that vulnerable plaque characteristics were most frequently associated with mild coronary artery lesions as opposed to severe lesions.

METHODS

STUDY POPULATION. We identified patients who underwent 3-vessel OCT examinations from the Massachusetts General Hospital (MGH) OCT registry and the 2nd Affiliated Hospital of Harbin Medical University. All nonculprit or nontarget lesions with >30% diameter stenosis on coronary angiograms were chosen. Three-vessel OCT examinations were performed in all 255 patients, whereas IVUS was only performed in 143 patients. The institutional review board in each participating site of the MGH registry and the ethics committee of the 2nd Affiliated Hospital of Harbin Medical University approved the study, and all subjects provided informed consent. Images were digitally stored and submitted for offline evaluation at the core laboratory.

ANGIOGRAM AND ANALYSIS. Patients were pre-treated with aspirin (≥300 mg) and clopidogrel (300 mg) at least 2 h prior to the index procedure. Coronary angiography was performed via the radial or femoral approach using 6- to 7-F guiding catheters after intracoronary administration of 100 to 200 μg of nitroglycerin. Angiographic images were analyzed using a quantitative coronary angiogram analysis program (CAAS version 5.10.1, Pie Medical Imaging BV, Maastricht, the Netherlands) by 2 investigators who were blinded to the OCT and IVUS measurements. Minimal luminal diameter was defined as the smallest lumen diameter in the segment of a lesion; reference vessel diameter was calculated as the averaged diameter of the proximal and distal coronary segments without obvious narrowing; diameter stenosis was calculated as: (reference vessel diameter − minimum lumen diameter)/(reference vessel diameter) × 100.

IVUS AND OCT EXAMINATIONS. After treatment of the culprit/target lesion, IVUS and OCT imaging were performed in all 3 coronary arteries. IVUS examinations were performed using the Atlantis Pro catheter (40 MHz, Boston Scientific, Natick, Massachusetts) after intracoronary administration of 100 to 200 μg nitroglycerin. The transducer was pulled back automatically at 0.5 mm/s. After the IVUS examination, OCT examinations were performed as previously described (8,9). Either the time-domain (M2/M3 Cardiology Imaging System, LightLab Imaging, Inc., Westford, Massachusetts) or the frequency-domain OCT system (C7-XR OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) were used in the study. In brief, with the M2/M3 system, an occlusion balloon (Helios, LightLab Imaging Inc., Westford, Massachusetts) was advanced proximal to the lesion and inflated ≤0.7 atm, and saline was infused into the coronary artery from the distal tip of the occlusion balloon catheter during image acquisition. The M2/M3 OCT wire was automatically pulled back from distal to proximal at 1.0 to 3.0 mm/s. With the C7-XR system, a 2.7-F OCT imaging catheter (Dragonfly, St. Jude Medical) was advanced distal to

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes

CSA = cross-sectional area

EEM = external elastic membrane

IVUS = intravascular ultrasound

OCT = optical coherence tomography

TCFA = thin-cap fibroatheroma

the lesion, and automatic pullback was started as soon as the blood was cleared.

OCT ANALYSIS. The 2 experienced investigators at the MGH OCT core laboratory analyzed the OCT images using proprietary software (St. Jude Medical). In case of discordance between the reviewers, a third reader was involved to reach a consensus on image matching and quality. To be considered as 2 separate plaques in the same vessel, the segment between them had to be >5 mm. If not, they were considered 1 long lesion. Fibrous cap thickness was measured at its thinnest part 3 times, the average value was calculated, and the minimum values of fibrous cap thickness in each plaque were selected. Lipid arc was measured at every 1-mm interval throughout the entire lesion. A TCFA was defined as a plaque with fibrous cap thickness <65 μm overlying a lipid-rich plaque (maximum lipid arc >90°) (2,8,9).

All TCFA lesions were further evaluated. Lipid length was measured on the longitudinal view. A microvessel was characterized by a black hole within a plaque with a diameter of 50 to 300 μm that was seen on at least 3 consecutive frames (2,8-10). Macrophage accumulation on the lesion was characterized by increased signal intensity within the lesion, accompanied by heterogeneous backward shadows (2). Presence of cholesterol crystals was characterized by the presence of linear and highly-reflecting structures within lesions. Calcification is an area with low backscatter signal and a sharp border (2,8,9).

IVUS ANALYSIS. The corresponding IVUS images of OCT-derived TCFA were selected using fiduciary points, such as calcifications, side branches, and/or stents. Two independent reviewers at the MGH core laboratory using EchoPlaque (Indec Systems, Mountain View, California) analyzed the IVUS images. Quantitative IVUS parameters included the external elastic membrane (EEM), the lumen cross-sectional area (CSA), the maximum atheroma diameter and the minimum atheroma diameter, and the plaque plus media (P+M) CSA. The plaque eccentricity index was calculated as: (maximum atheroma diameter − minimum atheroma diameter)/maximum atheroma diameter. The plaque burden was calculated as: (P+M CSA)/(EEM CSA) ×100. The reference was the frame showing the largest lumen area within 10 mm proximal and distal from the target lesions. The remodeling index was calculated as: (EEM CSA at the MLA slice)/(average of the proximal and distal reference EEM CSA).

DEFINITION OF RISK FACTORS. Diabetes mellitus was diagnosed if a patient met 1 of the following criteria: documented history of diabetes mellitus, use of hypoglycemic agents, fasting glucose ≥126 mg/dl, 2-h plasma glucose level ≥200 mg/dl in the oral glucose tolerance test, classic symptom with casual plasma glucose level ≥200 mg/dl, or glycated hemoglobin ≥6.5%. Hypertension was defined as a systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or antihypertensive therapy received at the time of the imaging. Hyperlipidemia was diagnosed in those with a history of hyperlipidemia, receiving lipid-lowering treatment, or newly diagnosed with hyperlipidemia (total serum cholesterol >240 mg/dl).

STATISTICAL ANALYSIS. Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, Illinois). Categorical data were presented as counts and proportions. Continuous variables were expressed as mean ± SD for normally distributed variables and as medians (25th to 75th percentiles) for non-normally distributed variables, as appropriate. On the basis of the angiographic diameter stenosis, all lesions were divided into 3 groups: Group A (30% to 49%), Group B (50% to 69%), and Group C (>70%). Angiographic, OCT, and IVUS findings of TCFA in each group were compared. Comparisons of patient and morphological characteristics among the 3 groups were carried out by means of the generalized estimating equations approach to take into account

TABLE 1 Patient Characteristics (n = 255)

Age, yrs	59.9 ± 10.8
Male	190 (75)
Smoking	86 (34)
Diabetes mellitus	105 (41)
Hypertension	169 (66)
Hyperlipidemia	171 (67)
Prior MI	67 (26)
PAD	9 (4)
Prior PCI	62 (24)
Indication for angiography	
STEMI	31 (12)
NSTE-ACS	120 (47)
Stable angina	104 (41)
Laboratory findings	
TC, mg/dl	178 ± 50
HDL-C, mg/dl	46 ± 15
LDL-C, mg/dl	93 ± 33
TG, mg/dl	145 (89, 212)
HbA1C, %	6.3 ± 1.4
hs-CRP, mg/dl	0.20 (0.10, 0.50)

Values are mean ± SD, n (%), or median (25th, 75th percentiles).

HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TC = total cholesterol; TG = triglyceride.

the multiple plaques identified from the same patient. Logarithmic transformation was performed for the non-normally distributed variables. For the multiple comparisons among the 3 groups, Bonferroni's correction was applied, thus a $p < 0.017$ was considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS. A total of 255 patients were included in this study. The patients' clinical characteristics are summarized in Table 1. In these 255 subjects, 643 plaques with >30% angiographic diameter stenosis were detected. Of 643 lesions, 325 (51%) had 30% to 49% diameter stenosis (Group A), 227 (35%) had 50% to 69% diameter stenosis (Group B), and 91 (14%) had >70% diameter stenosis (Group C) (Fig. 1A).

ABSOLUTE AND RELATIVE NUMBER OF TCFA IN EACH GROUP. Among 643 lesions, the number of TCFA was 58 of 325 in Group A, 40 of 227 in Group B, and 33 of 91 in Group C (Fig. 1B). Therefore, the prevalence of TCFA was twice as high among severe lesions compared with mild or moderate lesions: 36% in Group C, 18% in Group A, and 18% in Group B ($p = 0.003$ and $p = 0.002$, respectively) (Fig. 1C). A representative case with TCFA and a severe stenosis is shown in Figure 2.

CLINICAL CHARACTERISTICS OF TCFA. The clinical characteristics of patients with TCFA in each group are presented in Table 2. Group C had a significantly higher glycated hemoglobin level compared with Group A ($p = 0.006$). There were no statistically significant differences in other variables among the 3 groups.

IMAGING FINDINGS OF TCFA. The angiography data of all TCFA in each group are presented in Table 3. No significant difference was seen in reference vessel diameter or in the distribution of plaques among the 3 groups.

The mean length of coronary arteries imaged by OCT was 76 ± 23 mm in the left anterior descending coronary artery, 49 ± 17 mm in the left circumflex artery, and 96 ± 26 mm in the right coronary artery.

OCT findings of all TCFA are shown in Table 4. Fibrous cap thickness of TCFA was thinner in Group C compared with Groups A ($p < 0.001$) or B ($p = 0.001$). There were no significant differences among the 3 groups in lipid arc and lipid length. As compared with Group A, microvessel and cholesterol crystal within TCFA were more frequent in Group C ($p < 0.001$ and $p = 0.002$, respectively). The prevalence of macrophage accumulation and calcification were not statistically different among the 3 groups.

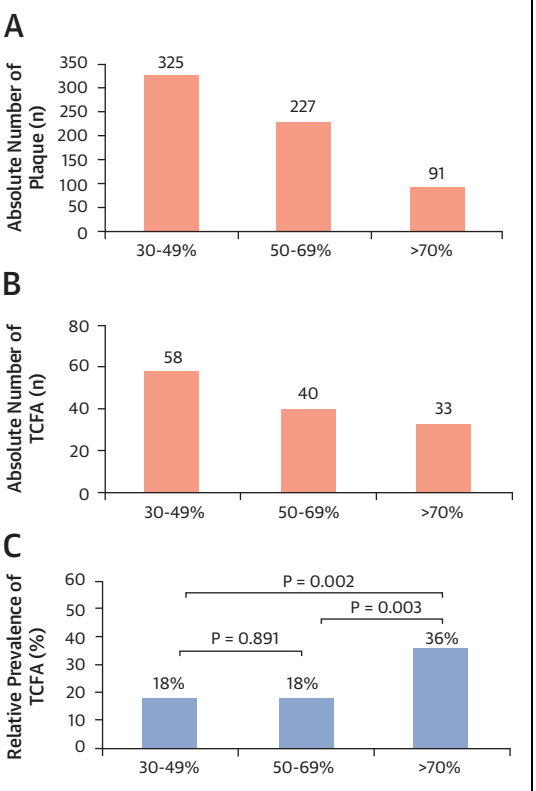

FIGURE 1 Correlation Between the Absolute Number and Relative Prevalence of TCFA and Degree of Stenosis

(A) Among the 643 lesions, 325 plaques had mild stenosis, 227 had moderate stenosis, and 91 had severe stenosis. **(B)** The absolute number of thin-cap fibroatheromas (TCFAs) was greater in plaques with mild to moderate stenosis compared with those with severe stenosis. **(C)** The relative prevalence of TCFA was significantly higher in Group C than in Groups A or B.

The mean length of coronary arteries imaged by IVUS was 83 ± 18 mm in the left anterior descending coronary artery, 71 ± 19 mm in the left circumflex artery, and 87 ± 26 mm in the right coronary artery.

IVUS findings are presented in Table 5. TCFA in Group C had smaller lumen CSA, larger P+M CSA, and higher remodeling index compared with those in Group A ($p < 0.001$, $p = 0.001$, and $p = 0.002$, respectively). The plaque burden was largest in the TCFA of Group C (80.1 ± 7.4%), followed by those in Groups B (67.5 ± 9.4%) and A (58.1 ± 8.4%). Plaque eccentricity of TCFA was greater in Group C than in Groups A ($p < 0.001$) or B ($p = 0.009$).

EEM CSA at the proximal and distal reference segments was similar among the 3 groups. Lumen

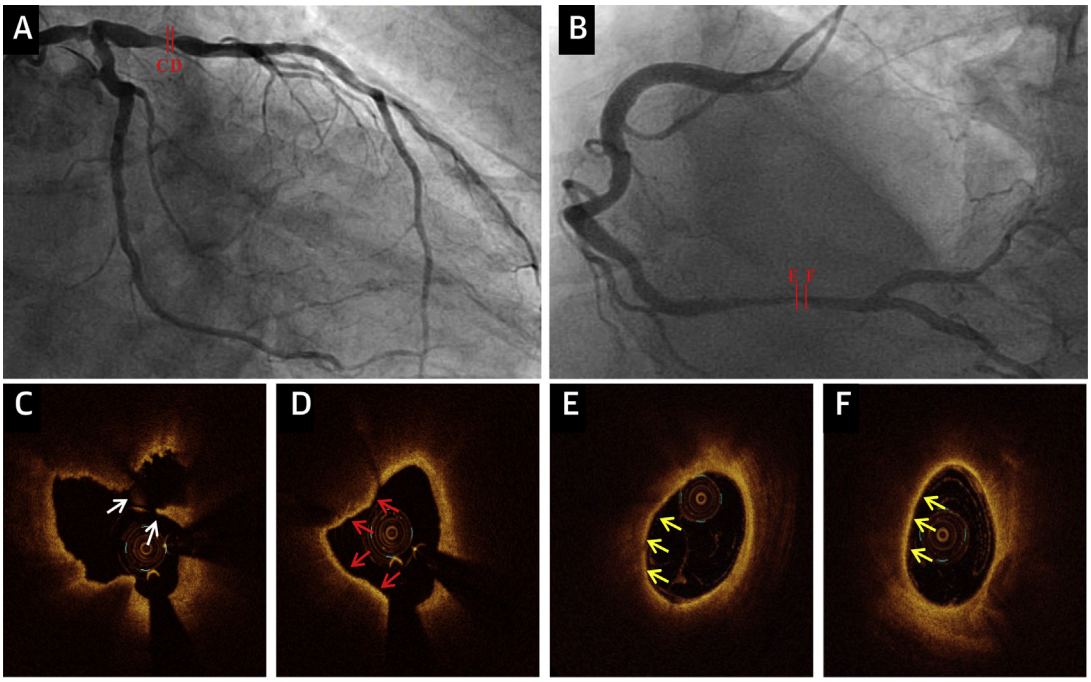

FIGURE 2 Representative Case of TCFA

This case demonstrates a ruptured thin-cap fibroatheroma (TCFA) at the tight stenosis in the left anterior descending artery (LAD) as well as nonruptured TCFA at a severe lesion in the distal right coronary artery (RCA) in the same patient. Angiogram **(A)** shows a culprit lesion in the proximal LAD. In the same patient, a severe nonculprit lesion was found in the distal RCA **(B)**. **Red lines on A and B** indicate the location where the optical coherence tomography (OCT) images were obtained. OCT images of the culprit lesion show plaque rupture **(white arrows) (C)** and TCFA **(red arrows) (D)**. In the nonculprit lesion with severe stenosis in the distal RCA, TCFA was identified **(yellow arrows) (E and F)**.

CSA at the distal reference site was significantly smaller in Group C than in Group A ($p < 0.001$).

DISCUSSION

To the best of our knowledge, this is the first in vivo study investigating the absolute number, relative prevalence, and characteristics of TCFA in relation to angiographic luminal narrowing using 3 imaging modalities. In this study, because the total number of plaques with mild to moderate stenosis is large, the absolute number of TCFA in this population was 3 times higher than in those with severe stenosis (**Central Illustration**). However, the prevalence of TCFA was twice as high in those plaques with severe angiographic stenosis >70% compared with those with mild or moderate stenosis. Moreover, TCFA in patients with severe lesions had greater plaque burden and more features of vulnerability, including microvessels, cholesterol crystal, thinner fibrous cap, and higher vessel remodeling index.

TCFA AT THE SITE OF SEVERE STENOSIS. TCFA is considered to be an in vivo equivalent of vulnerable plaque. The current study showed that prevalence of TCFA was higher in severely-stenotic lesions than in mild to moderate stenosis. A recent virtual histology IVUS study also reported that the frequency of TCFA increases with increasing angiographic diameter stenosis of the lesion (11). Moreover, TCFA in severely-stenotic areas had more features of plaque vulnerability.

The fibrous cap thickness is a major determinant in the vulnerability of atherosclerotic lesions to rupture (12). Although thin fibrous cap (<65 μm) defined by pathological study has been recognized as the most critical feature of TCFA, the fibrous cap thickness has been reported to be significantly different between ruptured plaque and nonruptured TCFA (12,13). A histology study from Narula et al. (12) has demonstrated that the best morphological characteristic to differentiate the ruptured plaque from TCFA was fibrous cap thickness <54 μm, suggesting that fibrous

TABLE 2 Clinical Characteristics of TCFA in the 3 Groups

	Group A (n = 58)	Group B (n = 40)	Group C (n = 33)	p Value A vs. B	p Value A vs. C	p Value B vs. C
Age, yrs	58.6 ± 11.2	60.1 ± 9.2	59.3 ± 12.1	0.423	0.770	0.763
Male	43 (74)	29 (73)	20 (61)	0.874	0.228	0.253
Smoking	21 (36)	12 (30)	15 (46)	0.548	0.393	0.182
Diabetes mellitus	25 (43)	19 (48)	18 (55)	0.699	0.305	0.550
Hypertension	30 (52)	25 (63)	23 (70)	0.349	0.109	0.548
Hyperlipidemia	36 (62)	26 (65)	20 (61)	0.790	0.895	0.679
Prior MI	14 (24)	9 (23)	5 (15)	0.871	0.319	0.445
PAD	1 (2)	1 (3)	4 (12)	0.101	0.022	0.062
Prior PCI	11 (19)	7 (18)	4 (12)	0.862	0.405	0.446
Indication for angiography						
STEMI	10 (17)	5 (13)	8 (24)	0.479	0.456	0.253
NSTE-ACS	34 (59)	25 (63)	22 (67)	0.716	0.467	0.713
Stable angina	14 (24)	10 (25)	3 (9)	0.928	0.071	0.049
Laboratory findings						
TC, mg/dl	191 ± 55	184 ± 43	194 ± 54	0.567	0.756	0.409
HDL-C, mg/dl	50 ± 18	50 ± 26	50 ± 15	0.959	0.929	0.995
LDL-C, mg/dl	101 ± 35	107 ± 32	97 ± 31	0.397	0.585	0.191
TG, mg/dl	158 (105, 206)	177 (121, 271)	195 (118, 252)	0.397	0.260	0.936
HbA1C, %	6.3 ± 1.1	6.6 ± 1.4	7.7 ± 2.5	0.406	0.006	0.038
hs-CRP, mg/dl	0.20 (0.10, 0.44)	0.12 (0.10, 0.59)	0.28 (0.10, 1.06)	0.442	0.340	0.759

Values are mean ± SD, n (%), or median (25th, 75th percentiles). $p < 0.017$ was considered significant.
TCFA = thin-cap fibroatheroma; other abbreviations as in Table 1.

cap overlying TCFA become thinner before rupture. Interestingly, the mean thickness of fibrous cap in TCFA with severe stenosis (49 ± 9.2 μm) was below this threshold in this study. Therefore, TCFA at severely-stenotic areas with thinner fibrous cap may make it more susceptible to rupture.

The current study also showed that severely-stenotic TCFA had a larger plaque burden and higher remodeling index. Histology studies have confirmed that plaque rupture, in combination with a severe pre-existing luminal narrowing, is a milieu that puts patients at a very high risk for occlusive thrombus formation and occurrence of the fatal acute myocardial infarction (12,14,15). Clinical studies using angiography (16), IVUS (17), and angioscopy (18) have confirmed that multiple plaque ruptures were common in patients with ACS. However, symptomatic rupture had a smaller lumen area, greater plaque burden, and more positive remodeling (17). Some prospective IVUS studies have confirmed that TCFA with >70% of plaque burden were more likely to develop recurrent clinical events during follow-up (3,4). It is conceivable that the thrombus formation following a ruptured TCFA with severe stenosis is more likely to further limit the blood flow leading to clinical events.

Additionally, we observed more frequent microvessels and cholesterol crystals in severely-stenotic TCFA in the present study. OCT has been widely used to visualize microstructures within plaques, including macrophage accumulation, microvessels, and cholesterol crystals (2,8-10,19). The intraplaque microvessel detected by OCT has been reported to be a feature of plaque vulnerability (8,10) and a predictive marker for plaque progression (2).

The role of coronary stenosis severity in the development of acute myocardial infarction is debated (20). On the basis of our findings, it is reasonable to speculate that patients with severely-stenotic lesions are at increased risk of cardiovascular adverse events

TABLE 3 Angiographic Findings of TCFA

	Group A (n = 58)	Group B (n = 40)	Group C (n = 33)	p Value A vs. B	p Value A vs. C	p Value B vs. C
MLD, mm	2.08 ± 0.47	1.44 ± 0.42	0.78 ± 0.22	<0.001	<0.001	<0.001
DS, %	40.0 ± 6.0	57.0 ± 6.0	76.0 ± 4.8	<0.001	<0.001	<0.001
RD, mm	3.45 ± 0.63	3.33 ± 0.71	3.23 ± 0.69	0.416	0.049	0.253
Lesion location						
LAD	15 (26)	17 (43)	15 (46)	0.077	0.040	0.825
RCA	34 (59)	11 (28)	14 (42)	0.002	0.137	0.196
LCX	9 (16)	12 (30)	4 (12)	0.095	0.654	0.079

Values are mean ± SD or n (%). $p < 0.017$ was considered significant.
DS = diameter stenosis; LAD = left anterior descending coronary artery; LCX = left circumflex artery; MLD = minimum lumen diameter; RCA = right coronary artery; RD = reference diameter; RVD = reference vessel diameter; TCFA = thin-cap fibroatheroma.

TABLE 4 OCT Findings of TCFA

	Group A (n = 58)	Group B (n = 40)	Group C (n = 33)	p Value A vs. B	p Value A vs. C	p Value B vs. C
FCT, μm	57.0 ± 6.6	56.0 ± 7.5	49.0 ± 9.2	0.762	<0.001	0.001
Lipid arc, °	214 ± 56	209 ± 55	204 ± 59	0.669	0.837	0.766
Lipid length, mm	9.4 ± 4.6	10.5 ± 5.5	9.6 ± 4.5	0.218	0.846	0.393
Microvessel	13 (22)	15 (38)	19 (58)	0.141	<0.001	0.082
Cholesterol crystal	8 (14)	10 (25)	13 (40)	0.048	0.002	0.429
Macrophage	44 (76)	29 (73)	28 (85)	0.749	0.215	0.234
Calcification	25 (43)	18 (45)	14 (42)	0.793	0.958	0.880

Values are mean ± SD or n (%). p < 0.017 was considered significant.
FCT = fibrous cap thickness; OCT = optical coherence tomography; TCFA = thin-cap fibroatheroma.

in the near future and are in need of more aggressive treatment. Supporting this notion, an angiographic study from Zaman et al. (21) had reported that high-grade coronary stenosis was an important predictor of acute coronary events in subsequent months. At the onset of acute myocardial infarction, most culprit lesions are found to have severe stenosis (22,23); this also suggests that severe lumen narrowing appears to be an important pre-condition for vulnerable plaques, resulting in acute coronary events. Frøbert et al. (22) have reported that >90% of patients with acute myocardial infarction presented with a stenosis severity >50%, and >60% presented with a stenosis severity >70%. Another study by Manoharan et al. (23) has demonstrated that only 10% of lesions in patients with acute myocardial infarction had diameter stenosis <50% after successful aspiration of thrombus.

TCFA AT THE SITE OF MILD TO MODERATE STENOSIS. Another important finding of the current study is that the absolute number of TCFA in nonseverely-stenotic lesions was 3 times higher than in severely-stenotic lesions due to a greater total number of plaques with mild to moderate stenosis. TCFA at mild to moderate stenosis may not cause clinical events during a short-term follow-up, but it may lead to an adverse event during long-term follow-up when the luminal narrowing reaches a critical level. In the current study, nonseverely-stenotic lesions had smaller plaque burden and larger lumen area compared with severely-stenotic lesions. A study by Cheng et al. (4) has demonstrated that TCFA with large plaque burden were related to higher short- and long-term clinical events, whereas TCFAs with small plaque burden were related to long-term clinical events (4). A greater number of TCFAs at nonseverely-stenotic sites may explain the findings, obtained from several previous studies with long intervals between baseline and follow-up, that acute coronary events commonly arise from nonseverely-stenotic lesions (24–26). It is important to note that most patients in the previous studies had an ST-segment elevation myocardial infarction (24–26), whereas the majority of our patients were undergoing angiography for non–ST-segment elevation ACS or stable angina.

STUDY LIMITATIONS. First, this study is retrospective and descriptive in nature, making selection bias unavoidable. Second, we selected the patients who underwent 3-vessel OCT imaging to minimize the potential bias; however, the decision to perform 3-vessel OCT was at the discretion of the operator. Third, the definition of OCT-derived TCFA is somewhat different from the histological definition of

TABLE 5 IVUS Findings of TCFA

	Group A (n = 36)	Group B (n = 25)	Group C (n = 14)	p Value A vs. B	p Value A vs. C	p Value B vs. C
Lesion site						
Lumen CSA, mm^2	5.8 ± 2.4	4.5 ± 2.1	3.2 ± 2.3	0.031	<0.001	0.055
P+M CSA, mm^2	7.7 ± 2.3	9.8 ± 4.3	11.8 ± 4.4	0.026	0.001	0.145
Remodeling index	0.98 ± 0.10	1.02 ± 0.13	1.09 ± 0.13	0.225	0.002	0.045
Plaque burden, %	58.1 ± 8.4	67.5 ± 9.4	80.1 ± 7.4	<0.001	<0.001	<0.001
Plaque eccentricity	0.77 ± 0.11	0.79 ± 0.14	0.88 ± 0.07	0.435	<0.001	0.009
EEM CSA, mm^2	13.5 ± 4.3	14.4 ± 5.3	14.9 ± 6.3	0.489	0.390	0.736
Proximal reference site, mm^2						
EEM CSA	14.3 ± 4.3	14.7 ± 5.7	14.2 ± 6.3	0.709	0.925	0.752
Lumen CSA	8.4 ± 2.8	8.4 ± 4.1	6.8 ± 3.6	0.976	0.551	0.169
Distal reference site, mm^2						
EEM CSA	13.2 ± 4.5	13.7 ± 5.5	13.3 ± 5.2	0.652	0.954	0.793
Lumen CSA	8.4 ± 3.2	7.3 ± 2.8	6.1 ± 3.1	0.187	<0.001	0.170

Values are mean ± SD. p < 0.017 was considered significant.
CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; P+M = plaque plus media; TCFA = thin-cap fibroatheroma.

TCFA due to the inability of OCT to determine the size of the necrotic core. Fourth, although OCT imaging was performed in 3 vessels, the very proximal segment was not visualized because of the proximal occlusion balloon when the time-domain OCT system was used. Fifth, both frequency- and time-domain OCT systems were used in the present study, although the percentages of imaged plaques by each modality were similar between the 3 groups. Sixth, the number of TCFAs in the Group C was relatively small. Seventh, a lack of longitudinal follow-up did not allow assessment of the clinical significance of TCFA. In addition, macrophage, microvessels, and cholesterol crystals on OCT have not been vigorously validated. Finally, IVUS was used only in a subset of patients.

CONCLUSIONS

The absolute number of TCFA is 3 times greater in nonsevere stenosis than in severe stenosis. It is, however, twice as likely for a lesion to be a TCFA in a severe stenosis as in a nonsevere stenosis. Furthermore, severely-stenotic TCFA has more features of plaque vulnerability and greater plaque burden. These findings suggest that severely-stenotic TCFA lesions may lead to clinical events in the near future, whereas a greater number of mild to moderate lesions may lead to adverse events during long-term follow-up.

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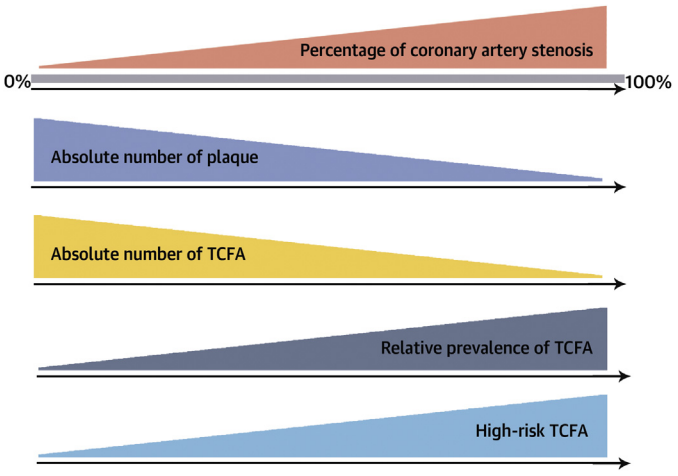

CENTRAL ILLUSTRATION **Plaque Vulnerability and Coronary Artery Stenosis**

The absolute number of plaque and thin-cap fibroatheroma (TCFA) is greater in the area with mild stenosis. The relative prevalence of TCFA increases as the degree of coronary artery stenosis increases. Furthermore, TCFA at a higher degree of stenosis has more features of plaque vulnerability.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Severely-stenotic coronary atherosclerotic lesions are associated with a higher risk of plaque rupture than less-stenotic lesions.

TRANSLATIONAL OUTLOOK: Additional research is needed to define optimal therapeutic strategies for patients with severely-stenotic high-risk atherosclerotic lesions.

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