Serial 3-Vessel Optical Coherence Tomography and Intravascular Ultrasound Analysis of Changing Morphologies Associated With Lesion Progression in Patients With Stable Angina Pectoris

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***Background*—**Optical coherence tomographic (OCT) morphologies associated with lesion progression are not well studied. The aim of this study was to determine the morphological change for untreated lesion progression using both OCT and intravascular ultrasound (IVUS).

***Methods and Results*—**We used baseline and 8-month follow-up 3-vessel OCT and IVUS to assess 127 nonculprit lesions (IVUS plaque burden ≥40%) in 45 patients with stable angina after target lesion treatment. Lesion progression was defined as an IVUS lumen area decrease >0.5 mm^2. A layered pattern was identified as a superficial layer that had a different optical intensity and a clear demarcation from underlying plaque. Lesion progression was observed in 19% (24/127) lesions, and its pattern was characterized into 3 types: type I, new superficial layered pattern at follow-up that was not present at baseline (n=9); type II, a layered pattern at baseline whose layer thickness increased at follow-up (n=7); or type III, no layered pattern at baseline or follow-up (n=8). The increase of IVUS plaque+media area was largest in type I and least in type III (1.9 mm^2 [1.6–2.1], 1.1 mm^2 [0.9–1.4], and 0.3 mm^2 [−0.2 to 0.8], respectively; *P*=0.002). Type III, but not types I or II, showed negative remodeling during follow-up (IVUS vessel area; from 14.3 mm^2 [11.4–17.2] to 13.5 mm^2 [10.4–16.7]; *P*=0.02). OCT lipidic plaque was associated with lesion progression (odds ratio, 13.6; 95% confidence interval, 3.7–50.6; *P*<0.001).

***Conclusions*—**Lesion progression was categorized to distinct OCT morphologies that were related to changes in plaque mass or vessel remodeling. **(*Circ Cardiovasc Imaging*. 2017;10:e006347. DOI: 10.1161/CIRCIMAGING.117.006347.)**

Key Words: angina, stable ■ follow-up studies ■ tomography, optical coherence ■ ultrasonography, interventional

Coronary artery lesion progression is associated with an increased risk of clinical events.[1] The process of lesion progression is not always linear[2]; and pathologically, silent plaque rupture or erosion with healing in layers has been reported to increase plaque burden leading to lesion-associated events.[3,4]

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See Clinical Perspective

Previous clinical studies investigating lesion progression have used intravascular ultrasound (IVUS) because it can provide insights into plaque burden and vessel remodeling. Intensive statin therapy has been associated with slowing plaque burden progression[5] with a positive correlation to low-density lipoprotein cholesterol (LDL-C).[6] On the contrary, serial IVUS studies have also shown lumen narrowing to be related to negative vessel remodeling, not plaque burden increase.[7–9] Optical coherence tomography (OCT) has a resolution of ≈10 μm, 10× greater than IVUS but at the expense of decreased penetration and limited ability to assess plaque burden and vessel remodeling.[10] Detailed visualization using OCT can identify morphologies, such as a thin-cap fibroatheroma (TCFA), and OCT-assessed lipidic plaque has been reported as one of the predictors of progressive lumen narrowing.[11]

We hypothesized that the combination of serial (baseline and follow-up) OCT and IVUS might provide a more

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complete pathophysiological assessment of lesion progression and vessel remodeling.

Methods

Study Design

This was a prospective, single-center, observational study to determine the morphological changes associated with untreated, nonculprit lesion progression using coregistered OCT and IVUS in patients with stable angina pectoris who underwent percutaneous coronary intervention. The study protocol was approved by the institutional ethics committee of Showa University Northern Yokohama Hospital, and written informed consent was obtained from all patients.

A total of 58 patients were enrolled between May 2012 and March 2013. Per protocol, IVUS and OCT imaging of the 3 epicardial coronary vessels were performed at baseline after target lesion stent implantation and at 8-month follow-up. Patients with acute coronary syndromes, prior myocardial infarction, severely calcified lesions, chronic total occlusions, or chronic kidney disease (creatinine >1.5 mg/dL) were excluded. Patient demographic data were confirmed by hospital chart review. Coronary risk factors included hypertension (medication treated only), diabetes mellitus (diet controlled, oral agent treated, or insulin treated), hyperlipidemia (medication treated or total cholesterol >220 mg/dL), current cigarette smoking, and family history of coronary artery disease. Laboratory data were obtained before cardiac catheterization for both the baseline and follow-up studies. Postpercutaneous coronary intervention dual antiplatelet therapy with aspirin (100 mg daily) and clopidogrel (75 mg daily) was continued for at least 8 months (the interval between baseline and follow-up imaging).

IVUS Imaging and Analysis

The IVUS catheter was advanced as far as possible using a commercially available IVUS system incorporating a 40 MHz IVUS catheter (OptiCross; Boston Scientific Corporation, Marlborough, MA) with motorized pullback at 0.5 mm/s after 0.2 mg of intracoronary nitroglycerin. Qualitative and quantitative analyses were done according to the American College of Cardiology standards.[12] Quantitative IVUS analysis was performed using planimetry software (echoPlaque; INDEC Systems, Inc, Mountain View, CA) to include external elastic membrane (EEM), lumen, plaque and media (EEM−lumen) cross-sectional area (CSA), and plaque burden (plaque and media CSA divided by EEM CSA). A remodeling index was calculated as the lesion EEM CSA at the minimum lumen CSA site divided by the average reference EEM CSA. A nonculprit lesion had a plaque burden of ≥40% that was ≥2 mm in length. Nonculprit lesions were independent if there was a gap of >5 mm between them or between the nonculprit lesion and the treated lesion.

We first analyzed the minimum lumen CSA site within the nonculprit lesion at follow-up, as well as the corresponding proximal and distal reference segments. If there were multiple cross-sections with the smallest lumen CSA, the image slice with the largest plaque burden was analyzed. For the baseline study, segments and cross-sections corresponding to the follow-up study were identified and analyzed. Lesion progression was defined as a decrease of IVUS lumen CSA >0.5 mm^2 at the minimum lumen CSA site at follow-up because in a study by Gerbaud et al,[13] intraobserver variability of lumen CSA was reported to be −0.05±0.25 mm^2 with 2 SDs of 0.5 mm^2.

OCT Imaging and Analysis

OCT images were acquired with the ILUMIEN OPTIS PCI optimization system and Dragonfly or Dragonfly JP imaging catheters (St. Jude Medical, Minneapolis, MN). The same segments imaged by IVUS were imaged by OCT. During image acquisition, blood was displaced by injection of commercially available dextran 40 and lactated Ringer solution (low molecular dextran L; Otsuka Pharmaceutical Factory, Tokushima, Japan). Qualitative and quantitative analyses were performed as described previously.[10,14]

A layered pattern was defined as a plaque with a superficial layer that had a different optical intensity and a clear demarcation from underlying plaque. Lipidic plaques were signal-poor regions with diffuse borders. The thinnest fibrous cap within the lipidic plaque was measured. A TCFA was a lipidic plaque with a cap thickness ≤65 μm. Macrophages were signal-rich, distinct, or confluent punctate regions exceeding the intensity of background speckle noise. Calcium was a low back-scattering heterogeneous region with a sharply delineated border. Calcium CSA was measured by manual segmentation.

Each underlying lesion phenotype was stratified according to the following hierarchy: (1) TCFA, (2) thick-cap lipidic plaque (lipidic plaque with cap thickness >65 μm), (3) fibrocalcific plaque, or (4) fibrous plaque.

Angiographic Analysis

Cine angiograms were analyzed with a computer-assisted, automated edge-detection algorithm (QAngio XA; Medis, Leiden, The Netherlands) by independent observers who were blinded to the clinical, IVUS, and OCT findings. Coregistration of the IVUS and angiograms was performed using fiduciary points, such as side branches. The minimum lumen diameter and reference vessel diameter were measured, and the diameter stenosis was calculated both at baseline and follow-up.

Clinical Follow-Up

Patients were followed for 12 months by hospital visit or phone call. Major adverse cardiac events were a composite of cardiac death, myocardial infarction, or nontarget lesion revascularization driven by symptoms or an evidence of ischemia.

Statistical Analysis

Statistical analysis was performed with SPSS, version 20.0 (IBM, Armonk, NY), and SAS, version 9.4 (SAS Institute, Inc, Cary, NC). Continuous variables were presented as median and first and third quartiles and compared using the Mann–Whitney *U* test. Categorical variables were expressed as count and percent and compared with χ^2 statistics or Fisher exact test. Comparison of laboratory data between baseline and follow-up was performed using the Wilcoxon signed-rank test. For lesion-level data, a model with a generalized estimating equation with compound symmetrical covariance structure approach was used to compensate for any potential cluster effect of multiple lesions in the same individual and presented as least square means with 95% confidence intervals. generalized estimating equation logistic regression was performed to determine the independent predictors of lesion progression using lesion-level data. A P value <0.05 was considered statistically significant.

Results

Of the 58 patients enrolled in the study, 12 asymptomatic patients refused follow-up imaging, and OCT images were inadequate for analysis in 1 patient. Thus, 45 patients with matched baseline and follow-up IVUS and OCT at 262±66 days (median interval, 252 days) were evaluated: 81.2±18.6-mm segments in the right coronary artery, 63.0±14.4-mm segments in the left anterior descending artery, and 51.5±22.7-mm segments in the left circumflex artery. Among these 45 patients, there were 6 hypoplastic coronary arteries and inadequate images in 8 coronary arteries. Finally, 127 nonculprit lesions in 121 arteries (average of 2.8 lesions per patient) were identified: 7 lesions in 1 patient, 6 lesions in 1 patient, 5 lesions in 4 patients, 4 lesions in 7 patients, 3 lesions in 14 patients, 2 lesions in 8 patients, 1 lesion in 8 patients, and no lesion in 2 patients.

Among 43 patients with at least 1 nonculprit lesion, we compared clinical findings and laboratory data between

patients with at least 1 lesion progression (n=16) versus patients without any lesion progression (n=27). As summarized in Table 1, patients with at least 1 lesion progression reported less statin use preadmission versus those without lesion progression (31.3% versus 70.4%; *P*=0.01), but there was no significant difference in terms of statin use at discharge (81.3% versus 77.8%; *P*=0.55).

Laboratory data are summarized in Table 2. At baseline, LDL-C and hs-CRP (high-sensitivity C-reactive protein) were higher in patients with lesion progression versus without lesion progression. LDL-C decreased significantly during follow-up in patients with lesion progression (*P*=0.049) but not in patients without lesion progression, and follow-up LDL-C and hs-CRP were similar in the 2 groups. Conversely, high-density lipoprotein cholesterol (HDL-C) was lower in patients with versus without lesion progression both at baseline and at follow-up.

Serial IVUS and OCT Findings

Overall, there were 24 lesions with progression and 103 lesions without progression. IVUS findings are summarized in Table 3. At baseline, there was a trend toward more plaque burden at the cross-section corresponding to the minimum lumen CSA site at follow-up in the progression group versus the nonprogression group (63.0% [60.0–65.9] versus 59.9% [57.9–61.9]; *P*=0.06), whereas baseline lumen area was not significantly different between the progression and

Table 1. Patient Characteristics and Medication

	Lesion Progression		*P* Value
	Yes (n=16)	No (n=27)	
Follow-up, d	261 (245–282)	248 (217–272)	0.18
Age, y	70 (64–75)	72 (64–74)	0.74
Women	3 (18.8%)	4 (14.8%)	0.53
Hypertension	10 (62.5%)	20 (74.1%)	0.32
Hyperlipidemia	12 (75.0%)	20 (74.1%)	0.62
Diabetes mellitus	7 (43.8%)	11 (40.7%)	0.85
Current smoking	4 (25.0%)	5 (18.5%)	0.45
Family history of coronary artery disease	3 (18.8%)	7 (25.9%)	0.44
Body mass index, kg/m^2	23.3 (21.4–26.2)	24.4 (22.8–26.8)	0.32
Medications on admission			
Statin	5 (31.3%)	19 (70.4%)	0.01
Antidiabetic	5 (31.3%)	10 (37.0%)	0.70
Insulin	1 (6.3%)	2 (7.4%)	0.69
ACE-I/ARB	7 (43.8%)	12 (44.4%)	0.97
β blocker	2 (12.5%)	2 (7.4%)	0.48
Medications at discharge			
Statin	13 (81.3%)	21 (77.8%)	0.55
Antidiabetic	6 (37.5%)	11 (40.7%)	0.83
Insulin	1 (6.3%)	2 (7.4%)	0.69
ACE-I/ARB	6 (37.5%)	15 (55.6%)	0.25
β blocker	4 (25.0%)	3 (11.1%)	0.22

Values are median (first quartile–third quartile) or n (%). ACE-I indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

Table 2. Patient Laboratory Data

	Lesion Progression		*P* Value
	Yes (n=16)	No (n=27)	
Baseline			
LDL-C, mg/dL	110 (95–126)	88 (68–104)	0.004
HDL-C, mg/dL	44 (33–55)	49 (43–57)	0.08
hs-CRP, mg/dL	0.097 (0.069–0.179)	0.051 (0.019–0.099)	0.008
HbA1c, %	6.5 (6.0–6.7)	6.1 (5.6–6.9)	0.76
Follow-up			
LDL-C, mg/dL	84 (68–107)	93 (73–115)	0.35
HDL-C, mg/dL	45 (33–56)	54 (46–60)	0.02
hs-CRP, mg/dL	0.059 (0.032–0.283)	0.058 (0.018–0.107)	0.34
HbA1c, %	6.5 (5.9–6.8)	6.2 (5.6–7.3)	0.58

Values are median (first quartile–third quartile). HbA1c indicates glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; and LDL-C, low-density lipoprotein cholesterol.

Table 3. Intravascular Ultrasound Findings

	Lesions With Progression (n=24)	Lesions Without Progression (n=103)	GEE-Adjusted *P* Value
Baseline			
Lesion location			0.26
Right	9 (37.5%)	35 (34.0%)	
Left anterior descending	6 (25.0%)	39 (37.9%)	
Left circumflex	9 (37.5%)	29 (28.2%)	
Lesion length, mm	17.7 (11.6–23.7)	14.7 (11.8–17.6)	0.38
Baseline site corresponding to minimum lumen area site at follow-up			
Lumen CSA, mm^2	4.8 (4.3–5.3)	5.2 (4.6–5.7)	0.36
EEM CSA, mm^2	13.3 (11.8–14.9)	12.7 (11.7–13.8)	0.51
P+M CSA, mm^2	8.5 (7.3–9.7)	7.6 (7.0–8.2)	0.14
Plaque burden, %	63.0 (60.0–65.9)	59.9 (57.9–61.9)	0.06
Remodeling index	0.94 (0.91–0.97)	0.95 (0.92–0.97)	0.60
Follow-up			
Minimum lumen area site			
Lumen CSA, mm^2	3.8 (3.2–4.3)	5.3 (4.7–5.8)	<0.001
EEM CSA, mm^2	13.2 (11.7–14.7)	12.8 (11.7–13.8)	0.64
P+M CSA, mm^2	9.4 (8.2–10.6)	7.5 (6.9–8.1)	0.004
Plaque burden, %	70.6 (67.4–73.8)	59.3 (57.4–61.2)	<0.001

Values are GEE least-square means (95% confidence interval) or n (%).

CSA indicates cross-sectional area; EEM, external elastic membrane; GEE, generalized estimating equation; and P+M, plaque plus media.

Table 4. Optical Coherence Tomographic Findings

	Lesions With Progression (n=24)	Lesions Without Progression (n=103)	GEE-Adjusted *P* Value
Baseline			
Lipidic plaque	20 (83.3%)	30 (29.1%)	<0.001
Thinnest cap thickness, mm	0.13 (0.09–0.17)	0.14 (0.12–0.16)	0.69
Macrophage	21 (87.5%)	66 (64.1%)	0.003
Calcium	15 (62.5%)	58 (56.3%)	0.55
Maximum CSA, mm^2	2.0 (1.3–2.7)	1.9 (1.6–2.2)	0.81
Microvessels	6 (25.0%)	28 (27.2%)	0.85
Cholesterol crystal	4 (16.7%)	7 (6.8%)	0.11
Thrombus	2 (8.3%)	5 (4.9%)	0.58
Follow-up			
Lipidic plaque	20 (83.3%)	30 (29.1%)	<0.001
Thinnest cap thickness, mm	0.16 (0.12–0.21)	0.15 (0.13–0.18)	0.62
Macrophage	20 (83.3%)	68 (66.0%)	0.050
Calcium	15 (62.5%)	58 (56.3%)	0.55
Maximum CSA, mm^2	1.9 (1.3–2.6)	1.9 (1.6–2.2)	0.95

Values are GEE least-square means (95% confidence interval) or n (%). CSA indicates cross-sectional area; and GEE, generalized estimating equation.

no progression groups (4.8 mm^2 [4.3–5.3] versus 5.2 mm^2 [4.6–5.7]; *P*=0.36). In the lesion progression group, a significant increase in plaque burden was observed from baseline to follow-up (63.0% [60.0–65.9] versus 70.6% [67.4–73.8]; *P*<0.001) without a change in EEM CSA (13.3 mm^2 [11.8–14.9] versus 13.2 mm^2 [11.7–14.7]; *P*=0.93). There were no morphometric changes between baseline and follow-up in the nonprogression group.

OCT findings are summarized in Table 4. The prevalence of lipidic plaque (83.3% versus 29.1%; *P*<0.001) and macrophages (87.5% versus 64.1%; *P*=0.003) was higher in the lesion progression group compared with the nonprogression group both at baseline and at follow-up. Conversely, comparing the 2 groups, minimum fibrous cap thickness was similar at baseline and at follow-up. Maximum calcium CSA did not change significantly from baseline to follow-up both in the progression group (*P*=0.80) and the nonprogression group (*P*=0.95).

Morphological Changes

By comparing OCT at baseline and follow-up in the progression group (24 lesions), there were 3 patterns of lesion progression: type I, new superficial layered pattern that was not seen at baseline, but that appeared at follow-up (measuring 0.39±0.11 mm; n=9); type II, layered pattern, superficial layer that was present at baseline and increased in thickness at follow-up (from 0.29±0.18 to 0.47±0.19 mm; n=7); and type III, no layered pattern either at baseline or at follow-up (n=8; Figures 1, 2, and 3). Two of 9 lesions with type I lesion progression showed fibrous cap disruption at baseline (Figure 1A). The increase in plaque and media CSA from baseline to follow-up was largest in type I and least in type III (type I, 1.9 mm^2 [1.6–2.1]; type II, 1.1 mm^2 [0.9–1.4], and type III, 0.3 mm^2 [−0.2 to 0.8]; *P*=0.002). Also the increase in plaque burden from baseline to follow-up was larger in type I and type II than in type III (type I, 8.3% [6.7–10.0]; type II, 7.8% [6.1–9.4]; and type III, 5.1% [3.2–7.1]; *P*=0.004). Conversely, in type III progression, EEM CSA decreased during follow-up (from 14.3 mm^2 [11.4–17.2] at baseline to 13.5 mm^2

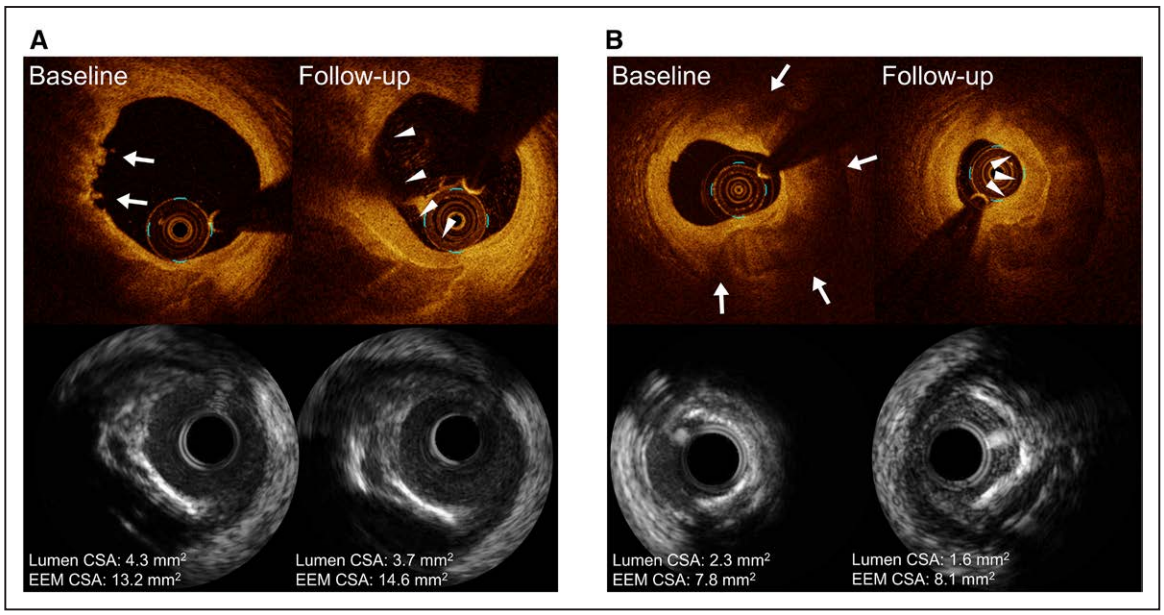

Figure 1. Representative cases of type I lesion progression. **A**, Case 1: optical coherence tomography (OCT; **top**) shows fibrous cap disruption (arrows) at baseline on top of lipidic plaque. At 8-month follow-up, a new layer appeared on the surface of the plaque (arrow heads) that had clearly different OCT intensity compared with the OCT intensity of the underlying plaque. **B**, Case 2: OCT (**top**) shows fibrocalcific plaque (arrows) at baseline. At 8-month follow-up, a new layer appeared on the surface (arrow heads). Corresponding intravascular ultrasound cross-sections (**bottom**) show progression (>0.5-mm^2 decrease in lumen cross-sectional area [CSA]). EEM indicates external elastic membrane.

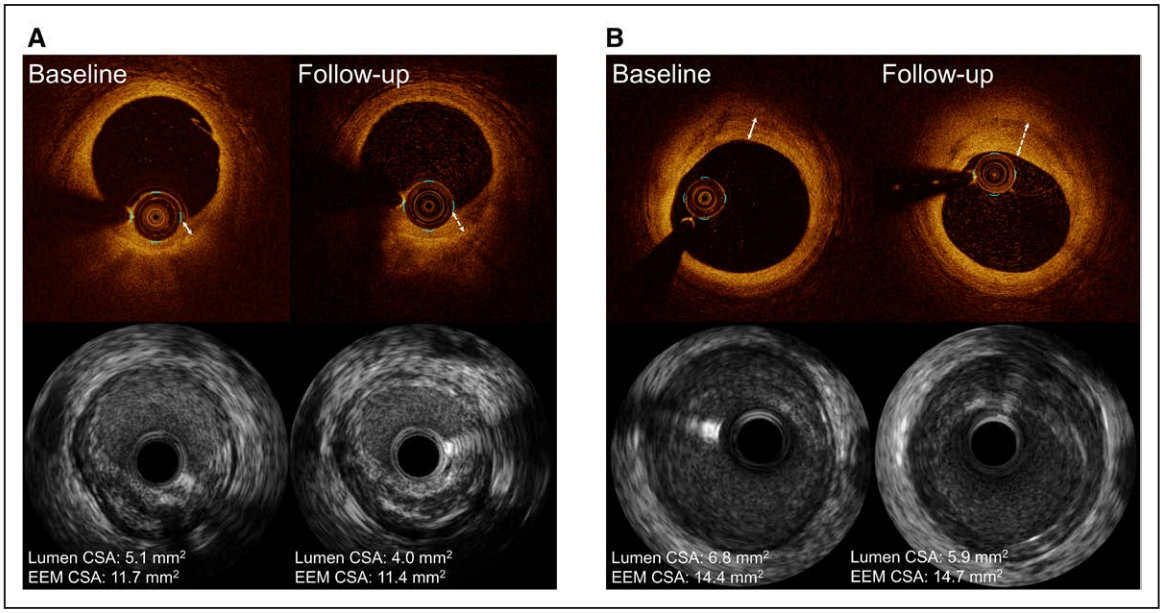

Figure 2. Representative cases of type II lesion progression. **A**, Case 1: optical coherence tomography (OCT; **top**) shows a layered pattern (double-headed arrow) at baseline, characterized as the most superficial region that showed different optical intensity from underlying plaque. At 8-month follow-up, the layer increased in thickness (dotted double-headed arrow). **B**, Case 2: OCT shows a layered pattern (double-headed arrow) at baseline. At 8-month follow-up, the layer increased in thickness (dotted double-headed arrow). Corresponding intravascular ultrasound cross-sections (**bottom**) show progression (>0.5 mm² decreased in lumen area). CSA indicates cross-sectional area; and EEM, external elastic membrane.

[10.4–16.7] at follow-up [ie, negative remodeling]; P=0.02) without any EEM CSA changes in type I or type II progression. In the nonprogression group, a layered pattern was seen in 10.7% (11/103) at baseline without any increase in thickness during follow-up. In the rest of the 92 nonprogression lesions, no new layered pattern was observed at follow-up.

Overall, 20 of 24 lesions with progression were lipidic plaques (TCFAs or thick-cap lipidic plaques), and 60% of TCFAs showed lesion progression. Conversely, lesion progression in fibrous or fibrocalcific plaques was rare (P<0.001; Figure 4).

Table 5 shows the evolution of underlying lesion phenotypes from baseline to follow-up. Among 10 TCFAs at baseline, 4 TCFAs evolved into thick-cap lipidic plaques: 3 because of a new, superficial layered pattern (type I; Figure 5A) with lesion progression and 1 because of an increase in existing

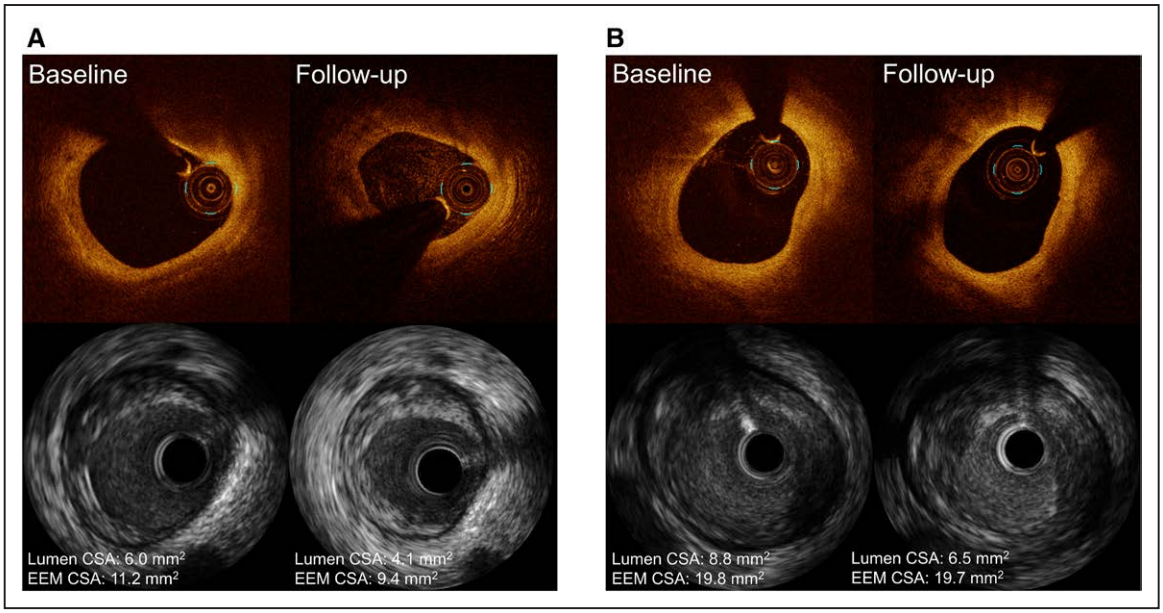

Figure 3. Representative cases of type III lesion progression. **A**, Case 1 and (**B**) case 2: optical coherence tomography (**top**) shows a lipidic plaque at baseline. At 8-month follow-up, lumen compromise was observed without a layered pattern. Corresponding intravascular ultrasound cross-sections (**bottom**) show progression (>0.5 mm² decreased in lumen cross-sectional area [CSA]). EEM indicates external elastic membrane.

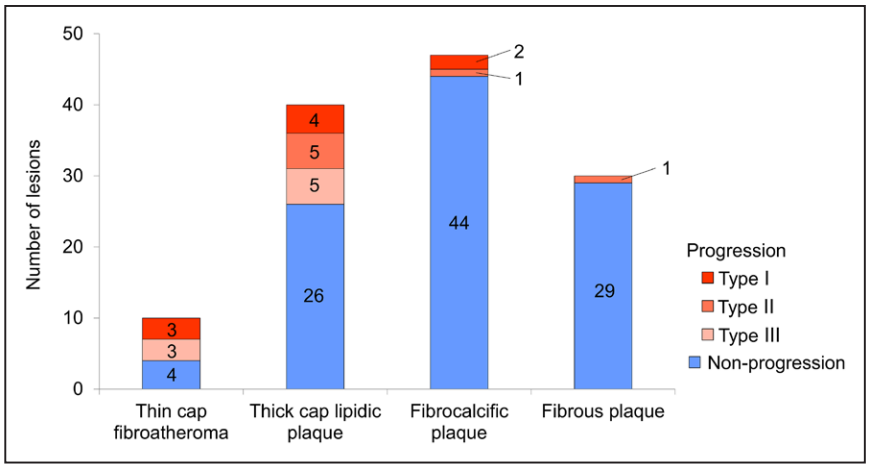

Figure 4. Underlying lesion phenotype and lesion progression. Distribution of lesion progression based on underlying lesion phenotype. Lesions with progression have been subcategorized into type I, type II, or type III.

fibrous cap thickness without lesion progression (Figure 5B). Among the 6 TCFAs at baseline that did not change during follow-up, 3 TCFAs showed type III lesion progression and 3 TCFAs showed neither lesion progression nor significant morphological changes. All 40 thick-cap lipidic plaques at baseline remained thick-cap lipidic plaques at follow-up; 14 showed lesion progression (type I=4, type II=5, and type III=5). All of the 47 fibrocalcific plaques identified at baseline remained fibrocalcific plaques at follow-up; only 3 progressed (type I=2 and type II=1). All of the 30 fibrous plaques identified at baseline remained fibrous plaques at follow-up; only 1 progressed (type II).

Only OCT lipidic plaque morphology at baseline was significantly associated with lesion progression (odds ratio, 13.6; 95% confidence interval, 3.7–50.6; $P<0.001$). Neither IVUS plaque burden ($P=0.61$) nor lumen area ($P=0.32$) at baseline was associated with lesion progression.

Serial Angiographic Findings

Angiographic findings are summarized in Table 6. Overall, baseline minimum lumen diameter was 2.35 mm (2.22–2.48), and diameter stenosis was 18.0% (16.1–19.9) without significant differences between lesions with and without progression. At follow-up, minimum lumen diameter was significantly smaller in lesions with progression versus lesions without progression (2.10 [1.84–2.36] versus 2.40 mm [2.24–2.56]; $P=0.046$).

Clinical Outcomes

There were no complications during IVUS and OCT other than 1 case of stent deformation caused by delivering the OCT catheter after stenting. Among 58 patients enrolled and followed in this study, 1 patient died from cancer. There was no myocardial infarction during follow-up. Nontarget lesion revascularization was performed in 5 patients (at day 267±17), and the major adverse cardiac event rate (5 revascularizations) was 8.6% (5/58). Among the 5 revascularizations, 1 lesion in a diagonal branch and 1 lesion in a left main did not have baseline images; and 1 thick-cap lipidic plaque without a layered pattern at baseline showed angiographic progression (diameter stenosis increased from 31.4% to 62.3%) and was revascularized without follow-up imaging. Thus, only 2 lesions with both baseline and follow-up imaging required revascularization. These 2 lesions were in the progression group, lumen areas decreased from baseline to follow-up (from 3.0 to 2.3 mm^2 and from 3.7 to 2.8 mm^2), and both had a thick-cap lipidic plaque with layered pattern at baseline that remained thick-cap lipidic plaque with an increased layer of superficial layered pattern (type II progression) at follow-up. There was no revascularization in nonprogression lesions.

Table 5. Underlying Lesion Phenotype

	Baseline	Follow-Up			
		TCFA	Thick-Cap Lipidic Plaque	Fibrocalcific Plaque	Fibrous Plaque
TCFA	10 (7.9%)	6 (3*[type III]/3†)	4 (3*[type I]/1†)	0	0
Thick-cap lipidic plaque	40 (31.5%)	0	40 (14*[4 type I, 5 type II, 5 type III]/26†)	0	0
Fibrocalcific plaque	47 (37.0%)	0	0	47 (3*[2 type I, 1 type II]/44†)	0
Fibrous plaque	30 (23.6%)	0	0	0	30 (1*[type II]/29†)
Total	127	6 (4.7%)	44 (34.7%)	47 (37.0%)	30 (23.6%)

Values are n or n (%). TCFA indicates thin-cap fibroatheroma.
*Progression.
†No progression.

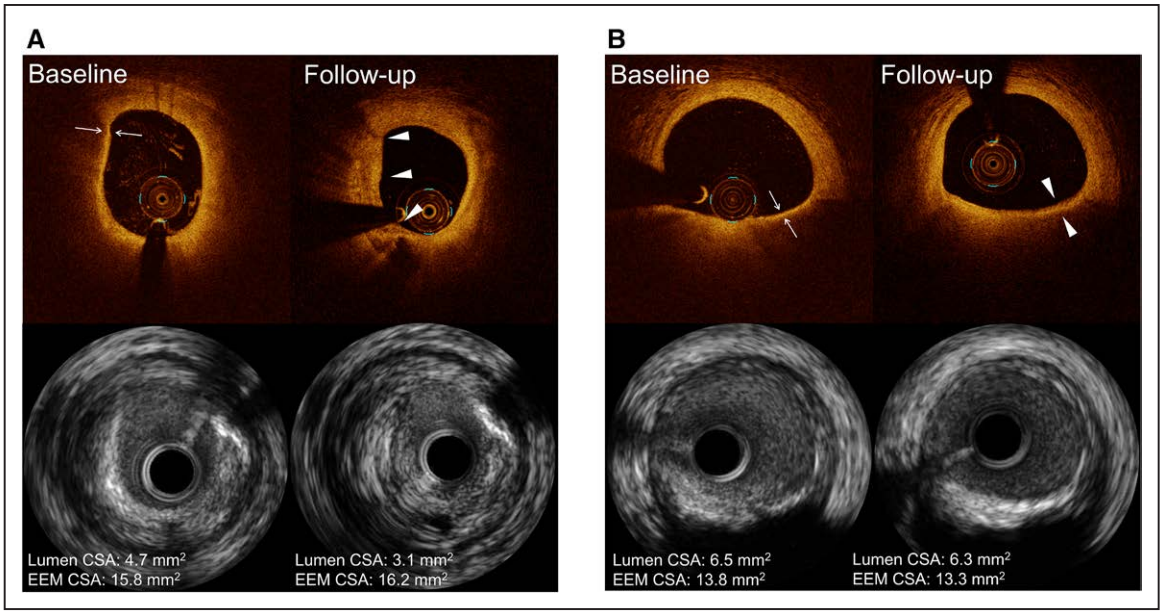

Figure 5. Representative cases of lesion phenotype change from thin-cap fibroatheroma to thick-cap lipidic plaque. **A**, Optical coherence tomography (OCT) shows a thin-cap fibroatheroma (arrows) at baseline. At 8-month follow-up, there was a layered pattern with a thick fibrous cap layer (arrow heads) and corresponding intravascular ultrasound cross-sections (**bottom**) show progression (>0.5-mm^2 decrease in lumen area). **B**, OCT shows a thin-cap fibroatheroma (arrows) at baseline. At 8-month follow-up, the fibrous cap increased in thickness (arrow heads) and corresponding intravascular ultrasound cross-sections (**bottom**) show no progression. CSA indicates cross-sectional area; and EEM, external elastic membrane.

Discussion

The main findings of the present study are as follows: OCT morphological patterns of lesion progression were seen with a layered pattern (type I and type II) or without a layered pattern (type III); type I and type II were associated with an increase in plaque, whereas type III was associated with negative remodeling. Lesion progression was predicted by OCT lipidic plaque. Patients with progression used statins less often pre-enrollment and had higher levels of serum LDL-C and hs-CRP at baseline than patients without lesion progression; conversely, HDL-C was lower in patients with lesion progression both at baseline and at follow-up.

Table 6. Angiographic Findings

	Lesions With Progression (n=24)	Lesions Without Progression (n=103)	GEE-Adjusted *P* Value
Baseline			
Reference vessel diameter, mm	2.80 (2.60–3.02)	2.86 (2.72–3.01)	0.61
Minimum lumen diameter, mm	2.24 (2.03–2.45)	2.38 (2.24–2.52)	0.29
Diameter stenosis, %	20.0 (16.2–23.8)	17.5 (15.4–19.6)	0.27
Lesion length, mm	6.2 (5.0–7.5)	5.3 (4.2–6.3)	0.20
Calcification	4 (16.7%)	11 (10.7%)	0.51
Follow-up			
Reference vessel diameter, mm	2.68 (2.43–2.93)	2.90 (2.75–3.05)	0.12
Minimum lumen diameter, mm	2.10 (1.84–2.36)	2.40 (2.24–2.56)	0.046
Diameter stenosis, %	21.8 (16.7–26.8)	17.5 (15.3–19.8)	0.15
Late loss, mm	0.13 (0.01–0.25)	−0.15 (−0.30 to −0.01)	0.04
Change of diameter stenosis ≥20%	2 (8.3%)	0 (0%)	0.12

Values are GEE least-square means (95% confidence interval) or n (%). GEE indicates generalized estimating equation.

A pathology study by Burke et al[4] reported that the mean percent CSA luminal narrowing (equivalent to plaque burden by IVUS) increased with the number of healed rupture sites within an individual lesion. On the contrary, serial IVUS studies have also shown that lumen reduction may result from negative vessel remodeling, not plaque burden increase.[7–9] Lesion progression with a layered pattern (type I and type II) in the current study was associated with a greater increase in plaque (without negative remodeling) than lesion progression without a layered pattern (type III) that was associated with negative remodeling during follow-up.

TCFAs can stabilize, especially when a patient is treated with statins.[15] TCFA stabilization can be attributed to silent plaque rupture and subsequent healed plaque or thickening of the fibrous cap. In a cohort of patients with both acute coronary syndrome (23%) and stable angina pectoris (77%), 75% of virtual histology (VH)-IVUS–derived TCFAs evolved into thick-cap fibroatheromas, and 25% remained VH-TCFAs.[16] On the contrary, in patients with ST-segment–elevation myocardial infarction, 78% of VH-TCFAs remained VH-TCFAs during 13-month follow-up.[17] In our study of patients with stable angina pectoris using OCT rather than VH-IVUS to assess lesion morphology, 60% of TCFAs remained TCFAs and 40% evolved into thick-cap lipidic plaques.

Lesion progression is associated with high LDL-C and hs-CRP and low HDL-C. Both reducing LDL-C and hs-CRP (with statin therapy) and raising HDL-C may reduce lesion progression and even lead to regression,[18,19] whereas ≈20% of patients demonstrated atheroma progression, despite achieving LDL-C ≤70 mg/dL.[19] However, in the current study, lesion progression was related to changes in HDL-C but not to changes in LDL-C or hs-CRP. Furthermore, treatment of these patients failed to achieve these ideal LDL-C levels, and 20% of patients were not taking statins.

There have been several reported predictors of lesion progression, including IVUS positive remodeling[20] and OCT-identified TCFAs and microvessels[11,20] but not in another study with serial intravascular imaging.[21] In our study with OCT and IVUS, lipidic plaque, including TCFA morphology, was related to lesion progression, whereas OCT-identified microvessels and baseline IVUS parameters did not show significant relationship with lesion progression; however, few lesions in the current study progressed to require revascularization during the follow-up period.

This study had several limitations. First, this was a single-center study with a modest number of patients with stable angina. Second, we did not study left main lesions, side branches, or distal segments. Third, we did not assess local endothelial shear stress.[22] Fourth, Japanese patients are reported to have better outcomes (both target and non-target revascularization) than US patients after coronary revascularization[23]; therefore, the current findings may not be generalizable to Western patients. Fifth, we did not have biomarkers data other than hs-CRP.[24] Finally, the changes in the baseline to follow-up OCT morphological patterns in the current study have not been validated by histology and may not correlate with any particular histological or clinical outcomes findings. The significance and accuracy to detect actual histological changes are unknown.

Conclusions

This serial 3-vessel OCT and IVUS study demonstrated that lesion progression was associated with distinct OCT morphologies (and IVUS morphometries) that changed from baseline to follow-up and were associated with various extents of plaque increase and vessel remodeling. Also, OCT lipidic plaque was associated with lesion progression in patients with stable angina.

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CLINICAL PERSPECTIVE

Coronary artery lesion progression is associated with an increased risk of clinical events. Previous clinical studies investigating lesion progression have used intravascular ultrasound (IVUS) because it can provide insights into plaque burden and vessel remodeling. Optical coherence tomography (OCT) has 10× greater resolution than IVUS and provides detailed visualization. This serial 3-vessel study of untreated lesion progression in patients with stable angina using combination of IVUS and OCT demonstrated distinct OCT morphologies, with or without a layered pattern, with or without an increase in IVUS plaque mass or IVUS remodeling. Furthermore, OCT lipidic plaque was associated with lesion progression. Larger and longer studies are needed to determine the relationship between IVUS lesion progression and OCT morphology, as well as future events.

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Serial 3-Vessel Optical Coherence Tomography and Intravascular Ultrasound Analysis of Changing Morphologies Associated With Lesion Progression in Patients With Stable Angina Pectoris

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