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ORIGINAL RESEARCH

Serial Optical Coherence Tomography Assessment of Coronary Atherosclerosis and Long-Term Clinical Outcomes

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BACKGROUND: The impact of high-risk coronary artery plaques identified using optical coherence tomography on late luminal narrowing and clinical events remains poorly understood.

METHODS AND RESULTS: This multicenter prospective study included 176 patients who underwent percutaneous coronary intervention and serial optical coherence tomography at baseline and 1-year follow-up to investigate nontarget regions with angiographically intermediate stenosis. At 1 year after percutaneous coronary intervention, the coronary artery lumen area decreased significantly from 6.06 (95% CI, 5.60–6.53) mm^2 to 5.88 (95% CI, 5.41–6.35) mm^2 (difference, −0.18; 95% CI, −0.22 to −0.14 mm^2; $P<0.001$), particularly in thin-cap fibroatheromas, thick-cap fibroatheromas, mixed plaques, and fibrous plaques. The prevalence of fibroatheroma decreased from 38% to 36% ($P<0.001$), whereas calcified plaque increased from 31% to 34% ($P<0.001$), accompanied by a significant increase in calcium thickness and angle. Diabetes and current smoking habits were independently associated with increasing calcium prevalence. Patients with thin-cap fibroatheroma had a significantly higher 3-year risk of ischemia-driven nontarget vessel revascularization (hazard ratio, 2.42 [95% CI, 1.03–5.71]; $P=0.04$), primarily due to revascularization in the imaged region. No significant association was observed between coronary artery calcium prevalence and clinical outcomes within 3 years.

CONCLUSIONS: The coronary artery lumen area significantly decreased over a 1-year interval, particularly in thin-cap fibroatheromas, thick-cap fibroatheromas, mixed plaques, and fibrous plaques. Although thin-cap fibroatheroma prevalence was associated with higher risk of ischemia-driven nontarget vessel revascularization, no significant association was noted between coronary artery calcium prevalence and clinical outcomes within 3 years. The interaction between calcium progression and long-term clinical events necessitates further investigation.

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Key Words: atherosclerotic ■ coronary artery disease ■ optical coherence tomography

See Editorial by Chamié and Pfau.

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CLINICAL PERSPECTIVE

What Is New?

- Coronary artery plaques assessed by optical coherence tomography, including thin-cap fibroatheromas, thick-cap fibroatheromas, mixed plaques, and fibrous plaques, were associated with luminal narrowing during the 1-year follow-up.
- There was a significant increase in calcium thickness and angle, particularly in patients with diabetes and current smokers, indicating a dynamic change in plaque composition.

What Are the Clinical Implications?

- The presence of thin-cap fibroatheromas was associated with an increased risk of ischemia-driven revascularization in nontarget regions, highlighting the need for close monitoring and potential preventive strategies in these patients.
- Despite the observed increase in coronary artery calcium during the 1-year follow-up, there was no clear association with adverse clinical outcomes within 3 years, suggesting the need for further long-term follow-up studies to clarify the impact on clinical outcomes.

Nonstandard Abbreviations and Acronyms

TCFA	thin-cap fibroatheroma

Recurrent coronary artery events following percutaneous coronary intervention (PCI) remain a significant clinical concern, particularly for long-term clinical adverse events, including cardiovascular death, acute myocardial infarction, and coronary artery revascularization.[1] Among the various pathological plaque phenotypes, thin-cap fibroatheromas (TCFAs) have emerged as pivotal precursors for coronary artery events occurring in nontarget regions.[2,3] The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study reported that the presence of TCFAs, reduced minimal lumen area, and increased plaque burden, as assessed using virtual histology intravascular ultrasound, were associated with major adverse events following acute myocardial infarction.[4,5] More recently, the prognostic significance of a large lipid-rich core with a large plaque burden was unveiled by the integration of near-infrared spectroscopy with intravascular ultrasound.[6,7]

Optical coherence tomography (OCT), with its 10-fold higher spatial resolution than intravascular ultrasound, allows for meticulous scrutiny of high-risk plaque features, including the presence of TCFAs. Previous OCT studies have revealed that the presence of TCFA and reduced minimum lumen area at baseline were associated with clinical events in nontarget regions.[8–12] Nevertheless, the dynamic changes within plaque components including fibroatheroma and coronary artery calcium and their potential consequences for luminal narrowing and subsequent clinical events were largely unknown. This study aimed to investigate the prognostic impact of plaque characteristics in nontarget regions assessed by using OCT on subsequent luminal narrowing and the occurrence of future clinical events.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

The PREDICTOR (Predicting Long-Term Clinical Outcomes by OCT Assessment of Plaque Characteristics in the Nonrevascularized Coronary Artery) study is a multicenter prospective observational study. Detailed inclusion and exclusion criteria are provided in Data S1. In brief, we enrolled patients who underwent PCI for target lesions and had at least 1 de novo nontarget region with intermediate stenosis (visually estimated percent diameter stenosis between 30% and 90%). Nontarget regions were defined as regions including intermediate stenosis in either nontarget vessels or within the target vessel but >5 mm apart from the culprit lesions. OCT image acquisition for nontarget regions was performed either before or after OCT-guided PCI for target lesions using the commercially available OPTIS OCT system (Abbott Vascular) with continuous intracoronary injection of contrast or low-molecular dextran. In cases where low-molecular-weight dextran was used, quantitative measurements were corrected via a flush media setting available to the region (Japan and European Union).[13] OCT image acquisition for nontarget regions was performed during the last PCI in cases of planned staged PCI. Follow-up OCT assessments for nontarget regions were performed either at the 1-year follow-up (330 to 390 days) or at the time of any unplanned coronary revascularization before the scheduled 1-year follow-up. The dual antiplatelet therapy duration was determined at the discretion of the operators. Standard medical therapy was recommended following current guidelines. However, in the study protocol, the specific

timing for initiating standard medical therapy was not explicitly outlined.

OCT Image Analysis

The ILUMIEN OPTIS offline review workstation or Ultreon 1.0 Software (Abbott Vascular) was used for OCT image analysis, which was performed by experienced investigators at the Kyoto University core laboratory (K.Y. and K.I.) and at the Kokura Memorial Hospital core laboratory (K.Y., K.Kanenawa, and T.M.). Preliminary screening of all OCT images was performed before commencing the analysis to ensure their image quality. Matched image pairs for baseline and 1-year follow-up were determined by using reference landmarks, including side branches and longitudinal center of calcifications with spline interpolation. We systematically analyzed all of the images in the baseline OCT pullbacks and corresponding regions of interest between the matched landmarks in the follow-up OCT pullbacks. Because OCT was not able to visualize plaque burden in lesions with fibroatheromas or dense calcium, lesions in the nonculprit vessels were not robustly determined using OCT, because we included moderately diseased vessels with luminal irregularity with low adaptive intimal thickening or normal vessel prevalence. Therefore, we did not assess OCT with lesion level but with patient level or image level. We assessed the mean lumen area within the imaged region rather than establishing reference and minimum lumen areas.

OCT image classification followed the international consensus statement in the following hierarchical order.[14] TCFA was identified on the basis of the presence of lipid pool, which is characterized by a region with reduced signal intensity and a diffuse boundary, along with the thinnest part of the fibrous cap thickness of ≤65 μm. In images with TCFAs, we assessed the total extension of lipid arc per image. Using Ultreon 1.0 Software (Abbott Vascular) powered by artificial intelligence technology, the maximum thickness and total angle of coronary calcium were automatically measured.[15] In cases wherein a lipid pool was observed along with the thinnest part of the fibrous cap thickness of >65 μm, we classified the plaques as thick-cap fibroatheromas when calcium was absent or as mixed plaques when calcium was present. For the remaining images, the plaques were categorized as fibrocalcific plaques if calcium was detected. Images with a homogeneous OCT signal with a high backscatter measuring >600 μm were categorized as fibrous plaques, those with >300 μm were classified as adaptive intimal thickening, and those with ≤300 μm were classified as normal vessels. In regard to patient-level analysis within the matched regions of interest, we calculated the mean lumen area (square millimeters) and the mean calcium area index. The calcium area index was calculated as the maximum calcium thickness (micrometers) multiplied by the total calcium angle (degree) and divided by 360°. The maximum calcium thickness and total calcium angle were considered 0 in cases wherein coronary artery calcium was not detected. We assessed eruptive or noneruptive calcified nodules, defining eruptive nodules as an accumulation of small calcium fragments protruding and disrupting the overlying fibrous cap, and noneruptive nodules as an accumulation of small calcium fragments protruding into the lumen with a smooth intact fibrous cap without an overlying thrombus.[16,17]

End Points and Definitions

The primary outcome measure in the present study was luminal narrowing over a 1-year period within the matched regions of interest in the nontarget regions. The secondary outcome measures included all-cause death, cardiac death, nonfatal myocardial infarction, and ischemia-driven coronary artery revascularization within 3 years. The safety outcome measures included any adverse events related to OCT procedure, amount of contrast used, radiation time, and intervention time.

Clinical follow-up information was obtained at post-procedure, at discharge, and annually up to 3 years. Unless clear evidence of noncardiac causes was identified, deaths were attributed to a cardiac origin. Nonfatal myocardial infarctions were adjudicated consistent with the fourth universal definition of myocardial infarction.[18] Any coronary revascularization was further categorized into target vessel revascularization, target lesion revascularization, nontarget vessel revascularization, imaged vessel revascularization, and imaged region revascularization. Target vessel revascularization, target lesion revascularization, and nontarget vessel revascularization were adjudicated according to the ARC-2 (Academic Research Consortium 2) definition.[19] Target lesion and vessel were indicated in those treated at the baseline procedure. Imaged region revascularization was defined as the revascularization of lesions located within the regions of interest in the baseline OCT pullbacks for nontarget regions. Imaged vessel revascularization was defined as the revascularization of the imaged vessel. Furthermore, any coronary revascularization was considered ischemia driven if it met ≥1 of the following criteria: (1) typical ischemic symptoms attributable to the target lesion with percent diameter stenosis of ≥50%, (2) percent diameter stenosis of ≥70%, (3) fractional flow reserve of the target lesion was ≤0.80, or (4) evidence of myocardial ischemia assessed using noninvasive tests, such as nuclear imaging, and stress echocardiography.[19]

This study was conducted in compliance with either the latest version of the Declaration of Helsinki or

the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare No. 3 dated December 22, 2014, whichever maximizes the protection of patients). Institutional review board approval was obtained from each participating institute. Written informed consent was obtained from all study patients.

Statistical Analysis

This study represents a pilot investigation aiming at addressing the predictive capability of baseline plaque characteristics assessed using OCT for subsequent late luminal changes. Considering the absence of prior studies providing plausible assumption for the calculation of study sample size, we included patients until the total number of angiographically intermediate lesions reported from each participating center reached 200 lesions. Categorical variables were presented as absolute values and percentages and compared using the Fisher exact test. Continuous variables were expressed as median values and interquartile ranges (IQRs) and compared using the Wilcoxon rank sum test. In regard to image-level OCT outcomes, we used generalized linear mixed models, wherein patients were included as random intercepts to account for the nonindependence of assessments from the same patients. For patient-level OCT outcomes, a paired Student *t* test was used for assessing differences between baseline and 1-year follow-up measurements. We constructed univariate and multivariable linear regression models, with the multivariable models incorporating explanatory variables listed in Table 1, to identify patient-level independent predictors for changes in the mean lumen area and mean calcium area index. Cumulative incidences of clinical events were estimated using the Kaplan-Meier method. We constructed univariate Cox proportional hazard models to evaluate the association of per patient OCT findings with clinical outcomes. The profile likelihood method was used for calculating 95% CIs. All analyses were performed using R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study flowchart is shown in Figure 1. Between May 16, 2018 and May 31, 2019, a total of 176 patients were enrolled from 15 participating centers (study organization in Data S1). Among them, the study population comprised 164 patients (172 imaged vessels) who underwent baseline OCT with sufficient image quality. Among 172 imaged vessels with intermediate stenosis, functional testing was conducted in 22 vessels (13%) and nuclear imaging was performed in 6 vessels (3.5%); the operators deemed the remaining 144 vessels (83.7%) as nonsignificant. The baseline characteristics and medication status at discharge are presented in Table 1. The median age of patients was 76 (IQR, 71–81) years, and 77% were men. Clinical presentations included non–ST-segment–elevation acute coronary syndrome and stable coronary artery disease in 10% and 90% of the patients, respectively, with no patients presenting with ST-segment–elevation myocardial infarction. In regard to comorbidities, 77%, 74%, and 46% of the patients had hyperlipidemia, hypertension, and diabetes, respectively, and 61% of patients were either current or former smokers. At 1 year, follow-up, OCT was conducted in 128 patients (134 imaged vessels) with sufficient image quality. No significant differences were observed in the baseline characteristics between the patients who underwent follow-up OCT and those who did not, except for the prevalence of malignancy (12% versus 31%, P=0.01). Medication status at 1, 2, and 3 years are shown in Tables S1 through S3. Notably, 88% of the study patients were prescribed statins at the time of discharge, and this percentage increased to 94% at 1-year follow-up.

OCT Outcomes

There were no complications attributable to OCT image acquisition including slow flow or no reflow, perforation, dissection, and embolization. The median procedure time was 58 minutes, with a median radiation exposure time of 18 minutes. Matched image pairs were identified using 7 (IQR, 5–9) reference landmarks per patient. Within the baseline OCT images, the analyzable length per patient was 51.4 (IQR, 37.2–65.5) mm, of which 33.2 (IQR, 21.6–45.3) mm corresponded to the matched regions of interest. Compared with the entire baseline OCT pullbacks, high-risk plaque phenotypes, such as TCFAs, thick-cap fibroatheromas, and mixed plaques, were more frequently observed, and fibrocalcific plaques, fibrous plaques, adaptive intimal thickening, and normal vessels were less commonly observed in baseline OCT pullbacks within the matched regions of interest (Table S4).

For the image-level analysis, the 1-year changes in plaque phenotypes within the matched regions of interest are summarized in Table 2 and Figure 2. Prevalence of each plaque phenotype per patient remained stable for 1 year (Table S5). There was a decrease in the prevalence of fibroatheromas (overall, 38% versus 36%; P<0.001; TCFAs, 3.4% versus 3.3%; P=0.82; thick-cap fibroatheromas, 35% versus 33%; P<0.001), and normal vessel (4.7% versus 3.8%, P<0.001), whereas there was an increase in the prevalence of calcified plaques (overall, 31% versus 34%; P<0.001; mixed plaques, 22% versus 24%; P<0.001;

Table 1. Baseline Characteristics Compared Between Patients With and Without Follow-Up OCT

Characteristic	Overall (N=164)	With follow-up OCT (N=128)	Without follow-up OCT (N=36)	*P* value
Patients' characteristics				
Age, y*	76 (71–81)	77 (70–81)	76 (72–83)	0.57
Men*	127 (77%)	99 (77%)	28 (78%)	1.00
Presentation				0.32
ST-segment–elevation myocardial infarction	0 (0%)	0 (0%)	0 (0%)	
Non–ST-segment–elevation myocardial infarction	15 (9.1%)	10 (7.8%)	5 (14%)	
Stable angina pectoris	149 (91%)	118 (92%)	31 (86%)	
Body mass index, kg/m^2*	24.1 (21.9–26.4)	24.1 (22.1–26.8)	23.9 (21.3–25.9)	0.77
Hyperlipidemia*	126 (77%)	100 (78%)	26 (72%)	0.50
Hypertension*	121 (74%)	95 (74%)	26 (72%)	0.83
Diabetes*	75 (46%)	59 (46%)	16 (44%)	1.00
Smoking*				0.07
None	64 (39%)	55 (43%)	9 (25%)	
Former smoker	71 (43%)	54 (42%)	17 (47%)	
Current smoker	29 (18%)	19 (15%)	10 (28%)	
Prior myocardial infarction	35 (21%)	25 (20%)	10 (28%)	0.36
Prior percutaneous coronary intervention*	70 (43%)	53 (41%)	17 (47%)	0.57
Prior stroke*	21 (13%)	18 (14%)	3 (8.3%)	0.57
Atrial fibrillation*	18 (11%)	14 (11%)	4 (11%)	1.00
Malignancy*	26 (16%)	15 (12%)	11 (31%)	0.01
Left ventricular ejection fraction, %*	62 (55–67)	62 (56–67)	61 (51–66)	0.45
Laboratory data at baseline				
Total cholesterol, mg/dL	161 (135–197)	161 (135–198)	160 (136–196)	0.75
LDL cholesterol, mg/dL	90 (69–118)	91 (68–119)	90 (73–116)	0.87
HDL cholesterol, mg/dL	47 (40–57)	46 (40–57)	50 (37–56)	0.55
Triglyceride, mg/dL	117 (80–164)	116 (79–159)	130 (84–170)	0.57
Hemoglobin A1c, %	6.1 (5.6–6.6)	6.1 (5.6–6.6)	6.1 (5.5–6.7)	0.94
Estimated glomerular filtration rate, mL/min per 1.73 m^2	77 (66–92)	76 (66–90)	80 (64–102)	0.47
Estimated glomerular filtration rate <60 mL/min per 1.73 m^2	146 (89%)	116 (91%)	30 (83%)	0.23
Procedure data				
Procedure time, min	58 (44–81)	58 (43–78)	62 (49–84)	0.30
Contrast media, mL	126 (100–160)	126 (99–160)	122 (100–175)	0.66
Radiation exposure time, min	18 (13–27)	18 (13–26)	20 (13–28)	0.52
Target vessel				
Left anterior descending coronary artery	104 (63%)	81 (63%)	23 (64%)	1.00
Left circumflex coronary artery	35 (21%)	29 (23%)	6 (17%)	0.50
Right coronary artery coronary artery	34 (21%)	25 (20%)	9 (25%)	0.49
Imaged vessel				
Left anterior descending coronary artery	57 (35%)	42 (33%)	15 (42%)	0.33
Left circumflex coronary artery	55 (34%)	46 (36%)	9 (25%)	0.24
Right coronary artery	63 (38%)	49 (38%)	14 (39%)	1.00
Imaged region in the target vessel	60 (37%)	45 (35%)	15 (42%)	0.56
Imaged region distally to the target lesion	29 (18%)	23 (18%)	6 (17%)	1.00
Medication status at discharge				
Dual antiplatelet therapy	153 (93%)	121 (95%)	32 (89%)	0.26
Aspirin	155 (95%)	122 (95%)	33 (92%)	0.41

(*Continued*)

Table 1. Continued

Characteristic	Overall (N=164)	With follow-up OCT (N=128)	Without follow-up OCT (N=36)	*P* value
P2Y12 receptor blockers	162 (99%)	127 (99%)	35 (97%)	0.39
Clopidogrel	89 (54%)	67 (52%)	22 (61%)	0.45
Prasugrel	73 (45%)	60 (47%)	13 (36%)	0.26
Oral anticoagulants	19 (12%)	14 (11%)	5 (14%)	0.57
Warfarin	5 (3.0%)	5 (3.9%)	0 (0%)	0.59
Non-vitamin K antagonist oral anticoagulants	14 (8.5%)	9 (7.0%)	5 (14%)	0.19
Statins	142 (87%)	113 (88%)	29 (81%)	0.27
Ezetimibe	36 (22%)	32 (25%)	4 (11%)	0.11
Omega-3 acid ethyl esters	16 (9.8%)	13 (10%)	3 (8.3%)	1.00
Fibrates	3 (1.8%)	2 (1.6%)	1 (2.8%)	0.53
Proprotein convertase subtilisin/kexin type 9 inhibitors	2 (1.2%)	2 (1.6%)	0 (0%)	1.00
Biguanides	14 (8.5%)	11 (8.6%)	3 (8.3%)	1.00
Sulfonylureas	10 (6.1%)	8 (6.2%)	2 (5.6%)	1.00
α-Glucosidase inhibitors	9 (5.5%)	6 (4.7%)	3 (8.3%)	0.41
Dipeptidyl peptidase-4 inhibitors	31 (19%)	24 (19%)	7 (19%)	1.00
Sodium-glucose transport protein 2 inhibitors	12 (7.3%)	11 (8.6%)	1 (2.8%)	0.47
Pioglitazone	2 (1.2%)	2 (1.6%)	0 (0%)	1.00
Insulin	4 (2.4%)	3 (2.3%)	1 (2.8%)	1.00
Calcium channel blockers	82 (50%)	68 (53%)	14 (39%)	0.19
Angiotensin-converting enzyme inhibitors	30 (18%)	23 (18%)	7 (19%)	0.81
Angiotensin receptor blockers	63 (38%)	51 (40%)	12 (33%)	0.56
Diuretics	18 (11%)	13 (10%)	5 (14%)	0.55
β-Blockers	55 (34%)	41 (32%)	14 (39%)	0.43
α1-Blockers	6 (3.7%)	6 (4.7%)	0 (0%)	0.34

Data are shown as number (percentage) or number (interquartile range). Values are missing for total cholesterol in 1 patient and for hemoglobin A1c in 1 patient. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and OCT, optical coherence tomography.

*Included as explanatory variables in the multivariable models.

and fibrocalcific plaques, 8.4% versus 9.3%; *P*<0.001). Within the matched regions of interest, lipid arc in images with TCFA significantly decreased from 186° (95% CI, 181°–190°) to 166° (95% CI, 161°–171°), with a difference of –20° (95% CI, –26° to 13°; *P*<0.001). The majority of plaque phenotypes remained stable over the course of 1 year; However, it was noteworthy that 12.7% of the thick-cap fibroatheromas transitioned to mixed plaques, whereas 6.0% of the fibrous plaques progressed to fibrocalcific plaques (Figure 2).

The coronary artery lumen area significantly decreased from 6.06 (95% CI, 5.60–6.53) mm^2 at baseline to 5.88 (95% CI, 5.41–6.35) mm^2 at the 1-year follow-up, with a difference of −0.18 (95% CI, −0.22 to −0.14 mm^2; *P*<0.001). The decrease in coronary artery lumen area varied across the baseline pathological plaque phenotypes, whereas the baseline lumen area was substantially smaller for TCFAs (4.37 [95% CI, 3.7–5.01] mm^2) compared with fibrous plaque (6.79 [95% CI, 6.20–7.39] mm^2) (Figure 3). The lumen area significantly decreased in TCFAs (−0.23 [95% CI, −0.36 to −0.10] mm^2; *P*<0.001), thick- cap fibroatheromas (−0.21 [95% CI, −0.28 to −0.14] mm^2; *P*<0.001), mixed plaques (−0.15 [95% CI, −0.22 to −0.068] mm^2; *P*<0.001), and fibrous plaques (−0.30 [95% CI, −0.37 to −0.23] mm^2; *P*<0.001). Conversely, no or marginally significant decrease was noted in fibrocalcific plaques (−0.027 [95% CI, −0.14 to 0.087] mm^2; *P*=0.64), adaptive intimal thickening (−0.086 [95% CI, −0.16 to −0.0085] mm^2; *P*=0.03), and normal vessels (0.04 [95% CI, −000027 to 0.080] mm^2; *P*=0.052).

Coronary artery calcium was present in 6704 images at the baseline and in 7337 images at the 1-year follow-up. In a subset of 5158 matched pairs wherein coronary artery calcium was present both at the baseline and 1-year follow-up, the maximum thickness of coronary artery calcium significantly increased from 605 (95% CI, 577–634) to 636 (95% CI, 607–664) μm (*P*<0.001). Additionally, the total angle of coronary calcium increased from 64.1° (95% CI, 59.5°–68.7°) to 72.1° (95% CI, 67.5°–76.6°; *P*<0.001). Consequently, the calcium area index increased from 112.5 (95% CI, 109.8–135.0) to 144.6 (95% CI, 131.9–157.1; *P*<0.001). At baseline, eruptive calcified nodules were observed

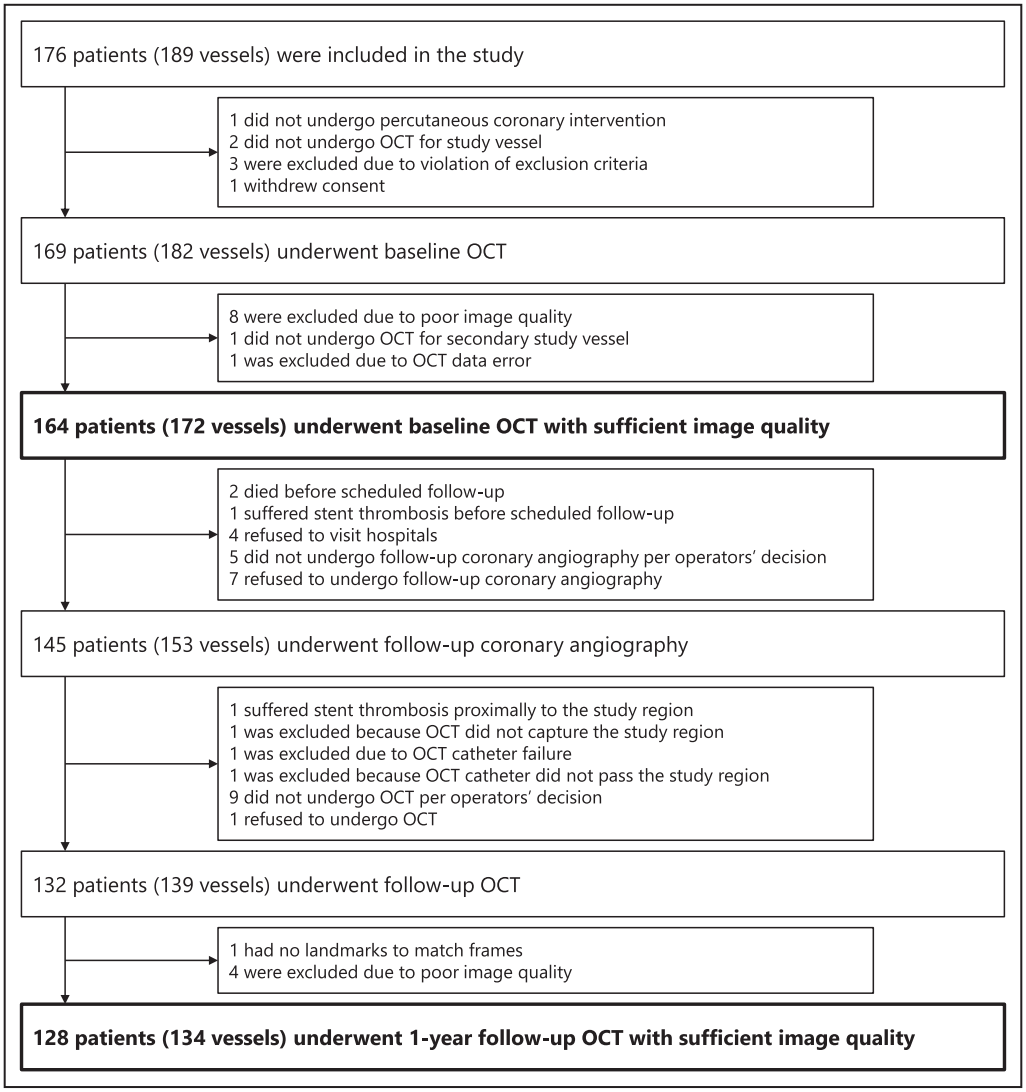


Figure 1. Study flowchart.
OCT indicates optical coherence tomography.

in 8 patients, whereas noneruptive calcified nodules were observed in 12 patients. Within the matched regions of interest, 3 patients showed eruptive calcified nodules, and 5 patients showed noneruptive calcified nodules at baseline, persisting in the same patients at the 1-year follow-up.

The results from the patient-level analysis were mostly consistent with those from the image-level analysis. Among the overall 164 patients, 53 (32.3%) had TCFAs within the baseline OCT pullbacks, whereas 41 out of 128 patients (32.0%) had TCFAs within the OCT pullbacks at 1-year follow-up (Figure S1). Within the matched regions of interest, 32 patients had TCFAs at both baseline and the 1-year follow-up, whereas 10 patients had TCFAs only at baseline and 8 patients only at the 1-year follow-up. The mean lumen area significantly decreased from 6.09 (95% CI, 5.58–6.59) to 5.90 (95% CI, 5.42–6.37) mm^2, representing a difference of −0.18 (95% CI, −0.051 to −0.33 mm^2; P=0.008). The decrease in the mean lumen area from the baseline to 1-year follow-up was significantly greater in patients with a larger mean lumen area at baseline (Figure S2). The mean calcium area index significantly increased from 43.2 (95% CI, 33.9–52.4) to 52.4 (95% CI, 41.8–63.1), with a difference of 9.2 (95% CI, 5.6–12.9; P<0.001). In both univariate and multivariable analyses, no significant associations were observed between the baseline clinical characteristics and the 1-year changes in the mean lumen area (Table 3). Conversely, the calcium area index significantly increased in patients with diabetes in the univariate analysis (estimates, 8.42 [95% CI, 1.22–15.62]; P=0.02). After adjusting for baseline characteristics, the calcium area index significantly increased in patients with diabetes (estimates, 7.47 [95% CI, 0.11–14.8]; P=0.049) and in those with a current smoking habit (estimates, 15.5 [95% CI, 3.15–27.9]; P=0.02) (Table 3).

Table 2. Number and Percentages of Images for Each Plaque Phenotype Within the Matched Regions of Interests at Baseline and at 1-Year Follow-Up

Plaque phenotype	At baseline (N=21 873)	At 1-year follow-up (N=21 873)	Odds ratio (95% CI)	*P* value
No. of patients	128			
No. of analyzable images per patient	166 (IQR, 108–226.2)			
Analyzable length per patient, mm	33.2 (IQR, 21.6–45.3)			
Fibroatheroma	8366 (38%)	7875 (36%)	0.89 (0.85–0.93)	<0.001
Thin-cap fibroatheroma	735 (3.4%)	727 (3.3%)	0.99 (0.88–1.10)	0.82
Thick-cap fibroatheroma	7631 (35%)	7148 (33%)	0.89 (0.85–0.93)	<0.001
Calcified plaque	6704 (31%)	7337 (34%)	1.19 (1.14–1.25)	<0.001
Mixed plaque	4858 (22%)	5299 (24%)	1.16 (1.10–1.22)	<0.001
Fibrocalcific plaque	1846 (8.4%)	2038 (9.3%)	1.16 (1.08–1.26)	<0.001
Fibrous plaque	4641 (21%)	4619 (21%)	0.99 (0.94–1.04)	0.78
Adaptive intimal thickening	1142 (5.2%)	1214 (5.6%)	1.08 (0.99–1.19)	0.09
Normal vessel	1020 (4.7%)	828 (3.8%)	0.74 (0.66–0.82)	<0.001

Data are shown as number (percentage). Odds ratios and their 95% CIs were calculated using generalized logistic regression models accounting for the nonindependence of assessments from the same optical coherence tomography pullbacks. IQR indicates interquartile range.

Clinical Outcomes

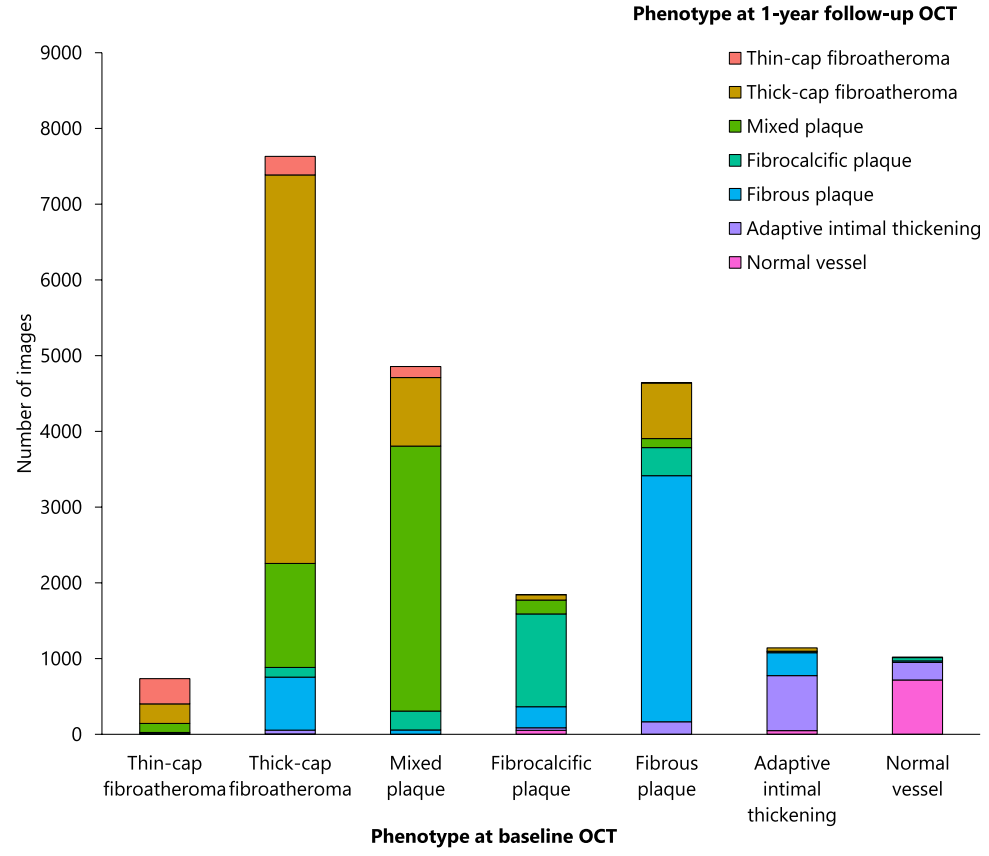
The 3-year clinical follow-up rate was 97.0%. The cumulative 3-year incidences of all-cause death, myocardial infarction, target vessel revascularization, and nontarget vessel revascularization were 1.8%, 3.1%, 6.2%, and 11.8%, respectively (Table 4). Notably, among the 10 patients who underwent imaged vessel revascularization, 8 were treated for lesions within the imaged region. All of these revascularizations were deemed ischemia driven according to the criteria (Figure S3). Of note, patients with TCFA were more likely to undergo nontarget vessel revascularization (hazard ratio [HR], 2.42 [95% CI, 1.03–5.71]; *P*=0.04), predominantly driven by a higher revascularization risk within the imaged region (HR, 15.8 [95% CI, 1.94–128]; *P*=0.01) (Figure 4 and Table 4). Similarly, the higher prevalence of fibroatheroma (either TCFA or thick-cap fibroatheroma) was associated with a numerically increased risk of imaged region revascularization (HR per 10%, 1.38 [95% CI, 0.97–1.97]; *P*=0.07) (Table 5). The percentage of coronary artery calcium and mean lumen area were not associated with clinical events within 3 years. In patients with TCFA, the minimal lumen area within the TCFA at baseline was comparable between patients with and without imaged region revascularization (Table 5 and Figure S4).

DISCUSSION

The PREDICTOR study, a multicenter prospective observational study with serial OCT assessments enrolling mostly patients with stable coronary artery disease, showed the following salient findings:

1. At 1 year after PCI, the coronary artery lumen area in nontarget regions significantly decreased from 6.06 (95% CI, 5.60–6.53) to 5.88 (95% CI, 5.41–6.35) mm^2, with a difference of −0.18 (95% CI, −0.22 to −0.14 mm^2; *P*<0.001). This decrease was pronounced in TCFAs, thick-cap fibroatheromas, mixed plaques, and fibrous plaques. Notably, patients with larger baseline lumen areas had a more significant decrease, indicating that smaller luminal areas were not necessarily indicative of propensity for further luminal narrowing.
2. The prevalence of fibroatheroma decreased from 38% to 36% (*P*<0.001), whereas that of calcified plaque increased from 31% to 34% (*P*<0.001). Patients with TCFAs had a significantly higher ischemia-driven nontarget vessel revascularization risk (HR, 2.42 [95% CI, 1.03–5.71]; *P*=0.04), primarily due to revascularization in the imaged region. The higher prevalence of fibroatheromas was associated with a numerically increased risk for imaged region revascularization (HR per 10%, 1.38 [95% CI, 0.97–1.97]; *P*=0.07).
3. Coronary artery calcium prevalence, automatically assessed using artificial intelligence technology, significantly increased from 31% at baseline to 34% at 1-year follow-up (*P*<0.001), accompanied by a significant increase in calcium thickness and angle. Diabetes and current smoking habits were independently associated with increasing calcium prevalence. No significant association was observed between the prevalence of coronary artery calcium and clinical outcomes within 3 years.

Previous OCT studies consistently demonstrated an association between the presence of TCFAs and clinical events in nontarget regions.[9–12] We reaffirm the

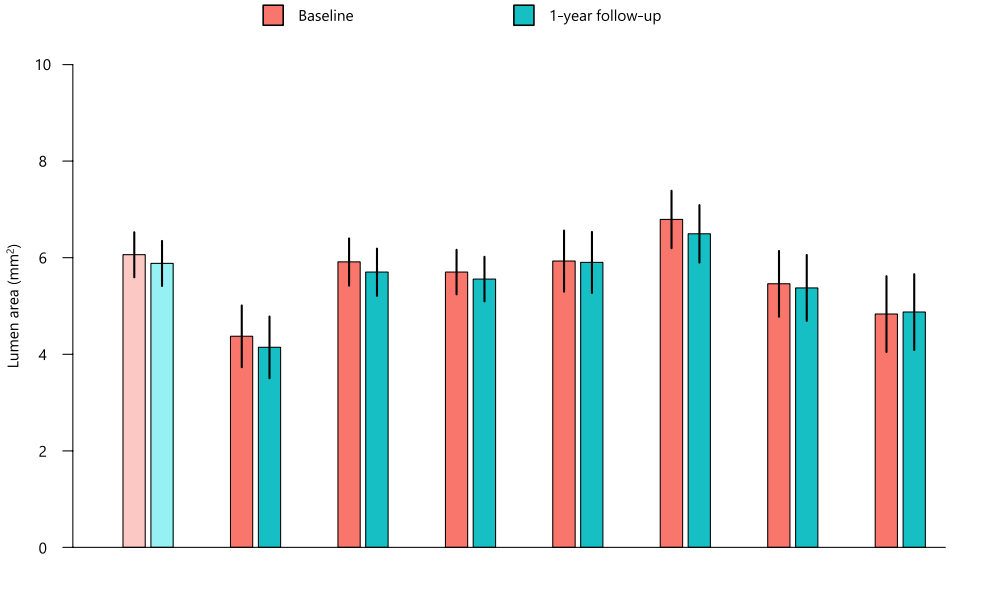


	Phenotype at baseline OCT							
	Thin-cap fibroatheroma	Thick-cap Fibroatheroma	Mixed plaque	Fibrocalcific plaque	Fibrous plaque	Adaptive Intimal Thickening	Normal Vessel	Total
Phenotype at follow-up								
Thin-cap fibroatheroma	333	258	118	7	16	3	0	735
Thick-cap fibroatheroma	245	5,129	1,374	127	699	51	6	7,631
Mixed plaque	146	905	3,500	249	57	0	1	4,858
Fibrocalcific plaque	2	70	184	1,225	277	35	53	1,846
Fibrous plaque	1	735	119	370	3,250	166	0	4,641
Adaptive intimal thickening	0	45	4	15	302	726	50	1,142
Normal vessel	0	6	0	45	18	233	718	1,020
Total	727	7,148	5,299	2,038	4,619	1,214	828	21,873

Figure 2. Image-level changes in coronary artery plaque phenotypes from baseline to 1-year follow-up.
OCT indicates optical coherence tomography.

predictive ability of the presence of TCFAs for luminal narrowing during a 1-year interval and for subsequent ischemia-driven revascularization within the imaged regions over 3 years. Although a majority of imaged region revascularization developed during the scheduled follow-up coronary angiography, we confirmed that all of these revascularizations were driven by myocardial ischemia, highlighting their clinical relevance. Furthermore, some patients experienced typical ischemic symptoms but were hesitant to seek medical attention owing to concerns about COVID-19 transmission until the 1-year scheduled follow-up.[20]

In the PROSPECT study, lesions in the nonculprit vessels, wherein >3 consecutive slices had >40% plaque burden, and those with minimal lumen areas of ≤4.0 mm^2 were identified as significant predictors for late clinical events.[4,5] Intriguingly, a significant association between the baseline mean lumen area and clinical events was not observed. Furthermore, patients with smaller baseline lumen areas exhibited even smaller luminal narrowing, suggesting that smaller luminal areas per se were not necessarily indicative of subsequent further luminal narrowing. These findings align with previous pathological studies that have shown that the



Plaque phenotypes at baseline	Overall	Thin-cap fibroatheroma	Thick-cap fibroatheroma	Mixed plaque	Fibrocalcific plaque	Fibrous plaque	Adaptive intimal thickening	Normal vessel
N of images	21,873	727	7,148	5,299	2,038	4,621	1,214	828
Baseline	6.06 (5.60 to 6.53)	4.37 (3.73 to 5.01)	5.91 (5.42 to 6.40)	5.70 (5.24 to 6.16)	5.93 (5.30 to 6.56)	6.79 (6.20 to 7.39)	5.46 (4.78 to 6.14)	4.83 (4.05 to 5.62)
1-year follow-up	5.88 (5.41 to 6.35)	4.14 (3.51 to 4.78)	5.70 (5.21 to 6.19)	5.56 (5.10 to 6.02)	5.90 (5.27 to 6.54)	6.50 (5.90 to 7.09)	5.38 (4.69 to 6.06)	4.87 (4.09 to 5.66)
Difference	-0.18 (-0.22 to -0.14), p < 0.001	-0.23 (-0.36 to -0.10), p < 0.001	-0.21 (-0.28 to -0.14), p < 0.001	-0.15 (-0.22 to -0.07), p < 0.001	-0.027 (-0.14 to 0.09), p = 0.64	-0.30 (-0.37 to -0.23), p < 0.001	-0.086 (-0.16 to -0.009), p = 0.03	0.04 (-0.0003 to 0.08), p = 0.052

Figure 3. Image-level changes in the lumen area from baseline to 1-year follow-up according to the coronary artery plaque phenotypes.
Data are shown as values (95% CIs).

majority of coronary artery events related to vulnerable plaques developed in lesions with nonsignificant stenosis.[2,3] In patients presenting with acute myocardial infarction, those with TCFAs and minimal lumen areas of <3.5 mm^2 assessed using OCT carried a higher risk of the composite of cardiac death and nonculprit lesion-related nonfatal myocardial infarction than those without (17.4% versus 3.9%, P<0.001).[12] In contrast, in our study, which predominantly included stable patients, a significant difference in minimal lumen areas within TCFA images between patients with and without subsequent clinical events was not observed. To evaluate whether smaller lumen areas are a precursor to late clinical events in low-risk stable patients, larger observational studies with longer follow-up duration are needed.

In the prospective IBIS-4 (Integrated Biomarker Imaging Study-4), patients with ST-segment–elevation myocardial infarction who received statin therapy exhibited a noticeable increase in the percentage of fibrocalcific plaques from 49.7% to 54.5% over 1 year.[21] Another retrospective observational study underlined the independent associations of diabetes and chronic renal failure with rapid coronary artery calcification progression.[22] In our study using artificial intelligence-derived assessments for coronary artery calcium, we observed a significant increase in coronary artery calcium prevalence in stable patients without chronic renal failure. Notably, this increase was particularly pronounced in patients with diabetes and those with a current smoking habit. We observed that thick-cap fibroatheromas were the primary sources of increasing coronary artery calcium prevalence, indicating the transition of lipid-rich regions into calcified regions even within a short-term period of 1 year. The serial intravascular ultrasound analysis of coronary atheroma demonstrates that, despite the association with plaque regression, statins possessed procalcific effects.[23] Recent randomized trials evaluating the impact of PCSK9is (proprotein convertase subtilisin/kexin type 9 inhibitors) on fibroatheroma stabilization demonstrated that patients treated with PCSK9is showed a

Table 3. Univariate and Multivariable Analyses for the Association of Clinical Characteristics With Changes in the Lumen Area and Calcium Area Index

	Lumen area (mm^2)				Calcium area index*			
	Univariate		Multivariable		Univariate		Multivariable	
Characteristic	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Age, 10 y	0.038 (−0.10 to 0.18)	0.59	0.081 (−0.092 to 0.25)	0.36	3.52 (−0.096 to 7.13)	0.06	1.45 (−2.93 to 5.84)	0.52
Men	−0.32 (−0.65 to 0.0044)	0.06	−0.34 (−0.76 to 0.075)	0.11	−5.90 (−14.60 to 2.79)	0.19	−7.79 (−18.41 to 2.83)	0.15
Body mass index, kg/m^2	0.015 (−0.018 to 0.048)	0.38	0.027 (−0.011 to 0.066)	0.16	−0.58 (−1.46 to 0.30)	0.20	−0.62 (−1.60 to 0.35)	0.21
Hyperlipidemia	0.12 (−0.22 to 0.45)	0.49	0.14 (−0.22 to 0.51)	0.45	−3.36 (−12.21 to 5.49)	0.46	−4.02 (−13.25 to 5.21)	0.40
Hypertension	0.19 (−0.12 to 0.51)	0.23	0.15 (−0.18 to 0.47)	0.37	6.87 (−1.42 to 15.16)	0.11	5.22 (−3.01 to 13.44)	0.22
Diabetes	0.056 (−0.22 to 0.33)	0.69	−0.033 (−0.32 to 0.26)	0.83	8.42 (1.22 to 15.62)	0.02	7.47 (0.11 to 14.84)	0.049
Smoking								
None	Reference		Reference		Reference		Reference	
Former smoker	−0.13 (−0.43 to 0.17)	0.39	0.048 (−0.31 to 0.41)	0.80	−0.057 (−7.90 to 7.79)	0.99	4.63 (−4.58 to 13.84)	0.33
Current smoker	0.095 (−0.32 to 0.51)	0.65	0.25 (−0.24 to 0.73)	0.32	10.47 (−0.43 to 21.37)	0.06	15.52 (3.15 to 27.90)	0.02
Prior percutaneous coronary intervention	0.081 (−0.20 to 0.36)	0.57	0.052 (−0.24 to 0.35)	0.73	0.075 (−7.37 to 7.52)	0.98	0.85 (−6.66 to 8.36)	0.83
Prior stroke	−0.10 (−0.50 to 0.30)	0.62	−0.11 (−0.55 to 0.33)	0.62	−0.49 (−11.03 to 10.05)	0.93	−1.00 (−12.06 to 10.06)	0.86
Atrial fibrillation	−0.20 (−0.64 to 0.24)	0.38	−0.24 (−0.71 to 0.23)	0.32	2.39 (−9.34 to 14.13)	0.69	4.85 (−7.11 to 16.81)	0.43
Malignancy	−0.064 (−0.49 to 0.36)	0.77	−0.079 (−0.55 to 0.39)	0.74	6.87 (−4.46 to 18.20)	0.24	5.46 (−6.41 to 17.32)	0.37
Left ventricular ejection fraction, 10%	0.087 (−0.066 to 0.24)	0.27	0.057 (−0.11 to 0.22)	0.50	2.86 (−1.20 to 6.91)	0.17	2.07 (−2.10 to 6.23)	0.33

*Calcium area index was calculated as the maximum calcium thickness (micrometers) multiplied by the total calcium angle (degrees) and divided by 360°. Maximum calcium thickness and total calcium angle were considered 0 in cases wherein coronary artery calcium was not detected.

Table 4. Clinical Outcomes Between Patients With and Without TCFA Within the Baseline Optical Coherence Tomography Pullbacks

Outcome	One year			Two years			Three years			Hazard ratio (95% CI)	*P* value
	Overall (N=164)	With TCFA (N=53)	Without TCFA (N=111)	Overall (N=164)	With TCFA (N=53)	Without TCFA (N=111)	Overall (N=164)	With TCFA (N=53)	Without TCFA (N=111)		
All-cause death	2 (1.2%)	1 (1.9%)	1 (0.9%)	3 (1.8%)	1 (1.9%)	2 (1.8%)	3 (1.8%)	1 (1.9%)	2 (1.8%)	1.03 (0.094–11.41)	0.98
Cardiovascular death	2 (1.2%)	1 (1.9%)	1 (0.9%)	3 (1.8%)	1 (1.9%)	2 (1.8%)	3 (1.8%)	1 (1.9%)	2 (1.8%)	1.03 (0.094–11.41)	0.98
Sudden death	2 (1.2%)	1 (1.9%)	1 (0.9%)	3 (1.8%)	1 (1.9%)	2 (1.8%)	3 (1.8%)	1 (1.9%)	2 (1.8%)	1.03 (0.094–11.41)	0.98
Noncardiovascular death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA	
Myocardial infarction	3 (1.8%)	0 (0%)	3 (2.7%)	3 (1.8%)	0 (0%)	3 (2.7%)	5 (3.1%)	2 (3.8%)	3 (2.7%)	1.36 (0.23–8.14)	0.74
Any coronary intervention	10 (6.1%)	4 (7.6%)	6 (5.4%)	26 (16.1%)	11 (21.1%)	15 (13.7%)	29 (18.0%)	13 (24.9%)	16 (14.7%)	1.80 (0.89–3.65)	0.10
Target vessel revascularization	5 (3.1%)	2 (3.8%)	3 (2.7%)	10 (6.2%)	3 (5.7%)	7 (6.4%)	10 (6.2%)	3 (5.7%)	7 (6.4%)	0.89 (0.23–3.45)	0.87
Target lesion revascularization	4 (2.5%)	1 (1.9%)	3 (2.7%)	9 (5.6%)	2 (3.8%)	7 (6.4%)	9 (5.6%)	2 (3.8%)	7 (6.4%)	0.59 (0.12–2.83)	0.51
Nontarget vessel revascularization	5 (3.1%)	2 (3.8%)	3 (2.7%)	16 (9.9%)	8 (15.3%)	8 (7.3%)	19 (11.8%)	10 (19.2%)	9 (8.3%)	2.42 (1.03–5.71)	0.04
Imaged vessel revascularization	3 (1.8%)	2 (3.8%)	1 (0.9%)	9 (5.6%)	7 (13.4%)	2 (1.8%)	9 (5.6%)	7 (13.4%)	2 (1.8%)	5.16 (1.33–20.0)	0.02
Imaged region revascularization	2 (1.2%)	2 (3.8%)	0 (0%)	7 (4.3%)	7 (13.4%)	0 (0%)	7 (4.3%)	7 (13.4%)	0 (0%)	15.8 (1.94–128.1)	0.01

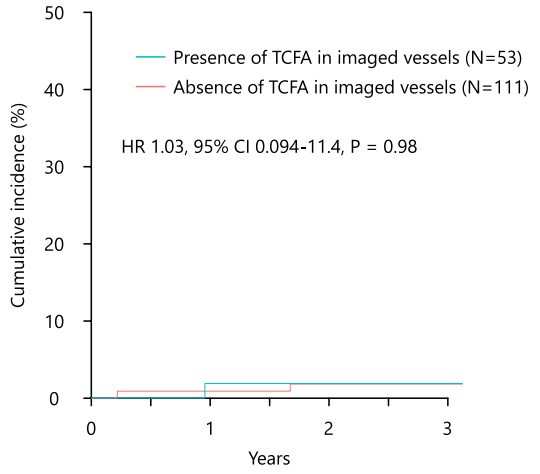
Data are shown as number of events (cumulative incidence). NA indicates not applicable; and TCFA, thin-cap fibroatheroma.

significantly greater increase in minimal fibrous cap thickness and reductions in percent atheroma volume than those without.[24–26] In our study, the lumen area was stable in regions with coronary artery calcium, whereas no significant associations were observed between calcium prevalence and imaged region-related events within 3 years. Fibroatheroma stabilization into coronary artery calcium may explain the reduced risk of clinical events following lipid-lowering therapy. Nevertheless, further longer-term study is warranted to evaluate the impact of the increase in coronary artery calcium prevalence on long-term clinical outcomes beyond 3 years.

Limitations

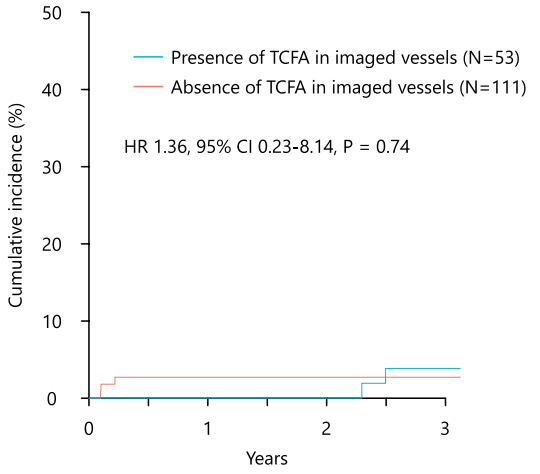
This study had a relatively small sample size, which could limit the generalizability of the findings to a broader population of patients with coronary artery disease. The follow-up duration was limited to 1 year for OCT assessments, which may not capture longer-term changes in plaque characteristics or clinical outcomes. Patient characteristics, such as the high prevalence of diabetes, might be different from those outside the Japanese population, but they were aligning with those observed in the contemporary Japanese nationwide registry.[27] Notably, our study revealed that 45% of patients, predominantly with stable coronary artery disease, were prescribed potent P2Y12 inhibitors. In the latest data sets from the J-PCI registry, potent P2Y12 inhibitors were prescribed in 56.9% of patients with stable coronary artery disease and in 74.6% of patients with acute coronary artery disease treated in 2022. This rate is comparable with the Japanese nationwide registry but higher than reported rates in other countries. It is important to acknowledge that it may not fully represent the diversity of patients with coronary artery disease, particularly those outside the Japanese population. Additionally, although the study protocol did not explicitly exclude patients with acute coronary syndrome including ST-segment–elevation myocardial infarction, their absence in the enrollment implies the possibility of selection bias. Follow-up OCT was performed only in 76.6% of the patients, partly because some of them were reluctant to undergo follow-up OCT during the COVID-19 pandemic.[20] The exclusion of those patients could introduce selection bias, despite there were no significant differences in patients' characteristics except for the prevalence of malignancy between patients with and without OCT follow-up. In our study, we noted a significant decrease in lumen area over a 1-year interval; however, it remains uncertain whether this reduction is attributable to de novo plaque progression or negative remodeling. Although we sought to identify matched image pairs using as many landmarks as possible, variations in longitudinal

A All-cause death



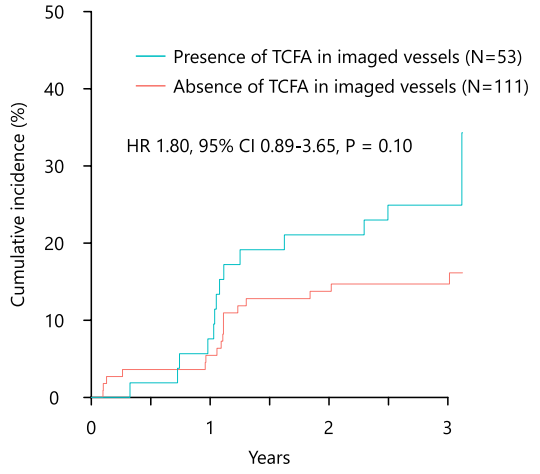
	0	1 year	2 years	3 years	
Presence of TCFA in imaged vessels	0	1	1	1	N of patients with event
	0%	1.9%	1.9%	1.9%	Cumulative incidence
	53	52	52	32	N of patients at risk
Absence of TCFA in imaged vessels	0	1	2	2	N of patients with event
	0%	0.9%	1.8%	1.8%	Cumulative incidence
	111	109	106	75	N of patients at risk

B Myocardial infarction



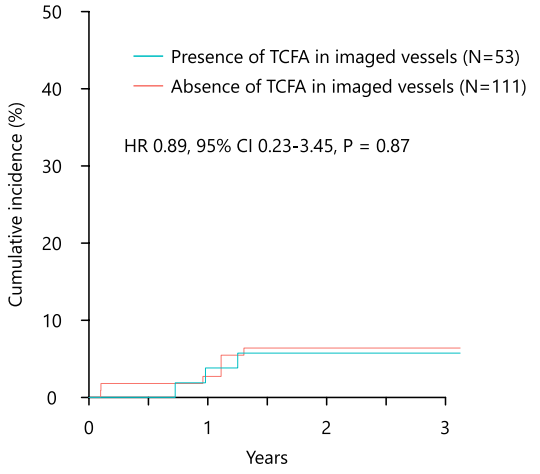
	0	1 year	2 years	3 years	
Presence of TCFA in imaged vessels	0	0	0	2	N of patients with event
	0%	0%	0%	3.8%	Cumulative incidence
	53	52	52	30	N of patients at risk
Absence of TCFA in imaged vessels	0	3	3	3	N of patients with event
	0%	2.7%	2.7%	2.7%	Cumulative incidence
	111	107	104	74	N of patients at risk

C Any coronary artery revascularization



	0	1 year	2 years	3 years	
Presence of TCFA in imaged vessels	0	4	11	13	N of patients with event
	0%	7.6%	21.1%	24.9%	Cumulative incidence
	53	48	41	24	N of patients at risk
Absence of TCFA in imaged vessels	0	6	15	16	N of patients with event
	0%	5.4%	13.7%	14.7%	Cumulative incidence
	111	103	91	63	N of patients at risk

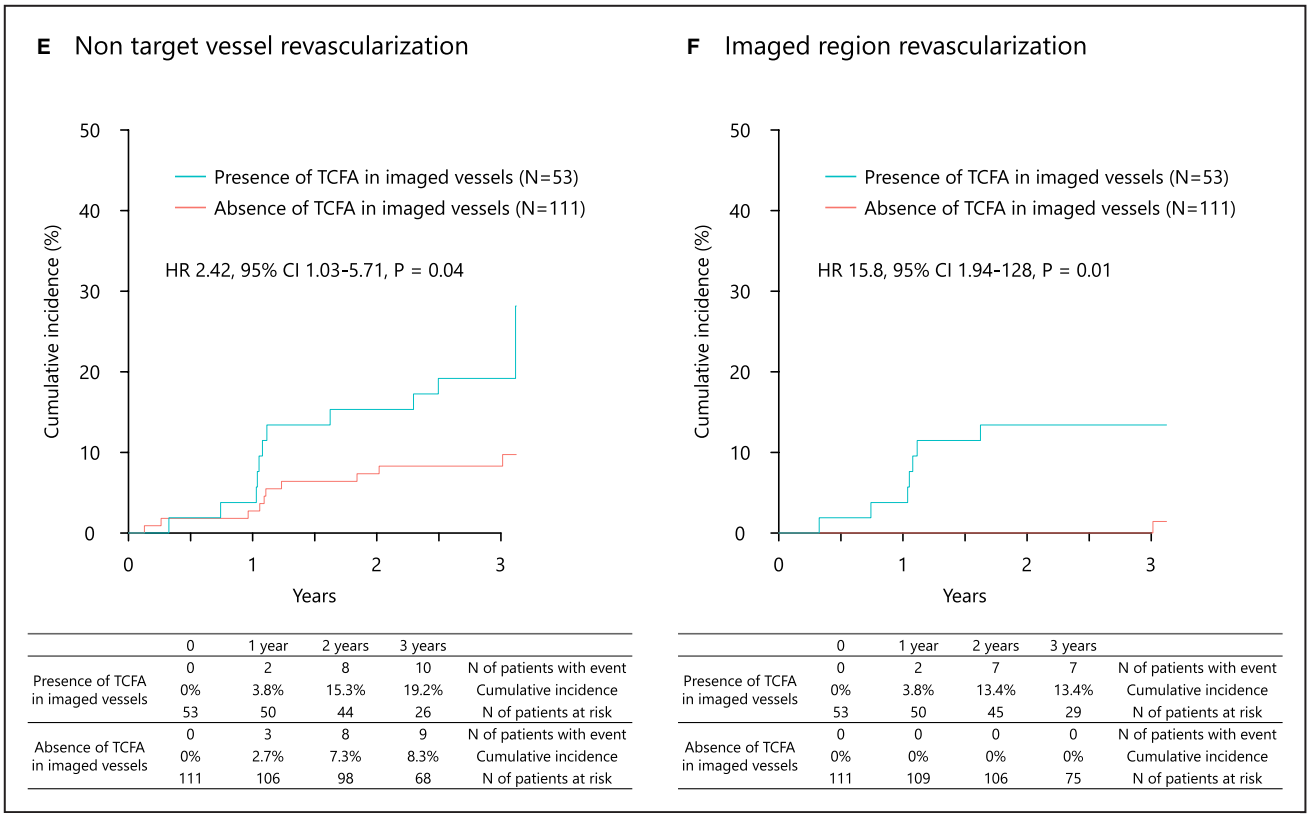
D Target vessel revascularization



	0	1 year	2 years	3 years	
Presence of TCFA in imaged vessels	0	2	3	3	N of patients with event
	0%	3.8%	5.7%	5.7%	Cumulative incidence
	53	50	49	30	N of patients at risk
Absence of TCFA in imaged vessels	0	3	7	7	N of patients with event
	0%	2.7%	6.4%	6.4%	Cumulative incidence
	111	106	99	70	N of patients at risk

Figure 4. Kaplan-Meier curves for clinical outcomes compared between patients with and without TCFA in the imaged vessels.

Clinical outcomes included (**A**) all-cause death, (**B**) myocardial infarction, (**C**) any coronary revascularization, (**D**) target vessel revascularization, (**E**) nontarget vessel revascularization, and (**F**) imaged region revascularization. Target vessel revascularization refers to the revascularizations performed in the coronary vessels treated during the baseline procedure. Nontarget vessel revascularization refers to the revascularizations performed in the nonintervened vessels. Imaged region revascularization refers to the revascularizations of lesions located within the regions of interest in the baseline OCT pullbacks. HR indicates hazard ratio; OCT, optical coherence tomography; and TCFA, thin-cap fibroatheroma.



	0	1 year	2 years	3 years	
Presence of TCFA in imaged vessels	0	2	8	10	N of patients with event
	0%	3.8%	15.3%	19.2%	Cumulative incidence
	53	50	44	26	N of patients at risk
Absence of TCFA in imaged vessels	0	3	8	9	N of patients with event
	0%	2.7%	7.3%	8.3%	Cumulative incidence
	111	106	98	68	N of patients at risk

	0	1 year	2 years	3 years	
Presence of TCFA in imaged vessels	0	2	7	7	N of patients with event
	0%	3.8%	13.4%	13.4%	Cumulative incidence
	53	50	45	29	N of patients at risk
Absence of TCFA in imaged vessels	0	0	0	0	N of patients with event
	0%	0%	0%	0%	Cumulative incidence
	111	109	106	75	N of patients at risk

Figure 4. Continued

positioning between baseline and follow-up might exist. Additionally, the wire position, leading to wire artifacts, could be different in the baseline and follow-up assessments. In our study, coronary artery calcium was automatically assessed using artificial intelligence technology, whereas the evaluation of fibroatheroma

Table 5. Association of Per Patient Optical Coherence Tomography Findings With Clinical Outcomes

	Increase in fibroatheroma, 10%		Increase in calcium, 10%		Increase in mean lumen area, 1 mm^2		Increase in minimal lumen area among TCFA images, 1 mm^2*	
Outcome	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause death	1.16 (0.64–2.10)	0.63	0.98 (0.59–1.63)	0.93	0.76 (0.44–1.32)	0.33	1.11 (0.40–3.10)	0.84
Cardiovascular death	1.16 (0.64–2.10)	0.63	0.98 (0.59–1.63)	0.93	0.76 (0.44–1.32)	0.33	1.11 (0.40–3.10)	0.84
Sudden death	1.16 (0.64–2.10)	0.63	0.98 (0.59–1.63)	0.93	0.76 (0.44–1.32)	0.33	1.11 (0.40–3.10)	0.84
Noncardiovascular death	NA		NA		NA		NA	
Myocardial infarction	1.07 (0.67–1.70)	0.78	1.17 (0.83–1.66)	0.36	1.01 (0.73–1.39)	0.96	1.24 (0.63–2.41)	0.54
Any coronary intervention	1.09 (0.91–1.32)	0.34	1.05 (0.91–1.22)	0.50	1.01 (0.89–1.15)	0.85	1.11 (0.83–1.48)	0.49
Target vessel revascularization	0.93 (0.66–1.30)	0.66	1.18 (0.92–1.50)	0.19	0.97 (0.77–1.22)	0.80	1.05 (0.57–1.94)	0.88
Target lesion revascularization	0.92 (0.64–1.32)	0.64	1.11 (0.85–1.45)	0.43	0.98 (0.77–1.25)	0.85	1.14 (0.56–2.32)	0.71
Nontarget vessel revascularization	1.18 (0.95–1.48)	0.14	0.98 (0.82–1.19)	0.87	1.03 (0.89–1.20)	0.66	1.11 (0.80–1.55)	0.53
Imaged vessel revascularization	1.31 (0.96–1.80)	0.09	0.95 (0.71–1.26)	0.70	0.98 (0.78–1.23)	0.86	1.21 (0.82–1.79)	0.35
Imaged region revascularization	1.38 (0.97–1.97)	0.07	0.83 (0.58–1.20)	0.32	1.01 (0.79–1.29)	0.94	1.21 (0.82–1.79)	0.35

HR indicates hazard ratio; NA, not applicable; and TCFA, thin-cap fibroatheroma.
*Models are constructed using data from 53 patients with TCFA.

was conducted manually in the core laboratory. It is important to highlight that interobserver variability was not negligible in the assessment of TCFA and thick-cap fibroatheroma, even within established core laboratories.[28] Advancements in artificial intelligence technology are necessary to minimize variability in the identification of high-risk plaque phenotypes.[29–31] Although we identified independent predictors for increasing coronary artery calcium prevalence, the underlying mechanisms driving this increase were not thoroughly explored.

CONCLUSIONS

The coronary artery lumen area significantly decreased over a 1-year interval, particularly in TCFAs, thick-cap fibroatheromas, mixed plaques, and fibrous plaques, whereas the baseline lumen area was substantially smaller for TCFA. The presence of TCFAs was associated with a significantly higher risk of clinical events in patients mostly presenting with stable coronary artery disease. Although no significant association was noted between coronary artery calcium prevalence and clinical outcomes within 3 years, the interaction between calcium progression and long-term clinical events required further investigation.

ARTICLE INFORMATION

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Supplemental Material

PREDICTOR Investigators
Data S1
Tables S1–S5
Figures S1–S4

REFERENCES

1. Yamaji K, Shiomi H, Morimoto T, Toyota T, Ono K, Furukawa Y, Nakagawa Y, Kadota K, Ando K, Shirai S, et al. Influence of sex on long-term outcomes after implantation of bare-metal stent: a multicenter report from the coronary revascularization demonstrating outcome study-Kyoto (CREDO-Kyoto) registry Cohort-1. *Circulation*. 2015;132:2323–2333. doi: 10.1161/CIRCULATIONAHA.115.017168
2. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med*. 1997;336:1276–1282. doi: 10.1056/NEJM199705013361802
3. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13–C18. doi: 10.1016/j.jacc.2005.10.065
4. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med*. 2011;364:226–235. doi: 10.1056/NEJMoa1002358
5. Maehara A, Cristea E, Mintz GS, Lansky AJ, Dressler O, Biro S, Templin B, Virmani R, de Bruyne B, Serruys PW, et al. Definitions and methodology for the grayscale and radiofrequency intravascular ultrasound and coronary angiographic analyses. *JACC Cardiovasc Imaging*. 2012;5:S1–S9. doi: 10.1016/j.jcmg.2011.11.019
6. Waksman R, Di Mario C, Torguson R, Ali ZA, Singh V, Skinner WH, Artis AK, Cate TT, Powers E, Kim C, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet*. 2019;394:1629–1637. doi: 10.1016/S0140-6736(19)31794-5
7. Erlinge D, Maehara A, Ben-Yehuda O, Botker HE, Maeng M, Kjoller-Hansen L, Engstrom T, Matsumura M, Crowley A, Dressler O, et al. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet*. 2021;397:985–995. doi: 10.1016/S0140-6736(21)00249-X
8. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y, Marco V, Boi A, Fineschi M, Fabbiocchi F, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J*. 2020;41:383–391. doi: 10.1093/eurheartj/ehz520
9. Xing L, Higuma T, Wang Z, Aguirre AD, Mizuno K, Takano M, Dauerman HL, Park SJ, Jang Y, Kim CJ, et al. Clinical significance of lipid-rich plaque detected by optical coherence tomography: a 4-year follow-up study. *J Am Coll Cardiol*. 2017;69:2502–2513. doi: 10.1016/j.jacc.2017.03.556
10. Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, IJsselmuiden AJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J*. 2021;42:4671–4679. doi: 10.1093/eurheartj/ehab433
11. Fabris E, Berta B, Roleder T, Hermanides RS, IJsselmuiden AJ, Kauer F, Alfonso F, von Birgelen C, Escaned J, Camaro C, et al. Thin-cap

Fibroatheroma rather than any lipid plaques increases the risk of cardiovascular events in diabetic patients: insights from the COMBINE OCT-FFR trial. *Circ Cardiovasc Interv*. 2022;15:e011728. doi: 10.1161/CIRCINTERVENTIONS.121.011728
12. Jiang S, Fang C, Xu X, Xing L, Sun S, Peng C, Yin Y, Lei F, Wang Y, Li L, et al. Identification of high-risk coronary lesions by 3-vessel optical coherence tomography. *J Am Coll Cardiol*. 2023;81:1217–1230. doi: 10.1016/j.jacc.2023.01.030
13. Kobayashi N, Shibata Y, Okazaki H, Shirakabe A, Takano M, Miyauchi Y, Asai K, Shimizu W. A novel technique of low molecular weight dextran infusion followed by catheter push (D-PUSH) for optical coherence tomography. *EuroIntervention*. 2021;17:e149–e151. doi: 10.4244/EIJ-D-20-00996
14. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, Bouma B, Bruining N, Cho JM, Chowdhary S, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the international working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol*. 2012;59:1058–1072. doi: 10.1016/j.jacc.2011.09.079
15. Accessed October 30, 2023. https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210458.pdf
16. Prati F, Gatto L, Fabbiocchi F, Vergallo R, Paoletti G, Ruscica G, Marco V, Romagnoli E, Boi A, Fineschi M, et al. Clinical outcomes of calcified nodules detected by optical coherence tomography: a sub-analysis of the CLIMA study. *EuroIntervention*. 2020;16:380–386. doi: 10.4244/EIJ-D-19-01120
17. Sato T, Matsumura M, Yamamoto K, Shlofmitz E, Moses JW, Khalique OK, Thomas SV, Tsoulios A, Cohen DJ, Mintz GS, et al. Impact of eruptive vs noneruptive calcified nodule morphology on acute and long-term outcomes after stenting. *JACC Cardiovasc Interv*. 2023;16:1024–1035. doi: 10.1016/j.jcin.2023.03.009
18. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Executive group on behalf of the joint European Society of Cardiology/American College of Cardiology/American Heart Association/world heart federation task force for the universal definition of myocardial I. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e618–e651. doi: 10.1161/CIR.0000000000000617
19. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al. Standardized end point definitions for coronary intervention trials: the academic research Consortium-2 consensus document. *Circulation*. 2018;137:2635–2650. doi: 10.1161/CIRCULATIONAHA.117.029289
20. Yamaji K, Kohsaka S, Inohara T, Numasawa Y, Ando H, Wada H, Ishii H, Amano T, Miyata H, Ikari Y, et al. Percutaneous coronary intervention during the COVID-19 pandemic in Japan: insights from the nationwide registration data. *Lancet Reg Health West Pac*. 2022;22:100434. doi: 10.1016/j.lanwpc.2022.100434
21. Raber L, Koskinas KC, Yamaji K, Taniwaki M, Roffi M, Holmvang L, Garcia Garcia HM, Zanchin T, Maldonado R, Moschovitis A, et al. Changes in coronary plaque composition in patients with acute myocardial infarction treated with high-intensity statin therapy (IBIS-4): a serial optical coherence tomography study. *JACC Cardiovasc Imaging*. 2019;12:1518–1528. doi: 10.1016/j.jcmg.2018.08.024
22. Nakajima A, Araki M, Kurihara O, Minami Y, Soeda T, Yonetsu T, Higuma T, Kakuta T, McNulty I, Lee H, et al. Predictors for rapid progression of coronary calcification: an optical coherence tomography study. *J Am Heart Assoc*. 2021;10:e019235. doi: 10.1161/JAHA.120.019235
23. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, Tuzcu EM, Nissen SE. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol*. 2015;65:1273–1282. doi: 10.1016/j.jacc.2015.01.036
24. Raber L, Ueki Y, Otsuka T, Losdat S, Haner JD, Lonborg J, Fahrni G, Iglesias JF, van Geuns RJ, Ondracek AS, et al. Effect of Alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA*. 2022;327:1771–1781. doi: 10.1001/jama.2022.5218
25. Biccire FG, Haner J, Losdat S, Ueki Y, Shibutani H, Otsuka T, Kakizaki R, Hofbauer TM, van Geuns RJ, Stortecky S, et al. Concomitant coronary atheroma regression and stabilization in response to lipid-lowering therapy. *J Am Coll Cardiol*. 2023;82:1737–1747. doi: 10.1016/j.jacc.2023.08.019
26. Nicholls SJ, Kataoka Y, Nissen SE, Prati F, Windecker S, Puri R, Hucko T, Aradi D, Herrman JR, Hermanides RS, et al. Effect of evolocumab on coronary plaque phenotype and burden in statin-treated patients following myocardial infarction. *JACC Cardiovasc Imaging*. 2022;15:1308–1321. doi: 10.1016/j.jcmg.2022.03.002
27. Ando H, Yamaji K, Kohsaka S, Ishii H, Wada H, Yamada S, Sawano M, Inohara T, Numasawa Y, Ikari Y, et al. Japanese Nationwide PCI (J-PCI) registry annual report 2019: patient demographics and in-hospital outcomes. *Cardiovasc Interv Ther*. 2022;37:243–247. doi: 10.1007/s12928-021-00832-0
28. Gruslova AB, Singh S, Hoyt T, Vela D, Vengrenyuk Y, Buja LM, Litovsky S, Michalek J, Maehara A, Kini A, et al. Accuracy of OCT Core labs in identifying vulnerable plaque. *JACC Cardiovasc Imaging*. 2023;17:448–450. doi: 10.1016/j.jcmg.2023.10.005
29. Chu M, Jia H, Gutierrez-Chico JL, Maehara A, Ali ZA, Zeng X, He L, Zhao C, Matsumura M, Wu P, et al. Artificial intelligence and optical coherence tomography for the automatic characterisation of human atherosclerotic plaques. *EuroIntervention*. 2021;17:41–50. doi: 10.4244/EIJ-D-20-01355
30. Shibutani H, Fujii K, Ueda D, Kawakami R, Imanaka T, Kawai K, Matsumura K, Hashimoto K, Yamamoto A, Hao H, et al. Automated classification of coronary atherosclerotic plaque in optical frequency domain imaging based on deep learning. *Atherosclerosis*. 2021;328:100–105. doi: 10.1016/j.atherosclerosis.2021.06.003
31. Niioka H, Kume T, Kubo T, Soeda T, Watanabe M, Yamada R, Sakata Y, Miyamoto Y, Wang B, Nagahara H, et al. Automated diagnosis of optical coherence tomography imaging on plaque vulnerability and its relation to clinical outcomes in coronary artery disease. *Sci Rep*. 2022;12:14067. doi: 10.1038/s41598-022-18473-5