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ORIGINAL ARTICLE

FFR-Negative Nonculprit High-Risk Plaques and Clinical Outcomes in High-Risk Populations: An Individual Patient-Data Pooled Analysis From COMBINE (OCT-FFR) and PECTUS-obs

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BACKGROUND: Despite fractional flow reserve (FFR)–guided deferral of revascularization, recurrent events in patients with diabetes or after myocardial infarction remain common. This study aimed to assess the association between FFR-negative but high-risk nonculprit lesions and clinical outcomes.

METHODS: This is a patient-level pooled analysis of the prospective natural-history COMBINE (OCT-FFR) study (Optical Coherence Tomography Morphologic and Fractional Flow Reserve Assessment in Diabetes Mellitus Patients) and PECTUS-obs study (Identification of Risk Factors for Acute Coronary Events by OCT After STEMI and NSTEMI Patients With Residual Non- Flow Limiting Lesions). Optical coherence tomography was performed on all FFR-negative (FFR >0.80) native nonculprit lesions. Patients or lesions with a high-risk plaque were compared with those without a high-risk plaque. A high-risk plaque was defined in the presence of at least 2 prespecified criteria: (1) lipid arc ≥90°, (2) minimum fibrous cap thickness <65 µm, and (3) presence of either plaque rupture or thrombus. The primary end points were native major adverse cardiovascular events (composite of all-cause mortality, nonfatal myocardial infarction, or unplanned revascularization excluding stent-failure–related events and nonattributable events) and target lesion failure (composite of cardiac death, target vessel myocardial infarction, or target lesion revascularization).

RESULTS: Among 810 patients, 450 (55.6%) had a history of diabetes and 482 (59.5%) presented with myocardial infarction. At least 1 high-risk plaque was identified in 271 (33.5%) patients and 287 (30.6%) lesions. Over a median follow-up of 761 (interquartile range, 731–1175) days, the presence of a high-risk plaque was associated with patient-level native major adverse cardiovascular events (hazard ratio, 2.127 [95% CI, 1.451–3.120]; $P<0.001$) and lesion-level target lesion failure (hazard ratio, 2.623 [95% CI, 1.559–4.414]; $P<0.001$). The risk of adverse outcomes increased with the copresence of multiple high-risk features.

CONCLUSIONS: FFR-negative but high-risk nonculprit lesions are associated with adverse patient- and lesion-level clinical outcomes. These findings emphasize the additional value of intracoronary imaging in patients with FFR-negative nonculprit lesions.

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Key Words: acute coronary syndrome ■ atherosclerosis ■ fractional flow reserve, myocardial ■ myocardial infarction ■ plaque, atherosclerotic

WHAT IS KNOWN

- Fractional flow reserve–guided deferral of revascularization yields less optimal results in patients with diabetes and after myocardial infarction.
- High-risk plaques may be related to this residual risk.

WHAT THE STUDY ADDS

- High-risk plaques in such fractional flow reserve-negative lesions are associated with both patient- and lesion-level adverse outcomes.
- Incremental risk is observed in the copresence of multiple high-risk plaque criteria, thereby increasing the positive predictive value.

Nonstandard Abbreviations and Acronyms

aTLF	attributable target lesion failure
FFR	fractional flow reserve
HR	hazard ratio
MACE	major adverse cardiovascular event
MI	myocardial infarction
OCT	optical coherence tomography
TCFA	thin-cap fibroatheroma
TLF	target lesion failure

Fractional flow reserve (FFR) is well established to evaluate ischemia and guide revascularization indications in the overall population with chronic coronary syndrome.[1,2] However, its effectiveness in specific populations and acute coronary syndrome has been questioned. Among patients with diabetes, FFR-guided deferral results in an up to 2-fold increased risk of adverse cardiovascular events including cardiac death compared with deferral in patients without diabetes.[3,4] Likewise, the incidence of major adverse cardiovascular events (MACE) after FFR-guided deferral in acute coronary syndrome exceeds the incidence in chronic coronary syndrome.[5] Moreover, the FLOWER-MI trial (Flow Evaluation to Guide Revascularization in Multi-Vessel ST-Elevation Myocardial Infarction) failed to demonstrate the superiority of an FFR-guided revascularization approach compared with an angiography-guided treatment strategy in patients with ST-segment–elevation myocardial infarction (MI) and multivessel disease.[6]

It has been postulated that the observed residual risk despite the absence of hemodynamically significant flow limitations may be related to the presence of atherosclerotic plaques that are prone to rupture, so-called vulnerable or high-risk plaques. Among these are thin-cap fibroatheromas (TCFA) that are characterized by a large lipid pool with an intact but thin overlying fibrous cap (originally defined as <65 µm). This high-risk plaque hypothesis,[7] which stresses the importance of also addressing nonobstructive lesions, was initiated by histopathologic studies in which it was demonstrated that almost all ruptured coronary plaques had a thin fibrous cap infiltrated by macrophages[8] and that coronary lesions often display positive remodeling before compromising the coronary lumen.[9] It has been postulated that high-risk plaques also implicate a more general vulnerability throughout the coronary tree.[7]

Recent advances in imaging technologies allow in vivo assessment of high-risk plaques, and multiple natural-history studies have demonstrated an association between such plaques and adverse clinical outcomes.[10–16] To date, only 2 prospective studies assessed this association in the confirmed absence of flow limitation. The COMBINE (OCT-FFR) study (Optical Coherence Tomography Morphologic and Fractional Flow Reserve Assessment in Diabetes Mellitus Patients) demonstrated a 5-fold increased risk of adverse clinical outcomes in patients with diabetes in the presence of an optical coherence tomography (OCT)-identified high-risk deferred lesion.[15] Similarly, high-risk nonculprit plaques were associated with a 2-fold increased risk of adverse clinical outcomes in patients with MI in the PECTUS-obs study (Identification of Risk Factors for Acute Coronary Events by OCT After STEMI and NSTEMI Patients With Residual Non-Flow Limiting Lesions).[16] However, these studies were modestly sized, which precluded assessment of individual clinical end points and lesion-level analyses. The aim of the present individual patient-level data, pooled analysis of these 2 studies was to further assess the additional value of identifying high-risk plaques in FFR-negative deferred lesions.

METHODS

Study Design

This is an individual patient-data pooled analysis of the prospective, investigator-initiated, international COMBINE (OCT-FFR) (NCT02989740) and PECTUS-obs (NCT03857971) natural-history studies. The study is reported in accordance with the

STROBE reporting guidelines (Strengthening of the Reporting of Observational Studies in Epidemiology). The rationale, design, and primary results of both studies were published previously.[15–18] In brief, both studies aimed to assess the association between OCT-identified high-risk plaques in FFR-negative, native coronary segments, and clinical outcomes. COMBINE (OCT-FFR) prospectively enrolled 550 patients with diabetes undergoing clinically indicated coronary angiography for chronic or acute coronary syndrome, among which 423 had at least 1 deferred FFR-negative intermediate (visually estimated 40%–80% stenosis) nonculprit lesion. Only these 423 patients were included in the present analysis. In PECTUS-obs, 438 patients presenting with an acute MI with at least 1 deferred FFR-negative intermediate (visually estimated 30%–90% stenosis) nonculprit lesion were prospectively included. Inclusion and exclusion criteria are listed in the Supplemental Methods. Included patients underwent OCT of all native, deferred, FFR-negative (FFR >0.80) intermediate nonculprit lesions, which are referred to as the target lesions. The FFR was evaluated using pressure wires during predominantly adenosine-induced maximal hyperemia according to the local site protocol. Structured clinical follow-up was obtained according to the respective study protocols. Both studies were conducted in accordance with the 1964 Declaration of Helsinki and were approved by the institutional review boards and medical ethics committees of each participating center. All patients provided written informed consent. The present analysis comprises all patients with at least 1 analyzable OCT pullback. The data that support the findings of this study are available from the corresponding authors upon reasonable request.

OCT Image Analysis

All OCT images for both studies were analyzed by the same independent OCT core laboratory, of whom the members were blinded to patient outcomes. Image analysis was performed using CAAS IntraVascular 2.0 (Pie Medical Imaging B.V., the Netherlands). The target lesion was identified on OCT using manual coregistration with the angiogram based on anatomic landmarks (eg, side branches). Pullbacks with image artifacts interfering with the assessment of the target lesion were excluded at the discretion of the core laboratory. Quantitative and qualitative image analyses were performed in accordance with the latest consensus document on OCT image analysis.[19] For the current analysis, the PECTUS-obs criteria of a high-risk plaque were adopted to define groups and were defined as the presence of at least 2 of the following 3 prespecified criteria: (1) a lipid arc ≥90°, (2) a minimum fibrous cap thickness <65 µm, and (3) presence of either plaque rupture or thrombus. TCFA was defined in the presence of a lipid arc ≥90° and a minimum fibrous cap thickness <65 µm (Figure 1). OCT image analysis results were blinded to patients, operators, and treating physicians.

Clinical End Points

The primary clinical end points of the present analysis were native MACE and target lesion failure (TLF). Native MACE was defined as the composite of all-cause mortality and nonfatal MI that was attributable and not related to stent failure, or unplanned revascularization not related to stent failure. TLF was defined as the composite of cardiac death, target vessel MI, or target lesion revascularization. Target vessel MI and target lesion revascularization were only considered if clearly attributable to the target vessel and lesion, respectively. Native MACE was evaluated at a patient level, and TLF was evaluated at a lesion level. Secondary end points include the individual components of the primary end points and attributable TLF (aTLF), defined as TLF excluding cases of cardiac death not clearly attributable to the target lesion. End point definitions of the respective studies are listed in the Supplemental Methods. Two blinded independent clinical end point committees consisting of at least 2 experienced interventional cardiologists adjudicated all potential clinical events for the respective studies. Events were adjudicated using medical records and by comparing baseline and follow-up angiograms.

Statistical Analysis

Categorical data are presented as numbers (percentages) and are compared using the χ^2 test or the Fisher exact test, whenever appropriate. Continuous variables are expressed as mean±SD if normally distributed or as median (interquartile range) if not normally distributed and were evaluated using the

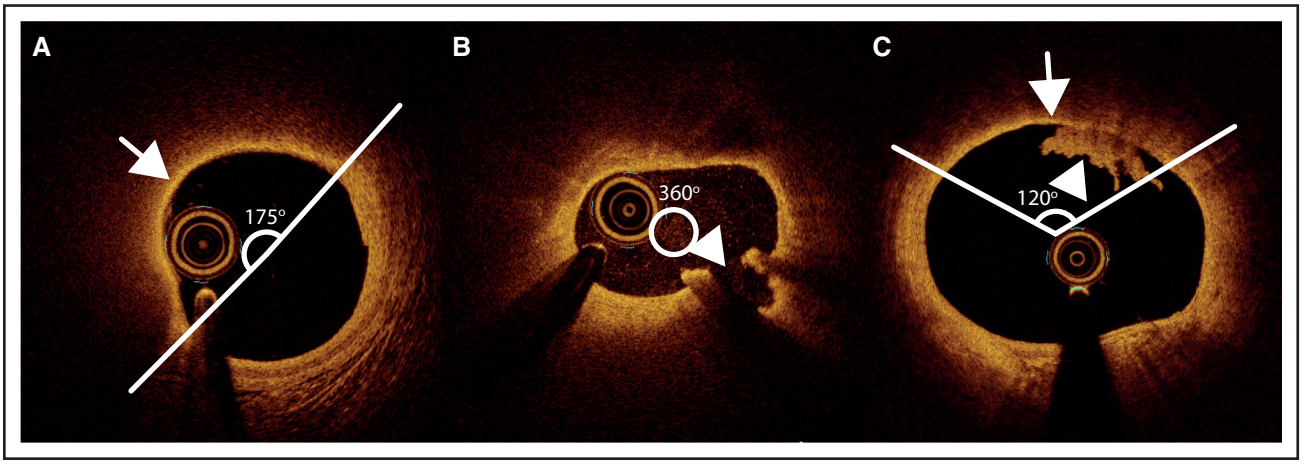

Figure 1. Examples of high-risk plaques.
Optical coherence tomography images meeting the criteria for a high-risk plaque based on (**A**) minimum fibrous cap thickness <65 µm (arrow) and lipid arc ≥90°, (**B**) lipid arc ≥90° and plaque rupture (arrowhead), and (**C**) minimum fibrous cap thickness <65 µm (arrow), lipid arc ≥90°, and thrombus (arrowhead).

Student independent samples *t* test or the Mann-Whitney *U* test, respectively. Time-to-first events for the primary end points were presented using cumulative incidence curves and were evaluated using the log-rank test. Patients were censored at their last known moment of follow-up. Univariable and multivariable Cox proportional hazards regression models were performed to estimate the hazard ratio (HR) between high-risk plaque characteristics and the patient-level primary or secondary clinical end points. For the lesion-level clinical end points, robust standard errors were estimated to account for within-patient clustering when patients had multiple target lesions. Baseline variables that were associated with either of the primary end points in univariable analysis were entered into the multivariable models after checking for collinearity. Subgroup analyses were evaluated with the use of interaction terms. For the secondary end points, multivariable models were performed only for those end points with $P<0.05$ in univariable analysis. The association between the number of high-risk plaque features and clinical outcome was evaluated using the *P* value for trend and regression models with non-high-risk plaque features as a reference standard. Missing data were not imputed. Data were analyzed using IBM SPSS Statistics software, version 27.0 (IBM Corp), and RStudio, version 2023.09.1 (PBC).

RESULTS

Study Flow

Patients were enrolled from March 2015 to December 2018 in COMBINE (OCT-FFR) and from December 2018 to September 2020 in PECTUS-obs. In total, 810 patients had at least 1 analyzable OCT and were enrolled in the present analysis, including 390 patients from COMBINE (OCT-FFR) and 420 patients from PECTUS-obs. The study flowchart is shown in Figure 2. A serious adverse event during OCT image acquisition occurred in 3 cases (Table S1). OCT image analysis revealed a high-risk plaque in 271 (33.5%) patients.

Baseline Characteristics

Baseline clinical and angiographic characteristics are presented in Table 1. The mean age of included patients was 65±10 years, and 585 (72.2%) patients were male; 511 (63.1%) and 450 (55.6%) patients had a history of hypertension and diabetes, respectively. MI during the index hospitalization was diagnosed in 482 (59.5%) patients, including 230 (28.4%) with ST-segment–elevation MI and 252 (31.1%) with non–ST-segment–elevation MI. The mean number of target lesions per patient was 1.18±0.43, and the mean FFR was 0.89±0.05. Patients with a high-risk plaque less frequently were on statin therapy before inclusion (44.6% versus 54.0%; $P=0.012$), had higher levels of low-density lipoprotein-cholesterol (3.02±1.21 versus 2.71±1.19 mmol/L; $P=0.004$), more frequently had a target nonculprit lesion located in the right coronary artery (41.2% versus 25.4%; $P<0.001$), and less frequently in the left anterior descending artery (42.1% versus 51.0%; $P=0.016$). Patients with a high-risk plaque more frequently underwent percutaneous coronary intervention of nontarget lesions at baseline (72.3% versus 64.2%; $P=0.020$). No difference in clinical risk profile (eg, history of diabetes and hypertension) was observed (Figure S1). Medical therapy during follow-up is described in Table S2.

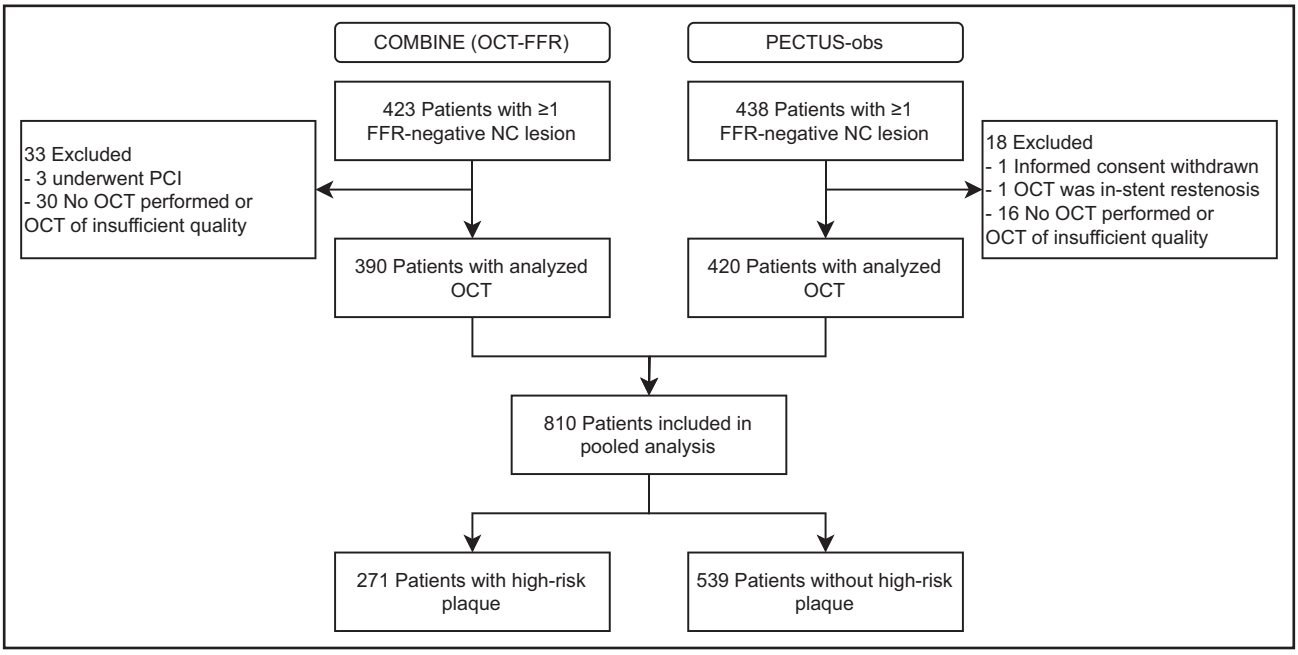

Figure 2. Study flowchart.
COMBINE (OCT-FFR) indicates Optical Coherence Tomography Morphologic and Fractional Flow Reserve Assessment in Diabetes Mellitus Patients; FFR, fractional flow reserve; NC, nonculprit; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; and PECTUS-obs, Identification of Risk Factors for Acute Coronary Events by OCT After STEMI and NSTEMI Patients With Residual Non-Flow Limiting Lesions.

Table 1. Baseline Characteristics

Variables	N=810	High-risk plaque (n=271)	Non-high-risk plaque (n=539)	*P* value
Age, y		65±11	66±10	0.353
Male sex		194 (71.6)	391 (72.5)	0.775
BMI, kg/m^2	780	28.9±4.9	28.6±4.8	0.374
Smoking status				
Current	764	70 (27.2)	128 (25.2)	0.076
Previous		83 (32.3)	132 (26.0)	
Never		104 (40.5)	247 (48.7)	
Diabetes		146 (53.9)	304 (56.4)	0.495
Hypertension	808	165 (61.1)	346 (64.3)	0.373
Hypercholesterolemia	808	126 (46.8)	259 (48.1)	0.745
Family history of premature CVD	796	96 (36.4)	172 (32.3)	0.257
Previous MI		65 (24.0)	126 (23.4)	0.847
Previous PCI		69 (25.5)	137 (25.4)	0.989
Previous CVA		15 (5.5)	25 (4.6)	0.578
MI at presentation		162 (59.8)	320 (59.4)	0.911
STEMI		83 (51.2)	147 (45.9)	0.271
NSTEMI		79 (48.8)	173 (54.1)	
MINOCA		6 (3.7)	16 (5.0)	0.519
ST-elevation		1 (16.7)	2 (12.5)	1.000
Non-ST-elevation		5 (83.3)	14 (87.5)	
Statin at presentation		121 (44.6)	291 (54.0)	0.012
Laboratory assessment				
Creatinine, µmol/L	743	88.2±25.2	87.0±25.1	0.531
C-reactive protein, mg/L	483	3.00 (1.10–6.00)	2.90 (1.00–5.60)	0.387
Total cholesterol, mmol/L	629	4.78±1.28	4.60±1.31	0.110
LDL-cholesterol, mmol/L	502	3.02±1.21	2.71±1.19	0.004
HDL-cholesterol, mmol/L	506	1.10 (0.94–1.38)	1.10 (0.92–1.35)	0.549
Triglycerides, mmol/L	521	1.63 (1.14–2.20)	1.67 (1.12–2.46)	0.754
Glycated hemoglobin, %	183	7.46±1.05	7.56±1.36	0.631
PCI of nontarget lesion(s)		196 (72.3)	346 (64.2)	0.020
No. of target lesions		1.28±0.51	1.13±0.37	<0.001
Target lesion distribution				
LM		2 (0.7)	10 (1.9)	0.355
LAD		114 (42.1)	275 (51.0)	0.016
LCx		94 (34.7)	194 (36.0)	0.714
RCA		112 (41.3)	137 (25.4)	<0.001
Target lesion FFR		0.88±0.05	0.89±0.05	0.073

BMI indicates body mass index; CVA, cerebrovascular accident; CVD, cardiovascular disease; FFR, fractional flow reserve; HDL, high-density lipoprotein; LAD, left anterior descending artery; LCx, left circumflex artery; LDL, low-density lipoprotein; LM, left main coronary artery; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; and STEMI, ST-segment–elevation myocardial infarction.

Lesion-Level OCT Characteristics

A total of 939 FFR-negative nonculprit lesions were analyzable, including 287 (30.6%) lesions with a high-risk plaque. Lesion-level quantitative and qualitative OCT analyses are shown in Table 2. Lesions harboring a high-risk plaque were longer (23.4±10.7 versus 19.8±9.9 mm; *P*<0.001) and had a smaller minimal lumen area (2.58±1.23 versus 2.84±1.54 mm^2; *P*=0.007) and higher percentage area stenosis (65.0±12.7 versus 60.9±15.0%; *P*<0.001). Macrophage accumulation and cholesterol clefts were more prevalent in high-risk plaques (*P*<0.001 for both), whereas non-high-risk plaques had more extensive calcification and more protruding calcifications.

High-Risk Plaques and Clinical Outcome

The mean time of follow-up was 952±375 days (median, 761 days; interquartile range, 731–1175 days). The

Table 2. Lesion-Level OCT Characteristics

Variables	N=939	High-risk plaque (n=287)	Non-high-risk plaque (n=652)	*P* value
MLA, mm^2		2.58±1.23	2.84±1.54	0.007
MLD, mm		1.47±0.37	1.55±0.44	0.007
Percentage area stenosis	937	65.0±12.7	60.9±15.0	<0.001
Lesion length, mm		23.4±10.7	19.8±9.9	<0.001
Calcification		221 (77.0)	476 (73.0)	0.197
Maximal calcification arc, °		142±91	163±98	0.007
Protruding calcification		61 (21.3)	191 (29.3)	0.010
Lipid		287 (100)	395 (60.6)	<0.001
Maximal lipid arc, °		238±76	194±78	<0.001
Lipid arc ≥90°		287 (100)	370 (56.7)	<0.001
Minimum FCT, µm		70±39	159±87	<0.001
Minimum FCT <65 µm		239 (83.3)	0 (0)	<0.001
Plaque rupture		88 (30.7)	7 (1.1)	<0.001
In the absence of minimum FCT <65 µm		23 (8.0)	7 (1.1)	<0.001
Thrombus	938	102 (35.5)	41 (6.3)	<0.001
In the absence of minimum FCT <65 µm		35 (12.2)	41 (6.2)	0.002
Macrophage accumulation	938	132 (46.2)	211 (32.4)	<0.001
Microvessel		133 (46.3)	265 (40.6)	0.104
Cholesterol clefts	935	107 (37.4)	152 (23.4)	<0.001
Layered plaque	937	65 (22.5)	124 (19.1)	0.209

FCT indicates fibrous cap thickness; MLA, minimum lumen area; MLD, minimum lumen diameter; and OCT, optical coherence tomography.

Table 3. Clinical Outcome

Variables	High-risk plaque	Non-high-risk plaque	Univariable HR (95% CI)	*P* value	Multivariable HR (95% CI)*	*P* value
Patient level	n=271	n=539				
Native MACE	52 (19.2)	53 (9.8)	2.127 (1.451–3.120)	<0.001	2.034 (1.380–2.998)	<0.001
All-cause mortality	15 (5.5)	21 (3.9)	1.471 (0.758–2.853)	0.251		
Nonfatal MI	13 (4.8)	9 (1.7)	2.975 (1.272–6.961)	0.008	3.104 (1.311–7.353)	0.010
Unplanned revascularization	39 (14.4)	30 (5.6)	2.793 (1.735–4.497)	<0.001	2.749 (1.697–4.453)	<0.001
Lesion level	n=287	n=652				
TLF	31 (10.8)	29 (4.4)	2.623 (1.559–4.414)	<0.001	2.413 (1.429–4.074)	<0.001
Cardiac death	10 (3.5)	15 (2.3)	1.557 (0.679–3.570)	0.296		
Target vessel MI	8 (2.8)	2 (0.3)	9.419 (2.013–44.070)	0.004	8.436 (1.832–38.850)	0.006
Target lesion revascularization	20 (7.0)	14 (2.1)	3.454 (1.744–6.841)	<0.001	3.161 (1.603–6.233)	<0.001
aTLF	22 (7.7)	14 (2.1)	3.803 (1.946–7.434)	<0.001	3.502 (1.795–6.833)	<0.001

aTLF indicates attributable target lesion failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; and TLF, target lesion failure.

*Multivariable Cox proportional hazards regression models (patient level) or robust standard errors (lesion level) with the following independent and dependent variables: presence of a high-risk plaque, history of diabetes, history of percutaneous coronary intervention, presentation with MI, statin therapy at discharge, oral anticoagulation therapy at discharge, target lesion in the left anterior descending artery, and target lesion in the left circumflex artery as independent variables with native MACE or its components as dependent variables. Presence of high-risk plaque, oral anticoagulation therapy at discharge, and lesion-level fractional flow reserve as independent variables with (a)TLF or its components as dependent variables.

primary and secondary end points are presented in Table 3. The primary end point of native MACE occurred in 52 (19.2%) patients with and 53 (9.8%) patients without a high-risk plaque (HR, 2.127 [95% CI, 1.451–3.120]; *P*<0.001; Figure 3A). The incidence of TLF was 10.8% among high-risk lesions compared with 4.4% in non-high-risk lesions (HR, 2.623 [95% CI, 1.559–4.414]; *P*<0.001; Figure 3B). Results were consistent in subgroup analyses (Figure S2). The difference in native MACE was mainly driven by a higher incidence of nonfatal MI (4.8% versus 1.7%; *P*=0.008) and unplanned revascularization (14.4% versus 5.6%; *P*<0.001). The difference in TLF was mainly driven by target vessel–related MI (2.8% versus 0.3%; *P*=0.004) and target lesion revascularization (7.0% versus 2.1%; *P*<0.001). None of the cardiac deaths were clearly attributable to the target lesion. High-risk lesions had an HR for aTLF of 3.803 (95% CI, 1.946–7.434; *P*<0.001; Figure 3C). In multivariable analysis, correcting for baseline characteristics associated with the primary end points (Tables S3 and S4), statistical significance remained for all end points tested (Table 3).

Two hundred twenty-four (27.7%) patients had a minimum fibrous cap thickness <65 µm, 592 (73.1%) had a maximum lipid arc ≥90°, 93 (11.5%) had plaque rupture, and 142 (17.5%) had thrombus presence. On a lesion level, the prevalence of these features was 25.5%, 70.0%, 20.1%, and 10.4%, respectively. Associations between the individual high-risk plaque criteria and the composite end points are presented in Figures 4 and 5 and Figure S3. The risk of native MACE, TLF, and aTLF increased when more high-risk plaque features coexisted (P_{trend}<0.001 for all end points; Figures 4 and 5; Figure S3).

TCFA was present in 224 (27.7%) patients (Table S5). Patients or lesions with a TCFA had a higher incidence of native MACE (HR, 1.941 [95% CI, 1.313–2.870]; *P*<0.001) and TLF (HR, 2.306 [95% CI, 1.375–3.869]; *P*=0.002), respectively (Figure S4). The presence of TCFA was associated with a higher incidence of nonfatal MI (HR, 3.264 [95% CI, 1.410–7.559]; *P*=0.003), unplanned revascularization (HR, 2.615 [95% CI, 1.630–4.197]; *P*<0.001), target vessel–related MI (HR, 7.028 [95% CI, 1.836–26.910]; *P*=0.004), and target lesion revascularization (HR, 3.138 [95% CI, 1.597–6.167]; *P*<0.001), also after correcting for potential confounders (Table S6).

DISCUSSION

This pooled analysis from the COMBINE (OCT-FFR) and PECTUS-obs studies, comprising all available prospective data on the association between FFR-negative but high-risk nonculprit plaques and clinical outcome, illustrates the value of intracoronary imaging complementary to physiology for identification of patients at risk of adverse clinical outcome. The presence of a high-risk plaque was associated with an approximately 2-fold increased risk of patient-level native MACE and lesion-level TLF, and over 3-fold increased risk of lesion-level aTLF, both in univariable and multivariable analyses. This increased risk was driven by any and target vessel–related nonfatal MI and by any and target lesion–related unplanned revascularization. The coexistence of multiple

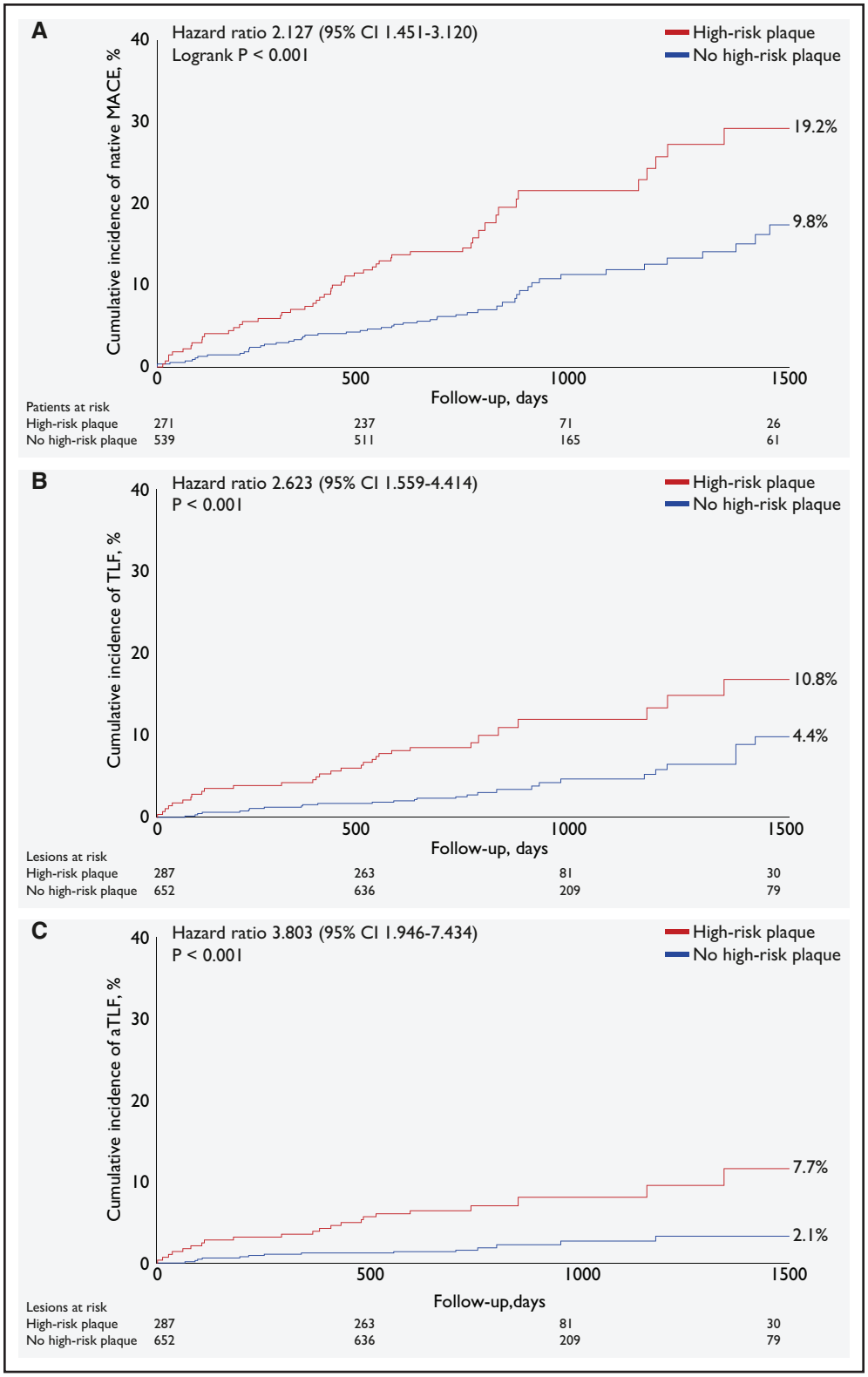

Figure 3. Cumulative incidences of the composite end points.
Cumulative incidence curve for the cumulative end points of native major adverse cardiovascular event (MACE; **A**), target lesion failure (TLF; **B**), and attributable TLF (aTLF; **C**) truncated at 1500 days.

high-risk plaque features resulted in an incremental risk of both native MACE and aTLF. Similar results were observed using TCFA as a marker of plaque vulnerability. These results support the high-risk patient and plaque hypotheses and ongoing studies on the treatment of high-risk plaques.

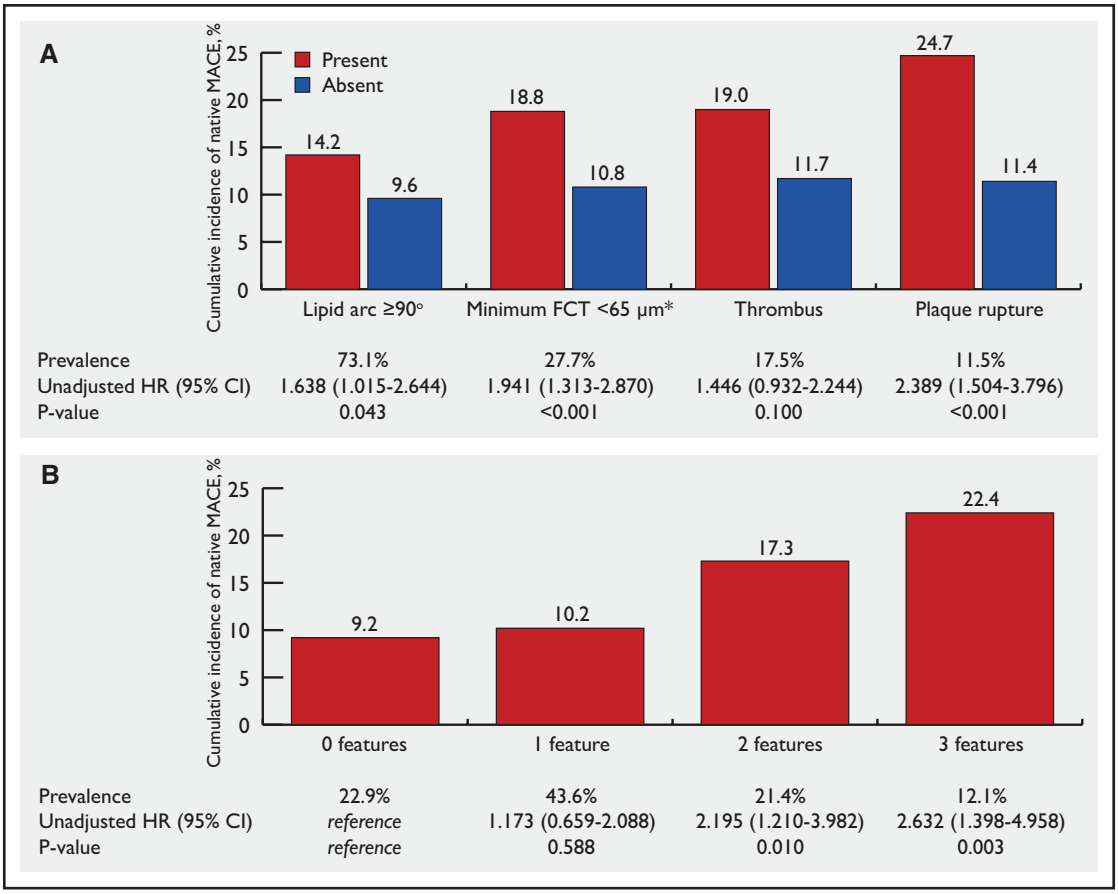

Figure 4. High-risk plaque components and major adverse cardiovascular events (MACE).
A, Association between individual high-risk plaque features and native MACE. **B**, Association between the number of high-risk plaque features and native MACE, in which the presence of plaque rupture and thrombus is considered 1 high-risk plaque feature. *Considering that all lesions with a minimum fibrous cap thickness (FCT) <65 µm had a lipid arc ≥90°, all these lesions are qualified as a thin-cap fibroatheroma. HR indicates hazard ratio.

High-Risk Plaques and Clinical Outcome

Multiple prospective natural-history studies provided evidence on the association between high-risk plaques and patient- or lesion-level clinical outcomes, among which are the PROSPECT study (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) using 3-vessel intravascular ultrasound,[10] PROSPECT-II and LRP (Lipid-Rich Plaque) studies using near-infrared spectroscopy,[11,12] and the CLIMA study (Relationship Between OCT Coronary Plaque Morphology and Clinical Outcome) using OCT of the left anterior descending artery in patients with MI.[13] In PROSPECT and PROSPECT-II (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II), including solely patients with acute coronary syndromes, the risk of patient- and lesion-level events was increased up to over 2-fold and 11-fold, respectively.[10,11] However, both studies included quantitative measures of luminal obstruction in the high-risk plaque criteria and therefore not only focus on plaque morphology but also on lesion severity. Nevertheless, the plaque morphology-related criteria were also significantly associated with adverse outcomes in both studies.[10,11] Intriguingly, the mean diameter stenosis of nonculprit lesions causing recurrent events in PROSPECT was only 32±21%, fueling the high-risk plaque hypothesis.[10] In the LRP study (≈17% MI and 37% diabetes), high-risk plaques were associated with a 2-fold increased risk in patient-level events and a 4-fold increased risk in lesion-level events at a 2-year follow-up.[12] More recently, Jiang et al[14] retrospectively studied 883 patients (3757 lesions) with acute MI in whom 3-vessel OCT was performed and found that the presence of TCFA and a minimum lumen area <3.5 mm^2 were independently associated with both patient- and lesion-level adverse cardiac events.

Importantly, however, functional assessment was not routinely performed in any of these studies. Therefore, we can only make estimations about the flow-limiting status of included lesions. In PROSPECT, only 6% of lesions had a diameter stenosis of at least 50%,[10] and only 0.15% of included lesions had an intravascular ultrasound-derived FFR ≤0.80.[20] The latter finding should, however, be treated with caution considering the lack of external validation and the modest

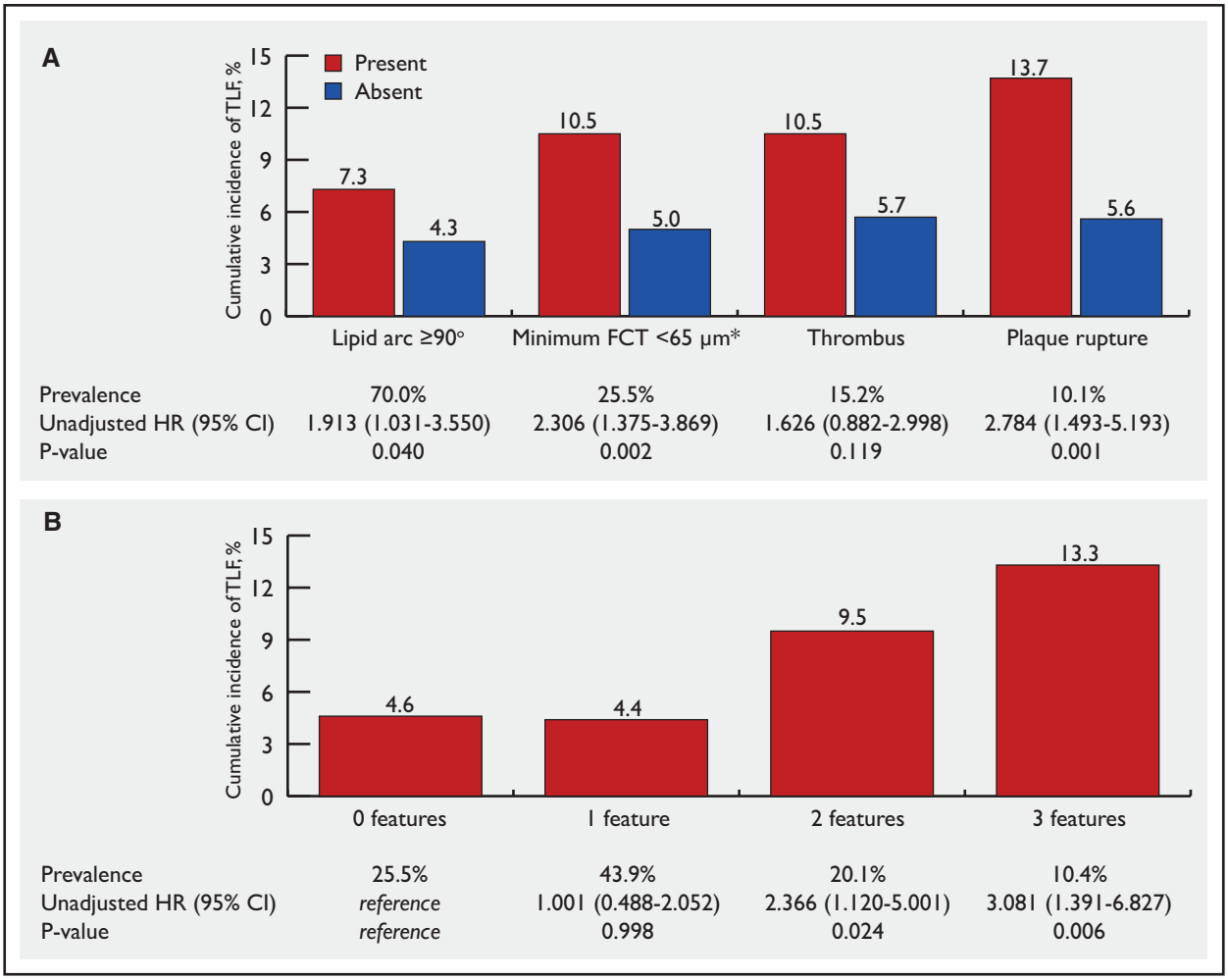

Figure 5. High-risk plaque components and target lesion failure (TLF).
A, Association between individual high-risk plaque features and TLF. **B**, Association between the number of high-risk plaque features and TLF, in which the presence of plaque rupture and thrombus is considered 1 high-risk plaque feature. *Considering that all lesions with a minimum fibrous cap thickness (FCT) <65 µm had a lipid arc ≥90°, all these lesions are qualified as a thin-cap fibroatheroma. HR indicates hazard ratio.

correlation between intracoronary imaging–derived FFR and pressure-wire–derived FFR.[21] Similarly, in the study by Jiang et al,[14] the mean percentage diameter stenosis assessed by quantitative coronary angiography (42.5±10.2%) and the OCT-derived percentage area stenosis (47.4±17.8%) were also limited. Nonetheless, the present analysis is unique in that the absence of flow limitation is confirmed in all included lesions and, therefore, truly emphasizes the additional value of intracoronary imaging complementary to physiological assessment in populations in which FFR-guided deferral is less safe.[4,5] Furthermore, the adopted approach of targeted imaging of FFR-negative nonculprit lesion imaging is more feasible in clinical care than 3-vessel intracoronary imaging.

High-Risk Plaque Definition

In the present analysis, the PECTUS-obs predefined criterion of a high-risk plaque that includes, but is not limited to, TCFA was adopted and was effective in identifying patients at risk of recurrent events. Multiple criteria have been used throughout the years to define high-risk plaques. A recent meta-analysis of 30 observational studies, including 4 studies using OCT, demonstrated that TCFA was the high-risk feature with the highest HR for patient-level events (3-fold increased risk) and second highest HR for lesion-level events (6-fold increased risk), with a positive predictive value of 24% (95% CI, 2%–46%) and 9% (95% CI, 3%–15%), respectively.[22] We now report a positive predictive value for TCFA of 18.8% for native MACE and 10.5% for TLF (negative predictive values, 89.2% and 95.0%, respectively) using a cutoff value of <65 µm and ≥90° for minimum fibrous cap thickness and lipid arc, respectively.

The presence of nonculprit plaque rupture as a marker of plaque vulnerability hitherto received little attention in natural-history studies. We observed an HR of over 2 for native MACE and TLF in the presence of nonculprit plaque rupture, which calls for attention in

future studies. Earlier findings support the concept of nonculprit plaque rupture as an indicator of vulnerability. First, plaque disruption requires an internal milieu predisposing the plaque to destabilization, which could be a combination of mechanical but also biochemical factors, the latter of which could affect the whole coronary tree. Indeed, culprit plaque rupture has been associated with signs of panvulnerability, including more nonculprit TCFA and plaque rupture.[23] Furthermore, multiple nonculprit plaque ruptures are more common among patients with acute coronary syndrome compared with patients with chronic coronary syndrome.[24] Second, subclinical nonculprit plaque rupture in the presence of a well-functioning healing capacity[25] contributes to rapid, stepwise lesion progression[26] and can consequently induce ischemia requiring revascularization.[27]

Importantly, we observed the highest HR and positive predictive value in lesions harboring all 3 features, which is in line with the referenced meta-analysis illustrating an incremental risk with multiple coexistent high-risk features.[22] The optimal tradeoff between the desired positive predictive value and the number of high-risk plaque features included in the definition, which is inversely related to the proportion of patients meeting the respective high-risk definition, remains to be determined. This is a critical consideration when defining treatment strategies targeting high-risk plaques, especially considering a large number of high-risk plaques not proceeding to cause future events. This is of particular importance for focal treatment strategies.

Limitations

This study has some limitations. First, the study only applies to intermediate FFR-negative nonculprit lesions. Second, inherent to the inclusion criteria, the high-risk clinical profile (ie, diabetes or MI) of the present cohort may impede extrapolating our results to the general population undergoing percutaneous coronary intervention. Specifically, the HR for adverse events may be lower in the overall population. Third, female patients were underrepresented in both cohorts. Fourth, the end point definitions differed slightly between studies. Fifth, target vessel MI was evaluated rather than target lesion MI. However, identifying the exact culprit lesion can be challenging with a large thrombus load. Sixth, analyses were limited to OCT features analyzed by the core laboratory. Therefore, other variables of potential interest (eg, type of calcified nodule or volumetric fibrous cap evaluations) could not be evaluated. Finally, the positive predictive value remains relatively low, potentially limiting the effectiveness of preventive treatment. Whether the addition of other nonanatomic factors (eg, inflammatory and thrombogenic milieu) would increment the predictive value of the diagnosis of high-risk plaques in selected high-risk patients remains unsettled and warrants further investigation.

Conclusions

In conclusion, the presence of an OCT-identified high-risk plaque in an FFR-negative nonculprit lesion is associated with patient-level native MACE and lesion-level TLF in patients with diabetes or after MI. Co-occurrence of multiple high-risk plaque features results in an incremental risk of adverse outcomes. These findings emphasize the additional value of intracoronary imaging in the absence of flow limitation and support the high-risk patient and plaque hypotheses, as well as ongoing studies on systemic or focal treatment of high-risk plaques.

ARTICLE INFORMATION

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Supplemental Material

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APPENDIX

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