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Fractional Flow Reserve–Negative High-Risk Plaques and Clinical Outcomes After Myocardial Infarction

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IMPORTANCE Even after fractional flow reserve (FFR)–guided complete revascularization, patients with myocardial infarction (MI) have high rates of recurrent major adverse cardiovascular events (MACE). These recurrences may be caused by FFR-negative high-risk nonculprit lesions.

OBJECTIVE To assess the association between optical coherence tomography (OCT)-identified high-risk plaques of FFR-negative nonculprit lesions and occurrence of MACE in patients with MI.

DESIGN, SETTING, AND PARTICIPANTS PECTUS-obs (Identification of Risk Factors for Acute Coronary Events by OCT After STEMI [ST-segment elevation MI] and NSTEMI [non-STEMI] in Patients With Residual Non–flow Limiting Lesions) is an international, multicenter, prospective, observational cohort study. In patients presenting with MI, OCT was performed on all FFR-negative (FFR > 0.80) nonculprit lesions. A high-risk plaque was defined containing at least 2 of the following prespecified criteria: (1) a lipid arc at least 90°, (2) a fibrous cap thickness less than 65 µm, and (3) either plaque rupture or thrombus presence. Patients were enrolled from December 14, 2018, to September 15, 2020. Data were analyzed from December 2, 2022, to June 28, 2023.

MAIN OUTCOME AND MEASURE The primary end point of MACE, a composite of all-cause mortality, nonfatal MI, or unplanned revascularization, at 2-year follow-up was compared in patients with and without a high-risk plaque.

RESULTS A total of 438 patients were enrolled, and OCT findings were analyzable in 420. Among included patients, mean (SD) age was 63 (10) years, 340 (81.0) were men, and STEMI and non-STEMI were equally represented (217 [51.7%] and 203 [48.3%]). A mean (SD) of 1.17 (0.42) nonculprit lesions per patient was imaged. Analysis of OCT images revealed at least 1 high-risk plaque in 143 patients (34.0%). The primary end point occurred in 22 patients (15.4%) with a high-risk plaque and 23 of 277 patients (8.3%) without a high-risk plaque (hazard ratio, 1.93 [95% CI, 1.08-3.47]; *P* = .02), primarily driven by more unplanned revascularizations in patients with a high-risk plaque (14 of 143 [9.8%] vs 12 of 277 [4.3%]; *P* = .02).

CONCLUSIONS AND RELEVANCE Among patients with MI and FFR-negative nonculprit lesions, the presence of a high-risk plaque is associated with a worse clinical outcome, which is mainly driven by a higher number of unplanned revascularizations. In a population with a high recurrent event rate despite physiology-guided complete revascularization, these results call for research on additional pharmacological or focal treatment strategies in patients harboring high-risk plaques.

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Supplemental content

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Recurrent coronary events are frequently observed after myocardial infarction (MI), despite advances in primary treatment, complete revascularization, and secondary prevention.[1,2] The substrate for many of these recurrent events are atherosclerotic lesions at other sites in the coronary tree, anatomically unrelated to the lesion causing the initial MI.[3] The natural history of and potential treatment strategies for such nonculprit lesions are widely studied. A 2020 meta-analysis in patients with ST-segment elevation MI (STEMI)[4] showed that preventive percutaneous coronary intervention (PCI) of nonculprit lesions with a significant stenosis results in fewer recurrent MIs and cardiovascular deaths, proving the benefit of additional treatment. A large registry of patients with non-STEMI (NSTEMI)[5] similarly showed a reduced death rate among patients who received complete revascularization. Additional PCI of nonculprit lesions is guided either by angiography or by fractional flow reserve (FFR). However, FFR-guided revascularization in patients with MI yields less favorable outcomes compared with patients with stable coronary artery disease.[6,7] Also, the benefit of FFR over angiography is not well established in patients with MI, and rates of major adverse cardiac events (MACE) in patients with MI and FFR-deferred nonculprit lesions remain considerable.[8,9] This is probably related to the fact that FFR alone reveals plaque morphology to a limited extent.[10,11] Moreover, FFR might be false negative in the acute setting of MI.[12] Hence, additional diagnostic tools are needed to unmask high-risk nonculprit lesions in MI.

Pathological studies[13] have identified the most important characteristics of lesions at high risk for plaque rupture and subsequent MI. Ruptured plaques contain a large necrotic core and a thin (<65 µm) overlying fibrous cap. Intact lesions harboring these features, termed *thin-cap fibroatheromas* (TCFA), are thought to be potential precursors to plaque rupture. Vessels containing TCFA often show positive remodeling, resulting in nonobstructive lesions.[14] Plaque rupture can also occur without initially becoming clinically overt. However, these silent plaque ruptures are associated with rapid lesion progression and are linked to worse outcome.[15,16] Assessing the morphology of nonculprit lesions for TCFA or plaque rupture might therefore aid in identifying plaques at high risk of causing future MACE. Intravascular optical coherence tomography (OCT), a high-resolution invasive imaging modality, allows for identification of these anatomical lesion features in vivo. The present study is, to our knowledge, the first prospective study to assess the association between OCT-detected high-risk plaques in FFR-negative nonculprit lesions and MACE among patients with MI.

Key Points

Question What is the association of optical coherence tomography–identified high-risk fractional flow reserve–negative nonculprit plaques with major adverse cardiovascular events (MACE) in patients presenting with myocardial infarction (MI)?

Findings In this cohort study of 420 patients with MI, MACE (defined as all-cause mortality, nonfatal MI, and unplanned revascularization) occurred in 22 of 143 patients with (15%) and 23 of 277 without (8%) a high-risk plaque after 2 years. After adjustment for clinical variables, presence of a high-risk plaque was associated with a 2-fold increased risk of MACE, driven primarily by higher rates of revascularization.

Meaning These findings suggest that among patients with MI, the presence of a fractional flow reserve–negative high-risk nonculprit plaque is associated with worse clinical outcome.

Methods

Study Design

PECTUS-obs (Identification of Risk Factors for Acute Coronary Events by OCT After STEMI and NSTEMI in Patients With Residual Non-flow Limiting Lesions) is a prospective natural history cohort study that was conducted in 14 hospitals in 4 different countries (eMethods 1 in Supplement 1).[17] The goal of the study was to determine whether the presence of OCT-determined high-risk FFR-negative nonculprit lesions in patients presenting with MI is associated with future adverse cardiovascular events. The study was approved by the medical ethics committee of the region Arnhem-Nijmegen and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.[18] Every participant gave written informed consent; however, some patients entered the study after providing oral consent, and gave written consent thereafter. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. A detailed description of the rationale and design of PECTUS-obs has been published previously.[19]

Patients presenting with MI (STEMI or NSTEMI) who underwent coronary angiography were screened for eligibility after treatment of the culprit lesion. Patients were eligible for inclusion in the study if the coronary angiography revealed at least 1 nonculprit lesion of intermediate stenosis (30%-90%) in any of the coronary arteries that was not hemodynamically significant as determined by FFR measurement (FFR >0.80). Exclusion criteria were age younger than 18 years, pregnancy, hemodynamic instability, history of or indication for coronary artery bypass grafting, and a life expectancy of less than 3 years. Additional target lesion (ie, the FFR-negative nonculprit lesion imaged by OCT)-related exclusion criteria were in-stent restenosis and anatomy unsuitable for OCT catheter crossing or imaging. The FFR measurements and OCT imaging were performed either during the index procedure or during a staged procedure within 6 weeks. Severe stenoses and FFR-positive intermediate stenoses were treated according to contemporary guidelines. Enrolled patients underwent OCT imaging (54 mm) of all eligible lesions under fluoroscopic guidance to attribute OCT findings to a specific vessel segment. Operators were not allowed to analyze the acquired images but were not completely blinded to allow for reimaging in case of insufficient image quality. After core laboratory analysis of OCT images, participants were divided into 2 groups. Patients with at least 1 OCT-determined high-risk plaque were regarded as at high risk, and patients without any high-risk plaques on OCT were considered at low risk, independently of the total amount of lesions assessed.

OCT Imaging Analysis

Analyses of OCT images were performed offline by a dedicated OCT core laboratory blinded to patient clinical characteristics and outcomes. The OCT analyses were performed on the targeted stenosis within the pullback. The process included a quality check to determine whether the imaging allowed for both qualitative and quantitative analysis of the targeted lesion. Images of insufficient quality were excluded from the analysis. Serial cross-sectional images of the vessel were scrutinized using CAAS IntraVascular software, version 2.0 (Pie Medical BV). Analyses were based on tissue characteristics as previously described in OCT expert consensus reports.[20,21] A detailed description of the analyses and a list of OCT definitions are provided in eMethods 2 in Supplement 1. A lesion was deemed high-risk if it contained at least 2 of the following 3 prespecified criteria: (1) a lipid arc of at least 90°, (2) a minimal fibrous cap thickness of less than 65 µm, and (3) either plaque rupture or thrombus presence (eFigure 1 in Supplement 1).

End Points

The primary end point was the occurrence of MACE (composite of all-cause mortality, nonfatal MI, or unplanned revascularization) before the 2-year (±30 days) follow-up. Secondary end points are the individual components of the primary end point, cardiac mortality, target vessel failure and revascularization, and target lesion failure and revascularization. Target vessel failure and target lesion failure were defined as any nonfatal MI or unplanned revascularization attributed to the target vessel or lesion, respectively. End point definitions are provided in eMethods 3 in Supplement 1.

Follow-Up and Event Adjudication

Structured follow-up was performed at 1 and 2 years (±30 days) after inclusion by telephone contact. Primary and secondary end points were verified using medical records from participating centers, primary care clinicians, and other medical centers. A clinical end point committee consisting of 2 independent, experienced interventional cardiologists blinded to the OCT data reviewed and adjudicated all (possible) events. When possible, any new MI or revascularization was allocated to a specific coronary vessel and lesion by comparison of baseline and event angiograms.

Statistical Analysis

Data were analyzed from December 2, 2022, to June 28, 2023. A sample size of 394 participants was needed to provide more than 80% power with a 1-sided α of .025. This was based on an expected presence of high-risk plaques in 60% of targeted lesions, a total event rate of 10% to 25% in patients with MI with FFR-deferred nonculprit lesions after 2 years,[9,22] and an expected hazard ratio (HR) of 2.00 to 3.50 for OCT-defined high-risk plaques.[3] To compensate for an estimated 5% loss to follow-up and 5% inadequate OCT scans, the sample size was increased to a total of 438 participants.

Continuous variables are presented as mean (SD) if normally distributed or median (IQR) if not normally distributed. Categorical variables are presented as numbers (percentages). For the comparison of the baseline characteristics between the high-risk and non-high-risk groups, the independent unpaired *t* tests, Mann-Whitney tests, and χ^2 tests were performed when appropriate.

The analysis of the primary end point was performed comparing patients with and without a high-risk plaque. Patients were censored at their last known moment of follow-up or at 2 years (±30 days) after inclusion. Time-to-event data for the primary end point were presented descriptively using Kaplan-Meier curves, and a log-rank test was used to evaluate whether there was a difference between the groups. A univariate Cox proportional hazards regression model was performed to estimate the HR. Two additional multivariate Cox proportional hazards regression models were performed to account for potential confounders. The first model (model A) included the presence of a high-risk plaque and age, prior MI, type 1 or 2 diabetes, STEMI or NSTEMI at presentation, and estimated glomerular filtration rate as characteristics that were a priori determined to be associated with worse prognosis. The second model (model B) included the presence of a high-risk plaque and the baseline characteristics that showed a univariate association with the primary outcome ($P < .05$, corresponding to a 95% CI that does not cross 1) after checking for collinearity. Subdistribution HRs for the secondary end points were estimated using the Fine-Gray model with noncardiac death and all-cause mortality as competing risk factors for cardiac death and all other secondary end points, respectively. Two-sided $P < .05$ was considered statistically significant. All analyses were performed using SPSS Statistics, version 24 (IBM Corp), and Stata, release 17 (StataCorp LLC). The trial protocol and full predefined statistical analysis plan are provided in Supplement 2.

Results

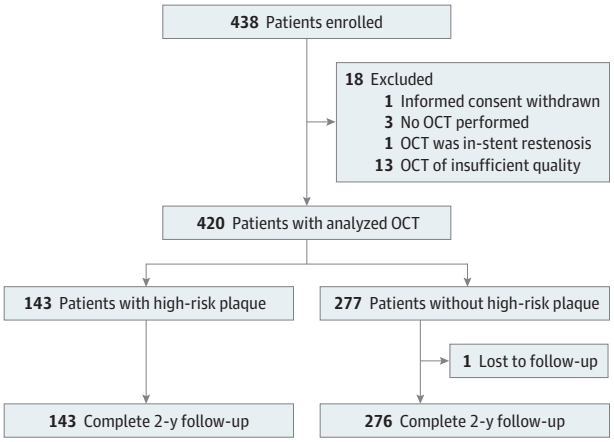
Study Flow

From December 14, 2018, to September 15, 2020, a total of 438 patients were enrolled in the study. The study flowchart is shown in **Figure 1**. In total, 420 patients had at least 1 OCT scan with sufficient quality and were included in the analysis. Imaging analysis resulted in 143 patients with (34.0%) and 277 patients without (66.0%) at least 1 high-risk plaque. Only 1 patient was lost to follow-up before the 2-year follow-up.

Clinical and Angiographical Characteristics

Baseline clinical and procedural characteristics are shown in **Table 1**. The mean age of included patients was 63 (10) years; 340 (81.0%) were men and 80 (19.0%) were women. Data on race and ethnicity were not collected. A total of 217 patients (51.7%) presented with STEMI and 203 (48.3%) with NSTEMI. A mean (SD) of 1.17 (0.42) nonculprit lesions per patient was imaged. Hypertension was present in 222 patients (52.9%), and diabetes was present in 61 (14.5%). Furthermore, 63 patients (15.0%) had a history of MI prior to the index event. Patients with a high-risk plaque had higher low-density lipoprotein cholesterol levels at presentation (131.3 [46.3] vs 115.8 [46.3] mg/dL [to convert to mmol/L, multiply by 0.0259]; $P = .03$) and a less

Figure 1. Study Flowchart



OCT indicates optical coherence tomography.

frequent history of PCI (14 [9.8%] vs 48 [17.3%]; *P* = .04). The culprit lesion was most often located in the left anterior descending artery (LAD) (167 [39.8%]). Targeted nonculprit lesions had a mean FFR of 0.89 (0.05) (eFigures 2 and 3 in Supplement 1) and were predominately located in the LAD (175 [41.7%]).

Lesion Characteristics

Among the 420 patients included in the final analysis, 494 FFR-negative nonculprit lesions were imaged. The OCT-derived qualitative and quantitative measurements at the lesion level are shown in eTable 1 in Supplement 1. By definition, none of the lesions in non-high-risk patients contained a high-risk plaque. Among high-risk plaques, 154 (100%) had a lipid arc of at least 90°, 136 (88.3%) had a minimal cap thickness of less than 65 µm, 45 (29.2%) had a plaque rupture, and 34 (22.1%) had a thrombus present. Thin-cap fibroatheromas were found in 136 of 494 assessed lesions (27.5%). Macrophage accumulation was more frequently present in lesions with a high-risk plaque compared with those without a high-risk plaque (46 [29.9%] vs 68 [20.0%]; *P* = .02). Other plaque features often associated with plaque instability such as neovascularization and presence of a healed plaque phenotype were equally distributed between both groups. Non-high-risk plaques had a somewhat larger minimal lumen area and showed more extensive calcification.

Clinical Outcomes

The primary and secondary end points in both groups are listed in **Table 2**. In the total population MACE occurred in 45 patients (10.7%) within 2 years after MI. The primary end point occurred in 22 patients in the high-risk group (15.4%) and 23 in the non-high-risk group (8.3%) (HR, 1.93 [95% CI, 1.08-3.47]; *P* = .02). The Kaplan-Meier curves for occurrence of the primary end point in both groups are shown in **Figure 2**A. **Table 3** shows the multivariate Cox proportional hazards regression models. In the predefined model A, the presence of a high-risk plaque was the only factor associated with 2-year MACE (HR, 1.99 [95% CI, 1.10-3.61]; *P* = .02). In model B, which included the variables that show a univariate association with the primary outcome (type of MI at presentation, estimated glomerular filtration rate, history of carotid artery disease, lipid-lowering therapy at discharge, and right coronary artery as infarct-related artery [eTable 2 in Supplement 1]), presence of a high-risk plaque was also independently associated with 2-year MACE (HR, 2.24 [95% CI, 1.21-4.13]; *P* = .01), next to history of carotid artery disease (HR, 3.80 [95% CI, 1.42-10.16]; *P* = .008), right coronary artery as the culprit artery (HR, 0.46 [95% CI, 0.22-0.97]; *P* = .04), and lipid-lowering therapy at discharge (HR, 0.20 [95% CI, 0.06-0.70]; *P* = .01). The primary end point was primarily driven by more unplanned revascularization in the high-risk plaque group (14 [9.8%] vs 12 [4.3%]; *P* = .02). The combined presence of either minimal lumen area less than 3.5 mm^2 or FFR less than 0.90 with a high-risk plaque did not increase the association with the primary end point compared with the presence of a high-risk plaque only (eFigure 4 in Supplement 1). All-cause mortality, cardiovascular death, nonfatal MI, and the composite of all-cause mortality and nonfatal MI (Figure 2B) occurred numerically more often in patients with a high-risk plaque but did not differ significantly between groups. Details on all unplanned revascularizations and nonfatal MIs are shown in eTables 3 and 4 in Supplement 1. The number of target vessel failures was 7 (4.9%) in the high-risk patient group and 4 (1.4%) in the non-high-risk patient group (*P* = .03), including 2 (1.4%) and 0 cases of target vessel MI, respectively. Target lesion failure occurred in 5 patients (3.5%) with a high-risk plaque and 3 (1.1%) without a high-risk plaque (*P* = .08). After exclusion of all stent-related events and all nonfatal MIs that were not attributable to a culprit segment, the combined primary end point occurred in 19 patients (13.3%) with a high-risk plaque compared with 18 (6.5%) without a high-risk plaque (*P* = .02) (eTable 5 in Supplement 1). Of note, guideline-directed medical treatment prescription was high and comparable between groups (eTable 6 in Supplement 1).

Discussion

Recurrent coronary events represent a major cause of morbidity and mortality in patients with MI. In the search for markers and underlying mechanisms for these recurrent events, the present cohort study shows for the first time in a prospective manner that in patients with MI, the presence of FFR-negative OCT-identified high-risk nonculprit lesions is associated with an increased risk of future MACE.

In a population of roughly equal numbers of patients with STEMI and NSTEMI, we observed recurrent MACE in 45 patients (10.7%) within 2 years after MI, even in the absence of FFR-positive nonculprit lesions. These events occurred more often in patients who had a high-risk plaque than in those who did not, with an HR of approximately 2. In the multivariate analyses, apart from the presence of carotid artery disease, the presence of a high-risk plaque resulted in the highest hazard ratio for future MACE. The increased MACE rate in patients with high-risk plaque was primarily driven by an increased rate of

Table 1. Baseline Characteristics[a]

Characteristic	Patient group		P value
	High-risk (n = 143)	Non–high-risk (n = 277)	
Age, mean (SD), y	62 (11)	64 (10)	.15
Sex			
Women	33 (23.1)	47 (17.0)	.13
Men	110 (76.9)	230 (83.0)	
BMI, mean (SD)	28.2 (4.7)	27.5 (4.5)	.18
Smoking status			
Current	44 (30.8)	79 (28.5)	.17
Previous	50 (35.0)	78 (28.2)	
Hypertension	72 (50.3)	150 (54.2)	.46
Type 1 or 2 diabetes	18 (12.6)	43 (15.5)	.42
Hypercholesterolemia	51 (35.7)	102 (36.8)	.86
Family history of premature atherosclerosis	43 (30.1)	85 (30.7)	.99
Previous MI	17 (11.9)	46 (16.6)	.20
Previous PCI	14 (9.8)	48 (17.3)	.04
Previous CVA	0	8 (2.9)	.06
History of carotid artery disease	3 (2.1)	10 (3.6)	.56
History of PAD	6 (4.2)	11 (4.0)	.91
STEMI presentation	78 (54.5)	139 (50.2)	.40
GRACE score, mean (SD)[b]	116 (34)	117 (32)	.57
Cholesterol level, mean (SD), mg/dL			
Total	200.8 (54.1)	193.1 (54.1)	.18
LDL	131.3 (46.3)	115.8 (46.3)	.03
Triglyceride level, mean (SD), mg/dL	159.3 (115.0)	185.8 (150.4)	.25
eGFR, mean (SD), mL/min	79 (20)	80 (19)	.45
CRP, mean (SD), mg/dL	0.6 (1.4)	0.7 (2.5)	.60
Leukocyte count, mean (SD), cells/μL	9600 (3200)	9800 (3200)	.50
Lipid-lowering therapy at presentation	32 (22.4)	76 (27.4)	.26
Infarct-related artery			
LM	5 (3.5)	0	.004
LAD	63 (44.1)	104 (37.5)	.20
Cx	41 (28.7)	67 (24.2)	.32
RCA	45 (31.5)	112 (40.4)	.07
Nonculprit lesion assessment			
Immediate	54 (37.8)	102 (36.8)	.85
Staged	89 (62.2)	175 (63.2)	.85
Time to staged procedure, mean (SD), d	15 (15)	17 (15)	.18
Nonculprit lesion revascularization at baseline	28 (19.6)	59 (21.3)	.68
Without prior functional assessment	14 (9.8)	39 (14.1)	.21
Following positive FFR[c]	19 (13.3)	25 (9.0)	.18
No. of FFR-negative nonculprit lesions			
Mean (SD)	1.29 (0.53)	1.12 (0.34)	<.001
1	107 (74.8)	245 (88.4)	<.001
2	31 (21.7)	31 (11.2)	.004
3	5 (3.5)	1 (0.4)	.01
Nonculprit lesion distribution			
LM	1 (0.7)	3 (1.1)	>.99
LAD	59 (41.3)	116 (41.9)	.90
Cx	50 (35.0)	104 (37.5)	.60
RCA	52 (36.4)	70 (25.3)	.02
Targeted nonculprit lesion FFR, mean (SD)	0.88 (0.05)	0.89 (0.05)	.02

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; CVA, cerebrovascular accident; Cx, circumflex artery; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; GRACE, Global Registry of Acute Coronary Events; LAD, left anterior descending artery; LDL, low-density lipoprotein; LM, left main coronary artery; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction.

SI conversion factors: To convert cholesterol levels to mmol/L, multiply by 0.0259. To convert triglyceride levels to mmol/L, multiply by 0.0113. To convert CRP to mg/L, multiply by 10. To convert leukocyte count to $\times 10^9$/L, multiply by 0.001.

[a] Unless otherwise indicated, data are expressed as No. (%) of patients.

[b] Scores range from 1 to 372, with higher scores indicating higher risk of mortality.

[c] A positive FFR indicates less than or equal to 0.80.

Table 2. Two-Year Clinical Outcome

Outcome	Patient group, No. (%)		HR (95% CI)	*P* value
	High-risk (n = 143)	Non-high-risk (n = 277)		
Primary end point	22 (15.4)	23 (8.3)	1.93 (1.08-3.47)	.02
Death (any)	7 (4.9)	7 (2.5)	1.99 (0.70-5.68)	.19
Cardiac death	5 (3.5)	5 (1.8)	1.96 (0.57-6.74)[a]	.27
Nonfatal MI	6 (4.2)	8 (2.9)	1.44 (0.50-4.15)[b]	.48
Unplanned revascularization	14 (9.8)	12 (4.3)	2.33 (1.08-5.03)[b]	.02
Target vessel failure[c]	7 (4.9)	4 (1.4)	3.44 (1.01-11.72)[b]	.03
Target vessel revascularization[c]	7 (4.9)	4 (1.4)	3.44 (1.01-11.72)[b]	.03
Target lesion failure[c]	5 (3.5)	3 (1.1)	3.26 (0.78-13.63)[b]	.08
Target lesion revascularization[c]	5 (3.5)	3 (1.1)	3.26 (0.78-13.63)[b]	.08

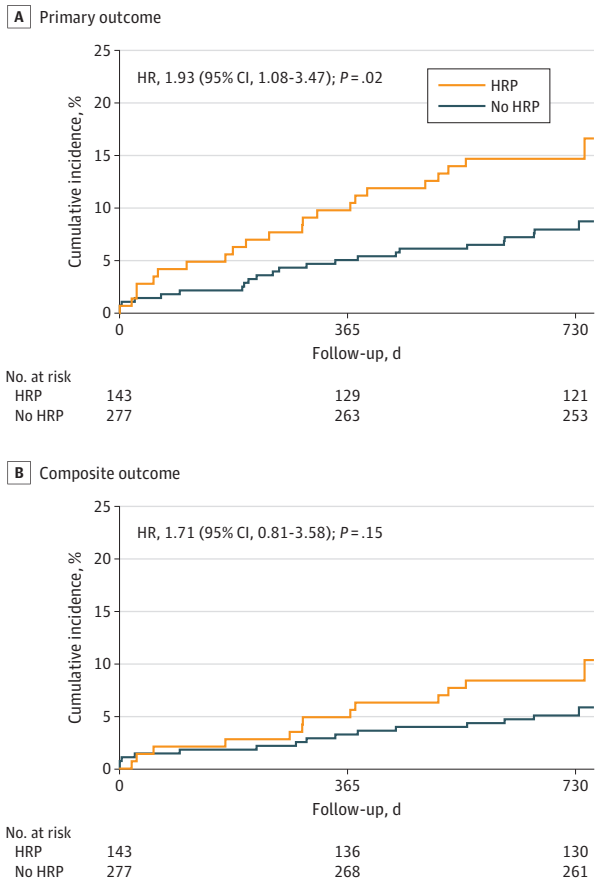
Abbreviations: HR, hazard ratio; MI, myocardial infarction.

[a] Estimated using the Fine-Gray model with noncardiac death as competing risk factor.

[b] Estimated using the Fine-Gray model with all-cause mortality as competing risk factor.

[c] Refers to the fractional flow reserve–negative nonculprit vessel or lesion imaged by optical coherence tomography.

Figure 2. Primary and Composite Outcomes



A, Kaplan-Meier curves for the primary outcome of major adverse cardiovascular events (including all-cause mortality, nonfatal myocardial infarction, or unplanned revascularization) at 2-year follow-up. B, Kaplan-Meier curves for the composite outcome of all-cause mortality or nonfatal myocardial infarction at 2-year follow-up. A hazard ratio (HR) greater than 1.00 indicates greater hazard in the high-risk plaque (HRP) group.

unplanned revascularization in this group. Also, the incidences of all secondary end points were numerically higher in the high-risk patient group. In our study, TCFA were found in 136 of 494 assessed lesions (27.5%). This is comparable to the prevalence of TCFA in nonobstructive nonculprit lesions in patients with STEMI in the COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) OCT substudy (23.2%)[23] or in FFR-negative lesions in patients with diabetes in the COMBINE (OCT-FFR) study (22.4%).[24]

These results highlight the additional value of intracoronary imaging in addition to physiological assessments of coronary lesions. Although an association is reported between FFR and certain plaque features,[10,11] FFR does not allow precise assessment of plaque morphology. Moreover, FFR measurements obtained during the index procedure in patients presenting with STEMI potentially underestimate lesion severity.[12] Nevertheless, FFR pullbacks could further help stratify patients at high risk of recurrent events by identifying lesions with a large translesional pressure gradient.[25,26]

PECTUS-obs adds to existing evidence that suggests a worse prognosis in patients with TCFA. In a large retrospective study by Kubo et al,[27] TCFA in nonculprit lesions of patients with acute coronary syndrome were associated with an increased risk of lesion level events (HR, 19.14 [95% CI, 11.74-31.20]) within a median follow-up of 6 years. Moreover, in the prospective COMBINE (OCT-FFR) study,[24] the presence of FFR-negative TCFA lesions was associated with an increased risk of MACE (HR, 4.64 [95% CI, 1.99-10.89]) at 18 months in patients with diabetes. In addition to TCFA, the a priori definition of high-risk plaques in the present study included thrombus or plaque rupture in the presence of significant lipid accumulation. These features were found in 34 (22.1%) and 45 (29.2%) high-risk lesions, respectively, and therefore only constitute a small number of the high-risk plaques. Several other plaque characteristics have also been associated with plaque instability. Among them are healed plaques, neovascularization, protruding calcification, and the presence of macrophages. Indeed, in our study, macrophages were more often seen in high-risk plaques. In the CLIMA study,[28] among patients who had undergone OCT of the LAD the simultaneous presence of 4 plaque features (minimal lumen area <3.5 mm^2, minimal fibrous cap thickness <75 µm, a lipid arc >180°, and the presence of macrophages) resulted in an HR of 7.54 (95% CI, 3.1-18.6) for a composite end point of cardiac death or target segment MI after 1 year. However, this primary end point

Table 3. Multivariate Cox Proportional Hazards Regression Model for the Primary End Point

Outcome	Patient group, No. (%)		HR (95% CI)	*P* value
	Patients with MACE (n = 45)	Patients without MACE (n = 375)		
Model A[a]				
Presence of high-risk plaque	22 (48.9)	121 (32.3)	1.99 (1.10-3.61)	.02
Age, mean (SD), y	64 (12)	63 (10)	0.99 (0.96-1.02)	.49
Prior MI	10 (22.2)	53 (14.1)	1.49 (0.71-3.13)	.29
Diabetes	10 (22.2)	51 (13.6)	1.35 (0.64-2.85)	.44
STEMI at presentation	16 (35.6)	201 (53.6)	0.55 (0.29-1.03)	.06
eGFR, mean (SD), mL/min	74 (24)	80 (18)	0.99 (0.97-1.01)	.18
Model B[b]				
Presence of high-risk plaque	22 (48.9)	121 (32.3)	2.24 (1.21-4.13)	.01
History of carotid artery disease	5 (11.1)	8 (2.1)	3.80 (1.42-10.16)	.008
STEMI at presentation	16 (35.6)	201 (53.6)	0.59 (0.31-1.12)	.11
eGFR, mean (SD), mL/min	74 (24)	80 (18)	0.99 (0.98-1.01)	.47
Lipid-lowering therapy at discharge	42 (93.3)	373 (99.5)	0.20 (0.06-0.70)	.01
RCA culprit	9 (20.0)	148 (39.5)	0.46 (0.22-0.97)	.04

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; RCA, right coronary artery; STEMI, ST-segment elevation MI.

[a] Multivariate Cox proportional hazards regression model with the presence of a high-risk plaque and age, prior MI, diabetes, STEMI or non-STEMI at presentation and eGFR as a priori determined independent variables.

[b] Multivariate Cox proportional hazards regression model with the presence of a high-risk plaque and all baseline characteristics that showed a univariate relationship with the primary outcome ($P < .05$) after checking for collinearity.

occurred only in 3.7% and the simultaneous presence of the prespecified OCT characteristics was found in only 3.6% of included patients in this study.[28]

In PECTUS-obs, only 5 patients (3.5%) in the high-risk plaque group had an event that was adjudicated to the target lesion and the yearly rate of target-vessel MI was only 0.7%. This is in line with the current view that atherosclerosis is a dynamic process in which plaques can develop and regress, and that lesions that rupture do not always result in clinical symptoms.[29] This could limit the effectiveness of focal treatment of high-risk lesions. Nonetheless, the presence of high-risk plaques was associated with MACE on a patient level. The worse prognosis seen in patients with a high-risk plaque might reflect a more advanced stage of atherosclerosis throughout the coronary tree. Considering that MI in itself is a marker of high-risk of future MACE, patients who also harbor high-risk plaques might especially benefit from aggressive lipid-lowering or anti-inflammatory therapy.[30,31] However, given the low rate of adverse events in contemporary PCI, focal stenting of high-risk plaques could also be proposed. The randomized PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II) ABSORB substudy[32] demonstrated that preventive PCI was safe and resulted in enlarged luminal dimensions directly after bioresorbable vascular scaffold implantation and remained larger compared with optimal medical therapy only after a median follow-up of 4.2 years. These data, however, are only hypothesis generating, given the small sample size, and the positive predictive value of distinct high-risk plaque features for lesion level events is low.[28] The effect of preventive PCI of high-risk plaques on clinical end points is currently under investigation in several large randomized trials.[33-36]

Limitations

This study has some limitations. We performed targeted imaging of FFR-negative nonculprit lesions instead of 3-vessel OCT. Therefore, we might have missed high-risk lesions. However, such targeted evaluation might be more feasible in clinical practice. We did not perform FFR pullbacks, which may further help identify high-risk patients. Operators were not blinded to OCT findings, which could potentially have led to altered decision-making. However, the OCT analyses were performed post hoc by an independent OCT core laboratory. Neither these analyses nor the group allocation was available to the operators or other clinicians involved. We did not perform OCT imaging of the culprit lesion. Therefore, a limited amount of nonculprit lesions with plaque rupture or thrombus could in fact be the culprit lesion, especially among patients with NSTEMI. Moreover, the assessment of the residual fibrous cap thickness in case of plaque rupture could be cumbersome. Women were underrepresented in the current cohort. Last, the prevalence of high-risk plaque and number of events in this study were lower than expected, and the study was not powered to assess differences in the individual components of the primary end point, of which only difference in unplanned revascularization was found to be statistically significant.

Conclusions

To our knowledge, PECTUS-obs is the first prospective cohort study to show that among patients with MI and FFR-negative nonculprit lesions, the presence of a high-risk plaque is associated with a worse clinical outcome, with higher number of unplanned revascularizations being a primary factor. In a population with a high rate of recurrent events, despite physiology-guided complete revascularization, these results call for research on the potential benefit of additional pharmacological or focal treatment strategies in patients harboring high-risk plaques.

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