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Eroded Versus Ruptured Plaques at the Culprit Site of STEMI

In Vivo Pathophysiological Features and Response to Primary PCI

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the pathophysiological features and response to primary percutaneous coronary intervention (PCI) of nonruptured/eroded plaque versus ruptured plaque as a cause of ST-segment elevation myocardial infarction (STEMI).

BACKGROUND Autopsy series identified nonruptured/eroded plaque and ruptured plaque as the principal pathological substrates underlying coronary thrombosis in STEMI. The real incidence of different plaque morphologies, associated biological factors, superimposed thrombus, and their interaction with primary PCI remain largely unknown.

METHODS In a prospective study, 140 patients with STEMI underwent optical coherence tomography of the infarct-related artery (IRA) before PCI, after everolimus-eluting stent implantation and at 9-month follow-up. Histopathology and immunohistochemistry of thrombus aspirates and serum biomarkers were assessed at baseline.

RESULTS Culprit plaque morphology was adjudicated in 97 patients: 32 plaques (33.0%) with an intact fibrous cap (IFC), 63 (64.9%) plaques with a ruptured fibrous cap (RFC), and 2 (2.1%) spontaneous dissections. Patients with an IFC and RFC had similar clinical characteristics, and serum inflammatory and platelets biomarkers. An IFC presented more frequently with a patent IRA (56.2% vs. 34.9%; $p = 0.047$), and had fewer lipid areas (lipid-rich areas: 75.0% vs. 100.0%; $p < 0.001$) and less residual thrombus before stenting (white thrombus: 0.41 mm^3 vs. 1.52 mm^3; $p = 0.001$; red thrombus: 0 mm^3 vs. 0.29 mm^3; $p = 0.001$) with a lower peak of creatine kinase-myocardial band (66.6 IU/l vs. 149.8 IU/l; $p = 0.025$). At the 9-month optical coherence tomography, IFC and RFC had similar high rates of stent strut coverage (92.5% vs. 91.2%; $p = 0.15$) and similar percentage of volume obstruction (12.6% vs. 10.2%; $p = 0.27$). No significant differences in clinical outcomes were observed up to 2 years.

CONCLUSIONS In the present study, an IFC was observed at the culprit lesion site of one-third of STEMIs. IFC, compared with RFC, was associated with higher rates of patent IRA at first angiography, fewer lipid areas, and residual endoluminal thrombus. However, no difference in vascular response to everolimus-eluting stent was observed. (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty [OCTAVIA]; NCT01377207)
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The cornerstone of ST-segment elevation acute myocardial infarction (STEMI) treatment is rapid flow restoration with primary angioplasty and stenting (1,2). Autopsy series showed that plaques underlying coronary thrombi in acute myocardial infarction may have different features, and the most common phenotypes are plaque rupture and plaque erosion (3). The potential impact of different culprit plaque characteristics in STEMI patients undergoing revascularization remains a matter of debate (4), but different plaque morphologies might be potentially amenable to different treatments (5). A tailored approach to STEMI treatment would require improved understanding of atherothrombosis, as well as the ability to distinguish in vivo various plaque morphologies. Finally, it remains unknown whether different plaque types might elicit a distinct vascular response to stent implantation.

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Postmortem data highlighted that a ruptured plaque is by far the most common cause of coronary thrombosis in acute myocardial infarction (3,6). Conversely, nonruptured/eroded plaque, the second cause of coronary thrombosis in ex vivo series, is characterized by endoluminal thrombosis without evidence of plaque rupture in serial sectioning of the arterial segment (3,6–8). However, pathology studies are limited by the potential patient selection bias, and they cannot assess the impact of plaque phenotypes on the results of coronary interventions. Therefore, in patients presenting with STEMI, the incidence, the biological characteristics, and the clinical impact associated with different culprit plaque morphologies remain unclear.

Optical coherence tomography (OCT) in patients with acute coronary syndromes allows accurate in vivo detection and measurements of culprit plaque with intact fibrous cap (IFC) and with ruptured fibrous cap (RFC), intracoronary thrombus, thin-cap fibroatheroma (TCFA), and the healing response to stent implantation, being closely correlated with pathology (9). In patients with STEMI, OCT has been shown to be safe and superior to other intravascular imaging modalities for plaque differentiation (10,11).

The objectives of this prospective, multicenter study in patients presenting with STEMI were the following: 1) to define the incidence of different culprit plaque morphologies detected by OCT in clinical practice; 2) to assess clinical characteristics, plaque features, and serum components associated with IFC compared with RFC; and 3) to compare the acute and chronic vascular response to current-generation drug-eluting stents implanted in patients with IFC versus RFC.

ABBREVIATIONS AND ACRONYMS

CSA = cross-sectional area
EES = everolimus-eluting stent
IFC = intact fibrous cap
IRA = infarct-related artery
MPO = myeloperoxidase
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
RFC = ruptured fibrous cap
STEMI = ST-segment elevation myocardial infarction
TCFA = thin-cap fibroatheroma
TIMI = Thrombolysis In Myocardial Infarction

METHODS

STUDY DESIGN AND POPULATION. The present study, which focused on the comparison of patients presenting with IFC versus RFC at the culprit site of STEMI, represents a pre-specified analysis of the OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty) trial (12). The full study design and methodology were previously reported (12). In brief, the OCTAVIA trial was a prospective, multicenter, investigator-driven trial that enrolled 140 STEMI patients presenting within 6 h of symptom onset. All patients underwent primary percutaneous coronary intervention (PCI) and received the Xience Prime everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California). The study was approved by the ethics committee at each participating center, and all enrolled patients provided written informed consent. For a list of the OCTAVIA Study Organization, please see the Online Appendix.

STUDY PROCEDURES. OCT pullback of the infarct-related artery (IRA) was performed before PCI, using a Frequency Domain OCT system (C7-XRTM

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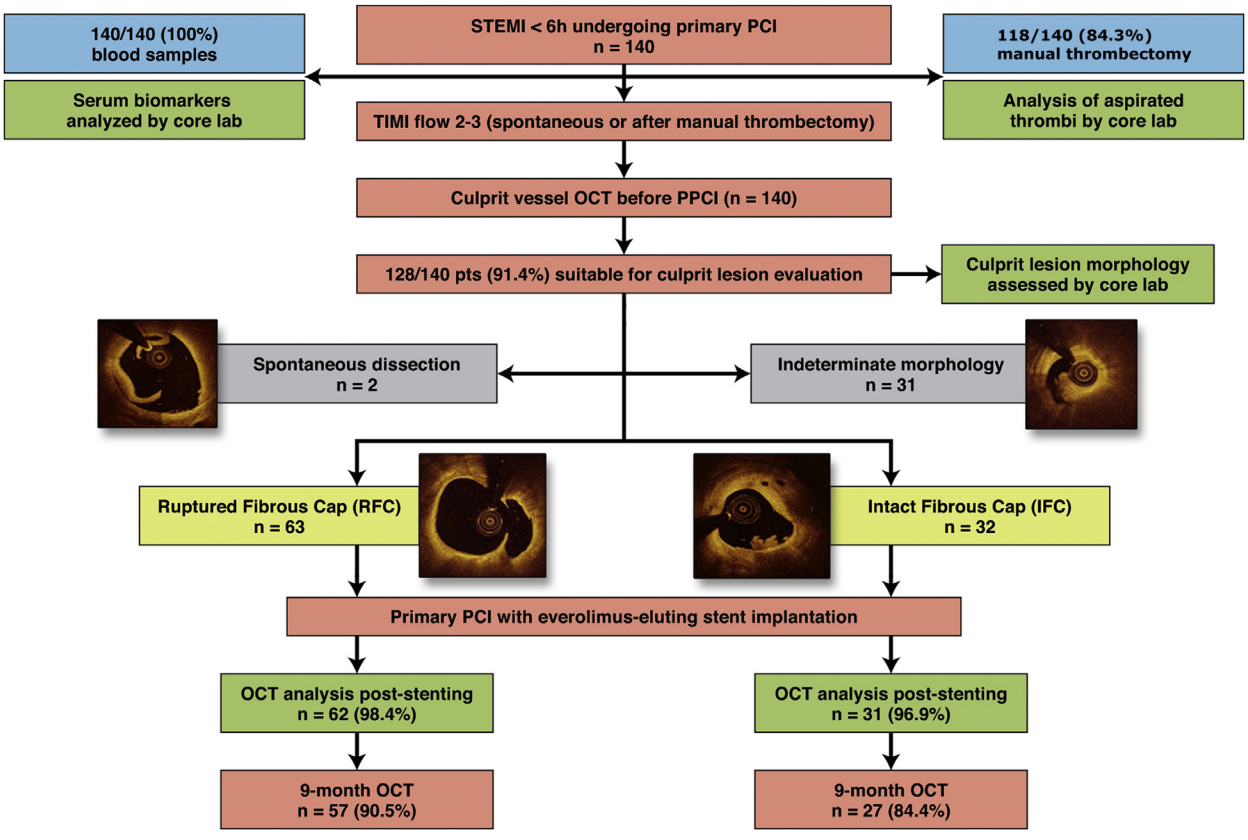
OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota). If Thrombolysis In Myocardial Infarction (TIMI) flow grade 0/1 or extensive thrombus was present at baseline, the OCT pullback was performed after manual thrombectomy. PCI was then performed according to local practice, and all patients received 1 or more EES. Aspirin 250 mg was given intravenously immediately before PCI, followed by 100 mg/day orally during hospitalization and indefinitely thereafter. A loading dose of clopidogrel (600 mg) or prasugrel (60 mg) was administered at the operator's discretion before PCI followed by a 75-mg (clopidogrel) or 10-mg (prasugrel) oral maintenance dose daily for 12 months. Clinical examinations were performed at 30 days, 9 months, and 1 and 2 years. Angiographic and OCT follow-up at 9 months after stent implantation was electively planned in all patients.

OCT ANALYSIS. All OCT images were analyzed by an independent core laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center, Cleveland, Ohio) using previously standardized criteria (13-16). Qualitative analysis was performed every 0.2 mm along the entire target segment. RFC was defined by the presence of a cavity formation in the plaque beginning at the luminal-intimal border with a clear discontinuity of the thin fibrous cap; IFC was defined by no evidence of cap rupture at the culprit site, evaluated in multiple adjacent frames, and the presence of thrombus on an irregular luminal surface; spontaneous dissection was identified by the presence of an intimal-medial flap with intramural hematoma; plaque morphology was defined unclassifiable when OCT was unable to distinguish the lesion type because of an excess of thrombus obscuring the underlying structures. Each OCT cross section was divided into 4 quadrants, and culprit plaques were classified as calcified, fibrous, or lipid rich when these components were present

FIGURE 1 Study Flow



OCT = optical coherence tomography; PCI = percutaneous coronary intervention; pts = patients; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

in ≥2 contiguous quadrants in any of the images within a plaque (12,14). If 2 adjacent quadrants fulfilled the criteria for 1 component and the other 2 adjacent quadrants fulfilled the criteria for another plaque component, plaque composition was attributed to both components. TCFA was defined as a lipid-rich plaque with a thin fibrous cap thickness <65 μm, and the mean cap thickness was computed as the mean of 3 evenly distributed measurements along the fibrous cap. Quantitative OCT analyses were performed using dedicated software (OCT system software B.0.1, LightLab Imaging Inc., Westford, Massachusetts). For red thrombus quantification, due to the limitations imposed by intense backscattering and signal attenuation, a careful analysis of adjacent frames, each 0.2 mm, was performed. Whenever the inmost thrombus border could not be identified, anchor points were positioned at the deepest identifiable side edges, and automatic software interpolation was used for determination of the thrombus border.

For morphometric analysis, standard definitions of cross-sectional area (CSA) were applied as previously reported (16). Proximal and distal references were measured at the site with the largest lumen within 5 mm proximal and distal to the lesion/stented segment. Stent, lumen, and neointimal hyperplasia CSA were measured each 0.6 mm throughout the entire length of the stent. The minimal stent CSA divided by the average of proximal and distal reference lumen CSA ratio was calculated as a parameter of stent expansion.

For the strut-level analysis, the strut-lumen distance was determined based on automated measurements performed from the center of the strut blooming to the luminal contour of the artery wall. Incomplete strut apposition was defined when this distance was greater than the sum of strut thickness plus the abluminal polymer thickness according to stent manufacturer specifications plus a compensation factor of 18 μm to correct for strut blooming. Struts were considered covered by OCT if tissue could be identified above the struts and uncovered if no evidence of tissue could be visualized above the struts. The percentage of covered and uncovered stent struts was calculated as the number of struts with or without distinct overlying tissue, respectively, divided by the total number of analyzable struts.

THROMBUS ANALYSIS. Thrombus aspirates were sent to the histopathology core laboratory (CV Path Institute, Gaithersburg, Maryland) (12,17). All sections were examined by light microscopy for the presence of platelets, fibrin, red blood cells, plaque constituents, and markers of inflammation. Five high-power fields (×400) demonstrating the greatest severity of inflammation were selected for semi-quantitative analyses. The mean values of total white blood cells and positive cells based on immunohistochemistry were obtained and averaged for the selected 5 high-power fields. Additionally, immunohistochemical staining including the granulocyte marker myeloperoxidase (MPO), CD68 (macrophages), and the eosinophil marker interleukin 5 was performed to further characterize specific inflammatory cell types. A CD42b stain was used for the detection of platelets.

SERUM BIOMARKERS. Blood samples were collected before baseline coronary angiography, stored at −80°, and sent to the core laboratory (Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy) for analysis. Serum C-reactive protein, MPO, eosinophil cationic protein, and thromboxane B_2 were measured as previously described (12).

CLINICAL OUTCOMES. Major adverse cardiac or cerebrovascular events, including cardiac death, recurrent myocardial infarction, stroke, target-lesion revascularization, and stent thrombosis, were assessed at 30 days and 1 and 2 years. Stent thrombosis was defined according to the Academic Research Consortium classification (18).

STATISTICAL ANALYSIS. Continuous data are reported as mean ± SD or median (first to third quartiles, depending on validity or lack of normality assumptions). Categorical data are reported as numbers and relative percentage. Overall comparisons across groups were based on the Student *t* test for continuous variables

TABLE 1 Baseline Clinical Characteristics

	IFC (n = 32)	RFC (n = 63)	p Value
Age, yrs	69.5 (59.0–74.5)	68.0 (60.0–76.0)	0.77
Male	16 (50.0)	32 (50.8)	0.94
BMI	26.7 (23.6–30.1)	26.0 (24.2–29.7)	0.78
Hypertension	18 (56.2)	34 (54.0)	0.83
Dyslipidemia	8 (25.0)	18 (28.6)	0.71
Smoking	18 (56.2)	33 (52.4)	0.72
Diabetes	4 (12.5)	6 (9.5)	0.73
Insulin-treated	2 (6.2)	0 (0.0)	0.11
Previous MI	0 (0.0)	1 (1.6)	1.00
Previous angina	4 (12.5)	4 (6.3)	0.44
Time from symptom onset to cath lab, min	153 (124–229)	140 (95–195)	0.09
Peak CK-MB, IU/l	66.6 (33.3–141.4)	149.8 (52.9–230.0)	0.025

Values are median (interquartile range) or n (%).

BMI = body mass index; CK-MB = creatine kinase-myocardial band; IFC = intact fibrous cap; MI = myocardial infarction; RFC = ruptured fibrous cap.

(or the Mann-Whitney *U* test in case of significant departures from normality assumptions, i.e., $p < 0.05$ on the Kolmogorov-Smirnov or Shapiro-Wilks test) and the chi-square test for categorical variables (or the Fisher exact test when an expected cell count was <5). In addition, variability in strut coverage and other quantitative OCT parameters was appraised by means of the Brown-Forsythe test for equality of variances. Event-free survival was estimated with Kaplan-Meier analysis, and the log-rank method was used for comparison between groups. All tests were 2 sided, and statistical significance was defined as $p < 0.05$. The interobserver and intraobserver kappa statistics for the qualitative assessment of plaque rupture/erosion were 0.845 (95% confidence interval: 0.769 to 0.921; $p < 0.001$) and 0.907 (95% confidence interval: 0.781 to 1.00; $p < 0.001$), respectively. The core laboratory relative difference for the quantitative OCT endpoints was ~1%, as previously reported (15).

TABLE 2 Angiographic and Procedural Characteristics

	IFC (n = 32)	RFC (n = 63)	p Value
Infarct-related artery			0.95
LAD	15 (46.9)	28 (44.5)	
LCX	2 (6.2)	6 (9.5)	
RCA	15 (46.9)	29 (46.0)	
Culprit lesion site			0.76
Proximal	9 (28.1)	21 (33.3)	
Mid-vessel	15 (46.9)	30 (47.6)	
Distal vessel	8 (25.0)	12 (19.0)	
Multivessel coronary disease	14 (43.8)	37 (58.7)	0.17
Thrombus aspiration	26 (81.2)	56 (88.9)	0.35
TIMI flow grade at presentation			0.047
0/1	14 (43.8)	41 (65.1)	
2/3	18 (56.2)	22 (34.9)	
Stent diameter, mm	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.85
Stent length, mm	22.1 (17.2–26.5)	22.3 (17.4–31.0)	0.65
Post-dilation	19 (59.4)	35 (55.6)	0.72
Final TIMI flow grade			1.00
0/1	0 (0.0)	0 (0.0)	
2	1 (3.1)	3 (4.8)	
3	31 (96.9)	60 (95.2)	
Baseline QCA			
Reference vessel diameter, mm	2.63 ± 0.56	2.66 ± 0.55	0.79
Minimal lumen diameter, mm	0.25 (0.00–0.50)	0.00 (0.00–0.54)	0.58
DS, %	88 (77–100)	100 (80–100)	0.54
Lesion length, mm	13.0 (10.0–17.2)	13.5 (9.4–20.9)	0.99
QCA post-procedure			
Reference vessel diameter, mm	2.83 ± 0.56	2.73 ± 0.50	0.40
Minimal lumen diameter, mm	2.48 (2.24–3.10)	2.35 (2.10–2.75)	0.28
DS, %	8.0 (4.0–12.0)	10.0 (6.5–14.0)	0.36
9-month QCA			
Reference vessel diameter, mm	2.57 ± 0.56	2.56 ± 0.49	0.96
Minimal lumen diameter, mm	2.00 (1.52–2.55)	1.96 (1.50–2.34)	0.66
DS, %	19.0 (9.0–29.0)	22.0 (13.0–32.5)	0.50
Late lumen loss, mm	0.20 (0.03–0.40)	0.22 (0.06–0.44)	0.66

Values are n (%) or median (interquartile range).

DS = diameter stenosis; LAD = left anterior descending artery; LCX = left circumflex artery; QCA = quantitative coronary analysis; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

RESULTS

PATIENTS AND BASELINE FEATURES. All 140 patients enrolled in the study had OCT assessment before primary PCI (Figure 1). A total of 12 patients were not further classified because OCT did not satisfy the pre-specified quality criteria (12). In 31 patients, culprit lesion morphology could not be clearly attributed because of excessive residual intraluminal thrombus (n = 22) or intimal dissection considered secondary to thrombectomy (n = 9). No differences in baseline and procedural characteristics were observed between patients with classified versus unclassified culprit plaques except for the rate of thrombus at presentation (81.4% vs. 96.8%; $p = 0.04$) (12). Hence, a fully identifiable culprit plaque morphology was adjudicated in 97 patients, with RFC identified in 63 (64.9%), IFC in 32 (33.0%), and spontaneous dissection in 2 (2.1%). There were no significant differences between RFC and IFC groups in demographic factors, risk factors, and clinical history (Table 1). However, patients with IFC presented more frequently with an open IRA (Thrombolysis In Myocardial Infarction [TIMI] flow grade of 2 or 3: 56.2% IFC vs. 34.9% RFC; $p = 0.047$) (Table 2). Baseline lesion severity was not significantly different (percentage of diameter stenosis, 88% IFC vs. 100% RFC; $p = 0.54$). Although the final TIMI flow grade was similar between groups (TIMI flow grade 3 >95% in both), patients with IFC had a lower peak level of creatine kinase-myocardial band (66.6 IU/l vs. 149.8 IU/l, $p = 0.025$). No difference in the type of antiplatelet agent was observed in patients with IFC versus RFC (clopidogrel, 84.4% IFC vs. 79.4% RFC; prasugrel, 15.6% IFC vs. 20.6% RFC; $p = 0.56$).

BASELINE OCT. The OCT analysis showed that IFC had residual thrombus less frequently before stent implantation (84.4% vs. 98.4%, $p = 0.016$) and lower volumes of both white (0.41 mm^3 vs. 1.52 mm^3; $p = 0.001$) and red thrombus (0 mm^3 vs. 0.29 mm^3; $p = 0.001$), but a similar minimal lumen area (mean 1.27 mm^2 vs. 1.17 mm^2; $p = 0.91$) (Table 3). Further, IFC had fewer lipid areas (75% vs. 100%; $p < 0.001$) and more fibrotic areas (25.0% vs. 0.0%; $p = 0.005$) at the culprit site. The incidence of any additional TCFA along the IRA was significantly lower in patients with IFC compared with those with RFC (46.9% vs. 93.7%; $p < 0.001$).

TABLE 3 Optical Coherence Tomography Analysis

	IFC (n = 32)	RFC (n = 63)	p Value
Pre-stent implantation			
Proximal reference area, mm^2	7.66 (5.89–11.42)	7.37 (5.96–9.96)	0.59
Distal reference area, mm^2	5.46 (4.04–8.65)	5.97 (4.46–8.61)	0.58
Minimal lumen area, mm^2	1.27 (1.21–1.55)	1.17 (0.93–1.67)	0.91
Culprit plaque components, %			
Calcified	0.0 (0.0–25.0)	0.0 (0.0–0.0)	0.08
Fibrotic	25.0 (0.0–43.8)	0.0 (0.0–0.0)	0.005
Lipid rich	75.0 (25.0–75.0)	100 (75.0–100.0)	<0.001
Normal	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.057
Mean fibrous cap thickness at culprit site, μm	203 (176.0–252.0)	171 (150.0–215.0)	0.0017
Minimal fibrous cap thickness at culprit site, μm	69 (51–77)	47 (38–48)	<0.001
Thrombus presence	27 (84.4)	62 (98.4)	0.016
White thrombus			
Presence	25 (78.1)	62 (98.4)	0.002
Volume, mm^3	0.41 (0.03–1.85)	1.52 (0.69–3.20)	0.001
Red thrombus			
Presence	14 (43.8)	36 (57.1)	0.22
Volume, mm^3	0.00 (0.00–2.76)	0.29 (0.00–1.31)	0.001
TCFA along the culprit vessel*	15 (46.9)	59 (93.7)	<0.001
Mean cap thickness, μm	49.4 (46.4–51.0)	50.9 (48.3–54.3)	0.13
Post-stent implantation†	31	62	
Mean stent area, mm^3	7.04 (5.65–10.36)	7.19 (5.65–9.44)	0.82
Stent expansion index	82.8 (77.1–88.3)	83.0 (76.7–87.5)	0.68
% Protrusion volume	7.4 (4.0–14.5)	9.1 (5.5–13.7)	0.07
Mean malapposition area, mm^2	0.07 (0.03–0.22)	0.09 (0.03–0.25)	0.62
9-month follow-up	27	57	
Frame level analysis			
Minimal stent area, mm^2	5.89 (4.50–9.12)	6.18 (4.60–7.96)	0.81
Minimal lumen area, mm^2	4.57 (3.09–7.36)	5.39 (3.38–6.79)	0.81
Mean NIH area, mm^2	0.87 (0.50–1.17)	0.70 (0.42–1.11)	0.28
Volume obstruction, %	12.6 (5.4–20.8)	10.2 (6.1–15.3)	0.27
Mean malapposition area, mm^2	0.14 (0.00–0.19)	0.02 (0.00–0.18)	0.58
Strut level analysis			
Total analyzed struts/patients	161 (113–196)	138 (114–220)	0.99
Covered struts, %	92.5 (82.4–99.5)	91.2 (81.7–96.3)	0.15
Malapposed struts, %	0.3 (0.0–5.1)	0.6 (0.0–4.6)	0.88
Mean NIH area, mm^2	101 (57–152)	97 (58–126)	0.28

Values are median (interquartile range), n (%), or n. *Number of TCFAs observed along the scanned segment into the culprit vessel, outside the culprit lesion. †No differences were observed between IFC and RFC in terms of not analyzed frames and struts, both post-stenting and at 9-month follow-up (data not reported).

NIH = neointimal hyperplasia; TCFA = thin-cap fibroatheroma; other abbreviations as in Table 1.

THROMBUS AND BIOMARKER ANALYSIS. Consistent with OCT findings, thrombus aspirates of sufficient amount for histology analysis were retrieved less frequently in patients with IFC (40.6% vs. 66.7%; p = 0.015), but there were no significant differences in thrombus components, inflammation scores, and thrombus age between groups (Table 4). The presence of plaque material was significantly lower in the IFC group (7.1% vs. 54.8%; p = 0.003). Immunohistochemistry did not show significant differences between IFC and RFC, with the notable exception of a higher amount of eosinophils in the IFC group (interleukin-5: 5 high-power fields, 1 [0 to 1] vs. 0 [0 to 1]; p = 0.01). There were no significant differences between groups in the analyzed blood biomarkers of inflammation and platelet activation (Table 4).

ACUTE RESULTS AND CLINICAL OUTCOMES. The acute results of primary PCI with the EES were also comparable between groups (Tables 2 and 3). At 9-month follow-up, the stent parameters were not significantly different between groups. Importantly, independent of the lesion morphology, we observed low levels of neointima obstruction, high rates of

TABLE 4 Histopathology and Immunohistochemistry of Aspirated Thrombus and Blood Biomarkers

	IFC (n = 32)	RFC (n = 63)	p Value
Analyzed thrombus	13 (40.6)	42 (66.7)	0.015
Thrombus volume, mm^3	9 (2–15)	6 (3–25)	0.47
Thrombus age			1.00
Early	10 (76.9)	32 (76.2)	
Organized	3 (23.1)	10 (23.8)	
Platelet presence	13 (100)	42 (100)	1.00
Average WBCs, cells/5HPF	75 (50–250)	75 (75–200)	0.96
Inflammation score	1.0 (1.0–2.5)	1.0 (1.0–2.0)	0.91
Plaque material	1 (7.7)	23 (54.8)	0.003
Immunohistochemistry			
MPO, cells/5HPF	46 (17–86)	43 (30–104)	0.73
CD68, cells/5HPF	15 (7–28)	20 (15–50)	0.12
IL-5, cells/5HPF	1 (0–1)	0 (0–1)	0.01
CD42b, score	2 (2–2.5)	2 (2–3)	0.98
Blood biomarkers	27	60	
hsCRP, mg/l	1.72 (1.02–3.49)	2.10 (0.79–4.93)	0.72
ECP, ng/ml	3.69 (2.00–9.40)	4.80 (2.70–9.62)	0.36
TXB2, pg/ml	93.2 (53.0–214.8)	134.8 (57.7–295.9)	0.19
MPO, µg/l	526.2 (289.5–905.8)	649.3 (300.0–1,695.0)	0.34

Values are n (%), median (interquartile range), or n.

ECP = eosinophil cationic protein; hsCRP = high-sensitivity C-reactive protein; MPO = myeloperoxidase; IL = interleukin; TXB2 = thromboxane B_2; 5HPF = 5 high-power fields (×400); WBCs = white blood cells; other abbreviations as in Table 1.

TABLE 5 Clinical Outcomes

	IFC (n = 32)	RFC (n = 63)	p Value
30 days			
MACCE	2 (6.2)	1 (1.6)	0.26
Death	1 (3.1)	0 (0.0)	0.34
Cardiac	1 (3.1)	0 (0.0)	0.34
Noncardiac	0 (0.0)	0 (0.0)	1.00
Reinfarction	0 (0.0)	1 (1.6)	1.00
Stroke	1 (3.1)	0 (0.0)	0.34
Stent thrombosis	0 (0.0)	1 (1.6)	1.00
Definite	0 (0.0)	1 (1.6)	1.00
Probable	0 (0.0)	0 (0.0)	1.00
Ischemia-driven TLR	0 (0.0)	1 (1.6)	1.00
Target vessel revascularization	0 (0.0)	1 (1.6)	1.00
1 Year			
MACCE	3 (9.4)	4 (6.3)	0.68
Death	3 (9.4)	2 (3.2)	0.33
Cardiac	2 (6.4)	0 (0.0)	0.11
Noncardiac	1 (3.1)	2 (3.2)	1.00
Reinfarction	0 (0.0)	1 (1.6)	1.00
Stroke	1 (3.1)	0 (0.0)	0.34
Stent thrombosis	0 (0.0)	1 (1.6)	1.00
Definite	0 (0.0)	1 (1.6)	1.00
Probable	0 (0.0)	0 (0.0)	1.00
Ischemia-driven TLR	0 (0.0)	4 (6.3)	0.30
Target vessel revascularization	1 (3.1)	7 (11.1)	0.26

Values are n (%).

MACCE = major adverse cardiac or cerebrovascular events; TLR = target lesion revascularization; other abbreviations as in Table 1.

strut coverage, and minimal rates of late malapposition (Table 3). At 1- and 2-year follow-up, the incidence of major adverse cardiac or cerebrovascular events was low, without statistically significant differences between the 2 study groups (Table 5, Figure 2). Stent thrombosis (subacute) occurred in only 1 patient in the RFC group.

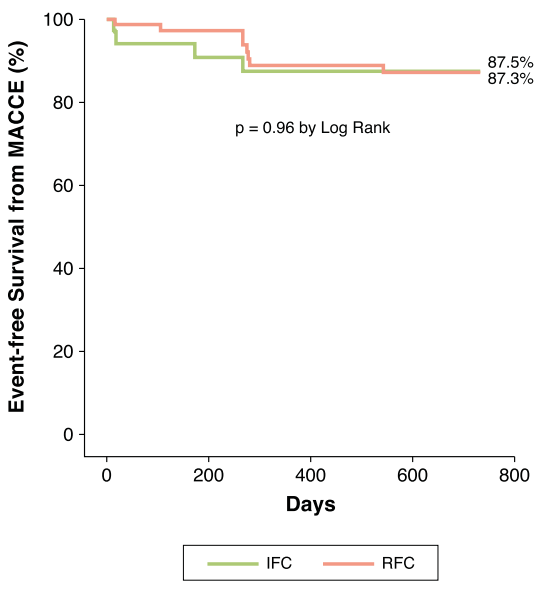
DISCUSSION

The principal findings of this study are the following. 1) An IFC was present in the culprit lesion in one-third of the cases of STEMI investigated in vivo. 2) The morphology of the culprit plaque was not associated with specific clinical factors or biological markers. 3) Compared with RFC, IFC presented more frequently with a patent IRA and was associated with fewer lipid areas, lower frequency of additional TCFAs along the culprit vessel, less thrombus presence and amount, and a lower creatine kinase-myocardial band peak post-PCI. 4) There were no major differences in acute and chronic vascular response to PCI with current-generation EES in patients with different culprit plaque morphology.

First, in our study that included patients of all ages and considered only culprit plaques with a clearly identified morphology, the incidence of IFC was 33%, whereas RFC was observed in 64.9%. This observation is consistent with pathology series and smaller OCT studies (3,6,10,19). Calcified nodules, i.e., nodular calcifications protruding into the lumen and described as a rare cause of coronary thrombosis in autopsy series, were not identified in our series. A plausible explanation can be found in the exclusion of patients with heavily calcified and tortuous coronary arteries (12), which are more likely to present calcified nodules (3). Nevertheless, our findings are consistent with no evidence of calcified nodules as culprit plaque in STEMI patients reported in vivo by others using OCT (20). In addition, calcific nodules were not shown to be related to future cardiovascular events in the prospective PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study (21).

Second, we compared clinical characteristics and blood biomarkers between patients with IFC and those with RFC and found no significant difference in all analyzed parameters (Tables 1 and 4). Plaque erosion has been observed in ex vivo studies more frequently in females and young individuals (3,6). In the main report from the OCTAVIA trial, we found that, when age matched, STEMI men and women did

FIGURE 2 Event-Free Survival According to Culprit Plaque Morphology



Survival free from major adverse cardiac or cerebrovascular events (MACCE). IFC = intact fibrous cap; RFC = ruptured fibrous cap.

not show different mechanisms of coronary thrombosis (12). Similar findings were recently reported by Jia et al. (20).

Previous studies found higher levels of serum MPO in patients with IFC compared with those with RFC, raising the hypothesis that increases in selective inflammatory biomarkers might be associated with different plaque morphologies (22). In our study, we did not observe significant differences in blood biomarkers of inflammation and platelet activation between patients with IFC and RFC, including MPO, suggesting that patient selection biases may be responsible for many of the observed discrepancies across studies (3).

Third, the presence of endoluminal thrombus initially detected by OCT at the culprit site was high in both groups but significantly lower in IFC compared with RFC, with less residual white and red clot volume after thrombus aspiration in the IFC group (Table 3). This is not surprising because in RFC, the exposed necrotic core is highly thrombogenic (3,23). The lower thrombus burden in IFC may explain the lower creatine kinase-myocardial band peak compared with patients with RFC, a finding consistent with previous intravascular ultrasound studies demonstrating larger infarct size in patients with evidence of plaque rupture as opposed to different plaque phenotypes (24,25). The composition of aspirated thrombi was similar between groups (Table 4), whereas less plaque material was retrieved in patients with IFC. This feature is consistent with the lower lipid content of eroded plaques observed by OCT both at the culprit site and along the IRA, combined with less TCFA. Immunohistochemistry analysis of aspirated thrombi showed only a slightly higher yet statistically significant different number of eosinophils, marked with interleukin-5, in association with eroded plaque. This observation may suggest an activation of eosinophils in a subset of patients with IFC, favoring thrombus growth even in the absence of plaque rupture due to the strong prothrombotic activity of eosinophilic granules (26).

Fourth, an important finding of our study is that there was not a significantly different vascular response to the EES between groups. Indeed, quantitative coronary analysis and OCT parameters at 9-month follow-up were very similar, including late lumen loss, diameter stenosis, neointimal area, stent strut coverage, and malapposition (Tables 2 and 3).

Whether plaque morphology underlying STEMI should lead to a different therapeutic approach remains speculative. Previous studies suggested that OCT may identify patients with eroded, subcritically occlusive plaque that can be treated with thrombectomy alone without stenting (4,5). In the present study, IFC and RFC showed similar degrees of stenosis and a high incidence of residual endoluminal thrombus after manual thrombectomy, raising doubts about a different treatment strategy. Furthermore, vascular response to the EES was excellent and similar in both groups.

STUDY LIMITATIONS. First, the population enrolled was not representative of a high-risk STEMI cohort, and a number of patients could not be included. The study was, in fact, designed to avoid any unnecessary delay due to OCT pullback before restoring myocardial reperfusion, and patients were not enrolled if good coronary flow could not be obtained with thrombus aspiration only. Second, 24% of lesions had indeterminate morphology on OCT. However, this was essentially due to the strict quality criteria applied by the OCT core laboratory, and comparable rates were found by other authors (20). Third, the extent to which OCT can identify all features recognized by pathology remains to be verified. Although the identification of RFC with OCT has a high level of evidence (13), IFC can be classified with a lower level of confidence, and its definition is

still debated. Fourth, OCT criteria for quantitative measurement of red thrombus have not been fully validated, and relative data should be interpreted cautiously. Finally, the sample size was underpowered for clinical endpoints, and comparison between the 2 study groups reported in Table 5 has only a descriptive purpose.

CONCLUSIONS

In the present study, an IFC consistent with plaque erosion was observed at the culprit lesion site in one-third of patients with STEMI. IFC compared with RFC was associated with higher rates of patent IRA at first angiography, fewer lipid areas, and endoluminal thrombus. However, no difference in vascular response to EES was observed.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The most common culprit plaque phenotype in STEMI is a lipid-rich plaque with RFC. Plaque erosion, i.e., coronary thrombosis in the presence of a plaque with an IFC, accounts for one-third of the cases. Apparently, there is no significant association of plaque morphology with clinical factors or standard markers of inflammation and platelet activation. IFC seems to be associated with higher rates of a patent IRA at first angiography, fewer lipid areas, and less endoluminal thrombus. However, no difference in vascular response to current-generation drug-eluting stents has been observed.

TRANSLATIONAL OUTLOOK: The best treatment for STEMI is rapid flow restoration with primary angioplasty and stenting, preferably with drug-eluting stents. In this setting, the potential impact of different culprit plaque characteristics is a matter of debate because different plaque morphologies might be amenable to different treatments. Further studies are necessary to better delineate the mechanisms of atherothrombosis in STEMI and to test the potential role of a tailored approach based on different culprit plaque phenotypes.

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KEY WORDS culprit plaque, optical coherence tomography, percutaneous coronary intervention, plaque erosion, ST-segment elevation myocardial infarction

APPENDIX For a list of the OCTAVIA Study Organization, please see the online appendix.