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CORONARY

Mechanisms of Atherothrombosis and Vascular Response to Primary Percutaneous Coronary Intervention in Women Versus Men With Acute Myocardial Infarction

Results of the OCTAVIA Study

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CME Objective for This Article: At the completion of this article, the learner should be able to: 1) describe the theoretical gender differences in the pathophysiology of STEMI as suggested by autopsy studies; 2) define the plaque phenotypes that can be observed by optical coherence tomography; and 3) identify the primary endpoints of the OCTAVIA study.

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Mechanisms of Atherothrombosis and Vascular Response to Primary Percutaneous Coronary Intervention in Women Versus Men With Acute Myocardial Infarction

Results of the OCTAVIA Study

ABSTRACT

OBJECTIVES This study sought to assess in vivo sex differences in the pathophysiology of ST-segment elevation myocardial infarction (STEMI) and vascular response to primary percutaneous coronary intervention (PCI).

BACKGROUND There is no consensus on whether differences in the pathophysiology of STEMI and response to primary PCI between women and men reflect biological factors as opposed to differences in age.

METHODS In this prospective, multicenter study, 140 age-matched men and women with STEMI undergoing primary PCI with everolimus-eluting stent were investigated with intravascular optical coherence tomography, histopathology-immunohistochemistry of thrombus aspirates, and serum biomarkers. Primary endpoints were the percentages of culprit plaque rupture at baseline and everolimus-eluting stent strut coverage at 9-month follow-up as determined by optical coherence tomography.

RESULTS Men and women had similar rates of plaque rupture (50.0% vs. 48.4%; risk ratio [RR]: 1.03; 95% confidence interval [CI]: 0.73 to 1.47; $p = 0.56$). Nonruptured/eroded plaques comprised 25% of all cases ($p = 0.86$ in men vs. women). There were no sex differences in composition of aspirated thrombus and immune and inflammatory serum biomarkers. At 9 months, women had similar strut coverage (90.9% vs. 92.5%; difference in medians: RR: 0.2%; 95% CI: -0.4% to 1.3%; $p = 0.89$) and amount of in-stent neointimal obstruction (10.3% vs. 10.6%; $p = 0.76$) as men did. There were no sex differences in clinical outcome either at 30-day or 1-year follow-up.

CONCLUSIONS In patients presenting with STEMI undergoing primary PCI, no differences in culprit plaque morphology and factors associated with coronary thrombosis were observed between age-matched men and women. Women also showed similar vascular healing response to everolimus-eluting stents as men did. (Optical Coherence Tomography Assessment of Gender Diversity In Primary Angioplasty: The OCTAVIA Trial [OCTAVIA]; NCT01377207) (J Am Coll Cardiol Intv 2014;7:958–68) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

EES = everolimus-eluting stent(s)

IQR = interquartile range

MI = myocardial infarction

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

RR = risk ratio

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Primary percutaneous coronary intervention (PCI) has been shown to significantly improve the survival of patients with ST-segment elevation myocardial infarction (STEMI) (1). Current STEMI guidelines apply equally to both sexes (2,3), although women have been underrepresented in randomized clinical trials of primary PCI and sex differences in the presentation, pathophysiology, and treatment of STEMI have been highlighted (4).

Clinical studies exploring sex diversity in STEMI are limited by the confounding effect of age at presentation (5,6). In addition, these studies lack the ability to assess in vivo characteristics and components of coronary plaques underlying thrombosis (7). On the other hand, autopsy series suggested a sex difference in the morphology of plaques responsible for coronary thrombosis (8), with plaque rupture, characterized by disruption of a fibrous cap over a necrotic core, occurring more frequently in men dying of acute myocardial infarction (9), and plaque erosion, characterized by absence of communication between the underlying plaque and coronary thrombus, being more frequently observed in younger individuals and women (10). Importantly, these observations are limited by the inherent selection bias of post-mortem investigations.

The effect of sex on vascular response to primary PCI has also never been systematically investigated in vivo. Women have smaller coronary vessels than men do, and their biological response to vascular damage worsens with aging and reduced exposure to circulating estrogens (11,12). Whereas current-generation everolimus-eluting stents (EES) have shown reassuring outcomes in STEMI patients undergoing primary PCI (13), there are no comparative data between women and men on vascular healing response to EES implanted in STEMI.

Optical coherence tomography (OCT) has been recently validated as a highly reproducible intracoronary imaging technique that enables in vivo characterization of culprit plaque features as well as vascular response to stent implantation with close correlation to histological findings (14,15).

This study was designed to characterize sex-related differences in the pathophysiology of STEMI and vascular healing response to primary PCI with current-generation EES, after accounting for the confounding effect of age. To this aim, a comprehensive investigation was undertaken with serial OCT, histopathology-immunohistochemistry of thrombus aspirates, and serum biomarkers.

METHODS

STUDY DESIGN. The OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty) study was a prospective, multicenter, controlled trial involving patients with STEMI undergoing primary PCI. The study was promoted and supported by the Italian Society of Invasive Cardiology with unrestricted grant support provided by Abbott Vascular (Santa Clara, California). OCT catheters for the study were donated by St. Jude Medical (St. Paul, Minnesota). Neither company was involved with any of the study processes, including site selection, data collection, analysis, and drafting of the present paper. The principal investigator had unrestricted data access after the database was locked, shared with the Steering Committee the decision to submit the results for publication, and prepared the paper. The ethics committee in each participating center approved the study, and all patients gave written informed consent.

STUDY POPULATION AND AGE MATCHING. Consecutive patients ≥18 years of age who presented within 6 h following the onset of symptoms, with ST-segment elevation of ≥1 mm in at least 2 contiguous leads, new left bundle branch block, or true

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posterior myocardial infarction (MI) were considered for enrollment. Clinical exclusion criteria comprised cardiogenic shock, renal failure, recent major bleeding, allergy to aspirin or clopidogrel, and anticoagulant therapy. Clinically eligible patients underwent coronary angiography and were enrolled in the study if they fulfilled explicit angiographic criteria. Detailed inclusion and exclusion criteria are listed in the Online Appendix.

Matching of sex by age was performed with the use of a computer-assisted, interactive voice response system that selectively blocked the enrollment of men or women to ensure recruitment of age-balanced groups. This procedure was carried out during the diagnostic phase of primary PCI and led to enrollment only provided that age matching was fulfilled.

STUDY PROCEDURES AND FOLLOW-UP. In patients presenting with TIMI (Thrombolysis In Myocardial Infarction) flow grades 2 to 3 in the infarct-related artery and no evidence of angiographic filling defect, OCT was performed before any intervention. Conversely, in case of TIMI flow grades 0 to 1 or filling defect, OCT was performed after manual thrombectomy. No balloon pre-dilation was allowed before the OCT pullback. All patients received EES (Xience Prime, Abbott Vascular, Santa Clara, California). Adequacy of stent placement and expansion were assessed based on angiographic evaluation only. Aspirin 250 mg was given intravenously before PCI, followed by 100 mg oral aspirin daily indefinitely thereafter. A loading dose of clopidogrel (600 mg) or prasugrel (60 mg) was administered before PCI followed by clopidogrel 75 mg or prasugrel 10 mg daily for 12 months.

Clinical examinations were performed at 30 days, 9 months, and 1 year. Angiographic and OCT follow-up at 9 months after stent implantation was electively planned for all patients.

QUANTITATIVE CORONARY ANGIOGRAPHY. Quantitative coronary angiography was performed at baseline, immediately after PCI, and at follow-up in at least 2 orthogonal views after administration of 200 μg intracoronary nitroglycerin. Digital coronary angiograms were analyzed off-line at the angiographic core laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center, Cleveland, Ohio) with a validated automated edge detection system (CAAS II, PIE Medical, Maastricht, the Netherlands) by operators blinded to group assignment. The full quantitative coronary angiography methodology is provided in the Online Appendix.

OCT ASSESSMENT. Image acquisition and quality screening. Images were acquired with a frequency domain OCT system (C7-XRTM FD-OCT Intravascular Imaging System, St. Jude Medical, St. Paul, Minnesota) at 3 time points: 1) after vessel patency restoration (baseline); 2) after stent implantation (post-procedural assessment); 3) at 9 months (follow-up assessment). Raw OCT data were digitally stored, deidentified, and submitted to an independent core laboratory (Cardiovascular Imaging Core Laboratory) for subsequent analyses. All cross-sectional images were screened for quality and excluded from analysis if any portion was out of the screen; if a side branch occupied $>45^{\circ}$ of the cross section; or if the image had poor quality caused by suboptimal blood clearance, excessive residual thrombus, or artifacts (11). In case of multiple pullbacks, integrated information was obtained by using fiducial points (i.e., stent edges, side branches). A dedicated software (OCT system software B.0.1, LightLab, Westford, Massachusetts) was used for quantification. Qualitative assessment was performed every 0.2 mm, whereas quantitative and morphometric analyses were performed every 0.6 mm along the entire target segment. OCT analysis was performed by 2 independent readers, blinded to the patient information and sex, and by the same readers at 2 separate time points, respectively. Interobserver reproducibility for primary endpoints was assessed by calculating the mean $\pm$ SD of between-observer differences. The kappa statistic was calculated as 0.845 (95% confidence interval [CI]: 0.769 to 0.921) ($p < 0.001$ to test kappa statistic $= 0$).

Baseline etiology assessment. OCT images were analyzed using previously validated criteria for plaque characterization (15). Plaque rupture was defined as presence of fibrous cap discontinuity and a cavity formation in the underlying plaque beginning at the luminal-intimal border. Plaque nonrupture/erosion was defined as the lack of evidence of a fibrous cap rupture at the culprit site, evaluated in multiple adjacent frames, with evidence of an irregular luminal surface. Spontaneous dissection was identified as the presence of intima-medial flap with mural hematoma in a vessel with no or mild atherosclerotic disease. Unclassified etiology was assigned when OCT was unable to rule out the presence of plaque rupture or erosion due to excess of residual thrombus obscuring the underlying structures or in the presence of procedural intimal dissection induced by the thrombectomy device. Intracoronary thrombus was identified as an intraluminal mass with irregular contour floating within the lumen or attached to the intimal surface. In ruptured plaques, minimum fibrous cap thickness was measured at the thinnest point of the remnant cap, whereas mean cap thickness

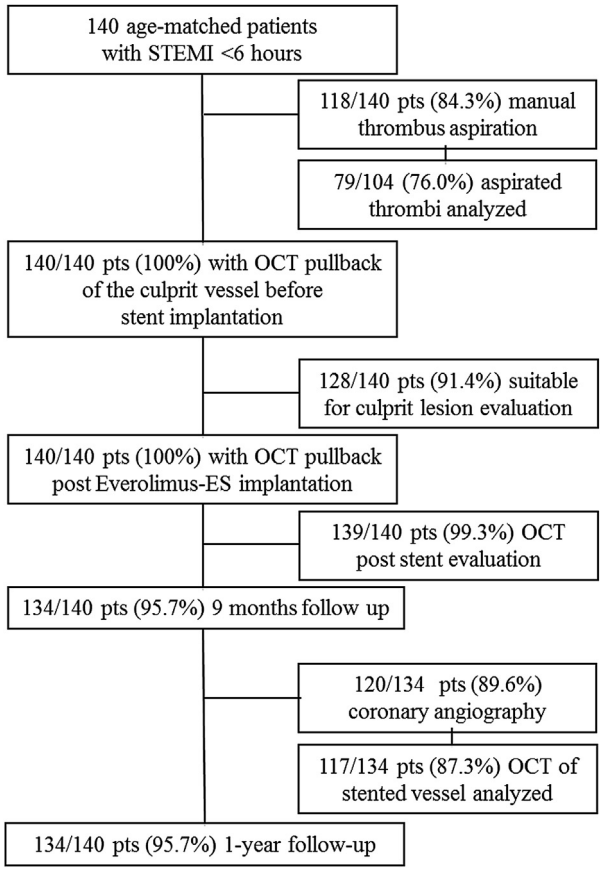

FIGURE 1 Study Enrollment

Of the 140 age-matched patients with ST-segment elevation myocardial infarction (STEMI), 118 received manual thrombus aspiration. Of the 104 retrieved thrombi, 79 were analyzed (25 were excluded for insufficient material). All the patients underwent an optical coherence tomography (OCT) pullback of the culprit vessel after thrombus aspiration, and 128 were suitable for culprit lesion evaluation. All patients received OCT pullback after stent implantation, and 139 of them were analyzable. Of the 140 patients, 134 were admitted at 9-month follow-up (6 of them died), 120 underwent coronary angiography, and 117 OCT pullbacks were analyzed. All 134 patients were admitted at 12-month follow-up. ES = eluting stent(s).

was computed as the mean of 3 evenly distributed measurements along the fibrous cap. Fibrocalcific plaques were identified as well-delineated, signal-poor regions with sharp borders; fibrotic plaques as homogeneous, signal-rich regions with low attenuation; and lipid plaques as signal-poor regions with high attenuation and diffused borders. When fibrocalcific, fibrotic, or lipid constituents were present in ≥2 contiguous quadrants in any of the images within a plaque, the cross section was classified accordingly as fibrocalcific, fibrous, or lipid rich.

Post-procedural and follow-up assessment. For the morphometric analysis, standard definitions of cross-sectional area and volume measurements were applied as previously reported (12). Stent, lumen, and neointimal hyperplasia cross-sectional areas were measured at 0.6-mm axial increments throughout the entire length of the stent, and respective volumes were calculated according to the Simpson rule. Proximal and distal references were measured at the site with the largest lumen within 5 mm proximal and distal to the stented segment. The minimum stent cross-sectional areas divided by the average of proximal and distal reference lumen cross-sectional areas ratio was calculated as a parameter of stent expansion.

OCT stent analysis immediately post-procedure and at follow-up was performed at the stent strut level. 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 higher than the sum of strut thickness plus abluminal polymer thickness according to stent manufacturer's specifications plus a compensation factor of 18 μm to correct for strut blooming. Struts were "covered" if tissue could be identified above the stent struts or "uncovered" if no evidence of tissue could be imaged above the struts. Percentage of covered and uncovered struts was calculated as the number of struts with/without distinct overlying tissue, in which the luminal reflection of the strut surface was directly interfacing with the lumen, divided by the total number of analyzable struts.

HISTOPATHOLOGICAL ASSESSMENT OF THROMBUS. Thrombus aspirate, if any, was collected and sent to the independent histopathology core laboratory (CV Path Institute, Gaithersburg, Maryland) for processing. Aspirated thrombus tissues were wrapped in filter paper and placed in tissue cassettes for histologic processing. All sections were examined by light microscopy for the presence of platelets, fibrin, red blood cells, plaque constituents, and inflammatory cells. Additionally, immunohistochemical stains including the granulocyte marker myeloperoxidase, CD68 (macrophages), and the eosinophil marker interleukin-5 were performed to further characterize specific inflammatory cell types. A CD42b stain was used for the detection of platelets. Coronary thrombus was classified into 2 stages of healing and organization, as modification of a previously reported scoring system: stage 1 (early thrombus), composed of alternating layers of platelets mixed with fibrin and

neutrophils without evidence of cellular organization; and stage 2 (organized thrombus), representing a healing thrombus characterized by infiltration of smooth muscle cells and/or endothelial cells with or without proteoglycan matrix (16). The full histopathological methodology is provided in the Online Appendix.

SERUM BIOMARKERS ASSESSMENT. In all patients, venous blood samples were drawn before coronary angiography. After centrifugation, serum was stored at -80°C and sent to the core laboratory (Institute of Cardiology, Catholic University of the Sacred Heart, Roma, Italy). Analyses of serum comprised high-sensitivity C-reactive protein, myeloperoxidase, eosinophil cationic protein, and thromboxane B_2. Detailed methodology is described in the Online Appendix.

STUDY ENDPOINTS. There were 2 pre-specified primary endpoints: 1) percentage of plaque rupture at the infarct-related lesion; and 2) percentage of stent strut coverage at 9 months after EES implantation. Secondary endpoints included histopathology and immunohistochemistry measurements of aspirated thrombus specimens; measurements of blood biomarkers collected at admission; the 9-month response to EES implantation, assessed as percentage of stent volume obstruction and percentage of incomplete strut apposition at OCT follow-up; and clinical outcomes.

Major adverse cardiac or cerebrovascular events (e.g., the composite of cardiac death, recurrent MI, stroke, or ischemia-driven target lesion revascularization), individual components of major adverse cardiac or cerebrovascular events, target vessel revascularization, and stent thrombosis were assessed at 30 days, 9 months, and 1 year and adjudicated by an independent clinical event committee after review of original clinical data source. Target lesion revascularization was considered to be ischemia-driven if documented by a positive functional study or in the presence of ischemic changes on an electrocardiogram referable to the target lesion. Stent thrombosis was defined according to the Academic Research Consortium (17).

STATISTICAL ANALYSIS. The study was designed to evaluate whether culprit lesions in men with STEMI have a different probability of having a ruptured plaque morphology than those in women. Assuming a plaque rupture rate of 82% in men and 60% in women (9), with 1:1 assignment of 140 patients to the 2 groups, and 94% of the patients available for the analysis, we calculated that the study would have 80% power, with 0.05 alpha (2-sided), and a superiority scope. The study was also powered to show the noninferiority of EES strut coverage at 9 months in women versus men. Assuming a noninferiority margin of 2% and an SD of uncovered strut percentage of 4%, a similar 94.3% per-segment prevalence of uncovered struts in men and women, and 80% of the patients available for the analysis at 9 months, a total sample size of 140 patients would achieve 85% power and 0.05 alpha (1-sided), with a noninferiority scope.

Patient, lesion, and procedural characteristics and event rates were analyzed using descriptive statistics with SAS (version 9.1 or higher, SAS Institute Inc., Cary, North Carolina), and SPSS (version 20.0, IBM, Armonk, New York). Categorical data were reported as simple proportions. Continuous data were reported as mean ± SD, or median (interquartile range [IQR]) depending on validity or lack of normality assumptions. Overall comparisons across groups were based on unpaired Student *t* test for continuous variables (or Mann-Whitney *U* and Kruskal-Wallis tests in cases of significant departures from normality

TABLE 1 Baseline Demographic and Clinical Characteristics

	Overall (N = 140)	Men (n = 70)	Women (n = 70)	p Value
Age, yrs	66.6 ± 11.1	65.3 ± 11.8	67.8 ± 10.4	0.19
Age group, yrs				1.00
≤60	40/140 (28.5)	20/70 (28.5)	20/70 (28.5)	
61–80	82/140 (58.6)	41/70 (58.6)	41/70 (58.6)	
>80	18/140 (12.9)	9/70 (12.9)	9/70 (12.9)	
Body mass index, kg/m^2	26.0 (24.2, 29.1)	26.1 (24.2, 29.4)	25.5 (23.4, 29.1)	0.27
Body surface area, m^2	1.8 ± 0.2	2.0 ± 0.2	1.7 ± 0.2	<0.001
Hypertension	80/140 (57.1)	41/70 (58.6)	39/70 (55.7)	0.73
Hyperlipidemia	40/140 (28.6)	21/70 (30.0)	19/70 (27.1)	0.71
Current smoker	75/140 (53.6)	39/70 (55.7)	36/70 (51.4)	0.61
Diabetes	17/140 (12.1)	6/70 (8.6)	11/70 (15.7)	0.20
Previous MI	2/140 (1.4)	2/70 (2.9)	0/70 (0)	0.50
Previous PCI	2/140 (1.4)	1/70 (1.4)	1/70 (1.4)	1.00
Previous CABG	1/140 (0.7)	1/70 (1.4)	0/70	1.00
Time from symptom onset to catheterization laboratory, h	2.4 (1.7–3.5)	2.3 (1.6–3.1)	2.5 (1.8–4.0)	0.05
Killip class				0.79
I	125/140 (89.3)	63/70 (90.0)	62/70 (88.6)	
II	15/140 (10.7)	7/70 (10.0)	8/70 (11.4)	
Anemia*	15/140 (10.7)	7/70 (10.0)	8/70 (11.4)	0.79
TIMI risk score†	3 (2–5)	3 (1–4)	4 (2–5)	0.001

Values are mean ± SD, n/N (%), or median (interquartile range). *Anemia was defined, according to the WHO criteria, as a hematocrit value at initial presentation of <39% for men and <36% for women. †TIMI risk score is defined considering the following variables: age, presence of diabetes, hypertension or angina, systolic heart pressure <100 mm Hg, heart rate >100 beats/min, Killip class II to IV, weight <67 kg, presentation as anterior STEMI or as left bundle branch block and time to treatment >4 h.

CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; WHO = World Health Organization.

assumptions, namely $p < 0.05$ at Kolmogorov-Smirnov or Shapiro-Wilks tests) and chi-square or Fisher exact test for categorical variables (with the latter used when the expected cell count was <5). The primary superiority endpoint was also reported as risk ratio (RR) (95% CI). Given the violation of normality assumption, noninferiority in strut coverage was tested with bootstrap resampling (10,000 samples) of the difference in medians between men and women. Statistical significance was set at the 0.05 level, 1-tailed for the strut coverage noninferiority analyses, and 2-tailed for all other analyses, including the etiology analyses, with p values unadjusted for multiplicity reported throughout.

RESULTS

BASELINE CHARACTERISTICS AND PROCEDURAL DATA. Between January 26, 2011 and January 19, 2012 140 STEMI patients (70 men and 70 women) were enrolled at 14 centers. The study flow is shown in Figure 1. Baseline characteristics were similar in the 2 groups (Table 1), with the exception of lower body surface area (1.7 ± 0.2 m^2 vs. 2.0 ± 0.2 m^2, $p < 0.001$) and higher TIMI risk score (median: 4 [IQR: 2 to 5] vs. 3 [IQR: 1 to 4], $p < 0.001$) in women versus men. Time from symptom onset to arrival in the catheterization laboratory was shorter in men than in women (median: 2.3 h [IQR: 1.6 to 3.1 h] vs. 2.5 h [IQR: 1.8 to 4.0 h], $p = 0.05$).

A radial approach was more frequently used in men (67.1% vs. 50.0%, $p = 0.04$), who were also more likely to receive glycoprotein IIb/IIIa inhibitors (44.3% vs. 28.6%, $p = 0.05$) than women were. A total of 120 patients (86%) had angiographic evidence of thrombus, of which 118 underwent thrombus aspiration, with no difference between men and women. Angiographic, OCT, and procedural characteristics are shown in Tables 2 and 3. Additional quantitative coronary angiography measures are reported in Online Table 1. Women had smaller vessels and accordingly were treated with smaller balloons (median: 3.0 mm [IQR: 3.0 to 3.5 mm] vs. 3.5 mm [IQR: 3.0 to 4.0 mm]; $p = 0.008$) (Table 2) and smaller stents (OCT minimum stent area 5.5 ± 1.9 mm^2 vs. 7.1 ± 2.3 mm^2; $p < 0.001$) (Table 3). Nevertheless, the stent expansion index at implantation was similar between women and men (85% vs. 87%; $p = 0.53$), as were the residual minimum lumen area stenosis (15.3% vs. 11.1%; $p = 0.21$) and the rate of acute incomplete stent strut apposition (5.0% vs. 5.1%; $p = 0.99$) (Table 3). The prevalence of final TIMI flow grade 3 was similar in the 2 groups (95.7% vs. 92.9%; $p = 0.72$).

TABLE 2 Angiographic and Procedural Characteristics

	Overall (N = 140)	Men (n = 70)	Women (n = 70)	p Value
Lesions treated, n	1.2 ± 0.5	1.2 ± 0.5	1.1 ± 0.5	0.72
Infarct related artery				0.40
Left anterior descending	62/140 (44.3)	27/70 (38.6)	35/70 (50.0)	
Left circumflex	11/140 (7.9)	6/70 (8.6)	5/70 (7.1)	
Right coronary	67/140 (47.9)	37/70 (52.9)	30/70 (42.9)	
Multivessel disease	62/140 (44.3)	34/70 (48.6)	28/70 (40.0)	0.47
Pre-procedural thrombus	120/140 (85.7)	62/70 (88.6)	58/70 (82.9)	0.33
Use of aspiration catheter	118/140 (84.3)	61/70 (87.1)	57/70 (81.4)	0.35
Use of GP IIb/IIIa inhibitor	51/140 (36.4)	31/70 (44.3)	20/70 (28.6)	0.05
Radial access	82/140 (58.6)	47/70 (67.1)	35/70 (50.0)	0.04
Stents implanted per patient, n	1.4 ± 0.6	1.3 ± 0.5	1.4 ± 0.7	0.15
Total stent length per patient, mm	23.0 (18.8-33.0)	23.0 (21.8-33.0)	23.0 (18.0-35.3)	0.38
Direct stenting	88/140 (62.9)	44/70 (62.9)	44/70 (62.9)	1.00
Maximum pressure per lesion, atm	18 (16-20)	18 (16-20)	18 (16-20)	0.91
Maximum balloon diameter, mm	3.25 (3.0-3.5)	3.5 (3.0-4.0)	3.0 (3.0-3.5)	0.008
Baseline TIMI flow grade				0.45
0/1	83/140 (59.3)	43/70 (61.5)	40/70 (57.2)	
2	44/140 (31.4)	19/70 (27.1)	25/70 (35.7)	
3	13/140 (9.3)	8/70 (11.4)	5/70 (7.1)	
Final TIMI flow grade				0.47
0/1	0/140 (0)	0/70 (0)	0/70 (0)	
2	8/140 (5.7)	5/70 (7.1)	3/70 (4.3)	
3	132/140 (94.3)	65/70 (92.9)	67/70 (95.7)	
Procedural success	128/140 (91.4)	63/70 (90.0)	65/70 (92.9)	0.76

Values are mean ± SD, n/N (%), or median (interquartile range).
GP = glycoprotein; other abbreviations as in Table 1.

CULPRIT LESION ASSESSMENT. Baseline OCT images of the culprit lesion were qualified for the etiology analysis in 128 patients (91%). Thirty-one of 128 culprit lesions (24%) qualifying for the etiology analysis were not classifiable by OCT, essentially due to the excessive amount of remaining thrombus. No differences in baseline and procedural characteristics were observed between patients with classified versus unclassified culprit plaques (Online Table 2) except for the rate of thrombus at presentation (81.4% vs. 96.8%; $p = 0.04$). The primary endpoint, percentage of plaque rupture at the culprit coronary site, was similar in men and women (50.0% vs. 48.4%; RR: 1.03, 95% CI: 0.73 to 1.47; $p = 0.56$ for superiority) (Figure 2). No sex differences were found at the rupture plaque site in terms of minimum cap thickness, length of plaque rupture, or plaque constituents (all $p > 0.05$) (Table 3). Nonruptured/eroded plaques comprised 25% of all cases, with similar distribution in men and women ($p = 0.86$).

STRUT COVERAGE AND VASCULAR RESPONSE AT 9 MONTHS. At 9 months, a similar total number of

struts were analyzed in both groups (total 10,147, median 169 struts [IQR: 129 to 225 struts] in men, and total 10,459, median 162 [IQR: 118 to 214 struts] in women; p = 0.30). The coprimary endpoint, percentage of covered EES struts, did not differ between men and women (92.5% [IQR: 83.7% to 97.5%] vs. 90.9% [IQR: 81.4% to 97.9%]; difference in medians: 0.2% [95% CI: -0.4% to 1.3%]; p < 0.001 for noninferiority). No sex differences were noted in the percentage of incomplete strut apposition (0.9% [95% CI: 0.0 to 6.4] vs. 0.3% [95% CI: 0.0 to 3.5]; p = 0.13) and in-stent volume obstruction (10.6% [95% CI: 6.7 to 16.1] vs. 10.3% [5.9 to 13.7]; p = 0.76).

HISTOPATHOLOGY, IMMUNOHISTOCHEMISTRY, AND BIOMARKER ANALYSES. A total of 104 samples were retrieved in filters. Seventy-nine specimens (40 from men and 39 from women) were suitable for pathologic analysis, whereas 25 samples were excluded for insufficient material collection (Figure 1). Qualitative histological analysis showed fibrin and platelet-rich thrombi with inflammatory cells, predominantly neutrophils in both groups (Table 4). All histologic and immunohistochemistry findings were similar in men and women. Assessment of serum biomarkers at the time of admission showed similar values in the 2 groups for C-reactive protein, myeloperoxidase, eosinophil cationic protein, and thromboxane B_2 (all p > 0.05) (Table 4).

CLINICAL OUTCOMES. In-hospital, 1-month, and 1-year adverse events occurred with similar frequency in men and women (Table 5). The 2 study groups received similar therapies and showed similar compliance over time (Online Table 3).

TABLE 3 OCT Findings at Baseline and 9-Month Follow-Up

Culprit Lesion Assessment	Overall (N = 140)	Men (n = 70)	Women (n = 70)	p Value
Residual thrombus	120/128 (93.8)	62/64 (96.9)	58/64 (90.6)	0.27
Rupture site assessment				
Minimum cap thickness, μm	47 ± 12	48 ± 15	46 ± 8	0.59
Mean cap thickness, μm	64 ± 15	66 ± 17	61 ± 12	0.28
Length of plaque rupture, mm	1.8 (1.2-3.0)	1.8 (1.2-3.0)	1.8 (1.2-3.0)	0.80
Plaque constituents, %				
Fibrocalcific	4.6 ± 12.7	4.5 ± 13.7	4.6 ± 11.9	0.74
Fibrous	14.8 ± 17.0	13.0 ± 16.4	16.8 ± 17.6	0.32
Lipid-rich	74.5 ± 20.0	79.2 ± 24.0	69.8 ± 23.5	0.09
Normal	6.0 ± 12.0	3.3 ± 8.8	8.8 ± 14.2	0.10
Nonrupture/erosion site assessment				
Plaque constituents, %				
Fibrocalcific	10.2 ± 20.9	14.1 ± 25.8	6.3 ± 14.4	0.40
Fibrous	25.0 ± 31.8	14.1 ± 27.3	35.9 ± 32.9	0.03
Lipid-rich	56.3 ± 36.5	60.9 ± 38.7	51.6 ± 34.7	0.36
Normal	8.6 ± 21.6	10.9 ± 27.3	6.3 ± 14.4	0.96
Post-Stent Implantation	**(N = 139)**	**(n = 70)**	**(n = 69)**	
Mean reference vessel area, mm^2	6.9 (5.5-9.7)	8.5 (6.2-10.7)	6.3 (5.1-8.3)	<0.001
Minimum stent area, mm^2	6.3 ± 2.2	7.1 ± 2.3	5.5 ± 1.9	<0.001
Minimum lumen area, mm^2	5.8 (4.5-7.6)	6.8 (5.2-8.6)	5.2 (4.4-6.3)	<0.001
Minimum lumen area stenosis, %	13.2 ± 19.9	11.1 ± 20.5	15.3 ± 19.2	0.22
Stent expansion index, %*	86 (70-96)	87 (69-100)	85 (71-96)	0.53
Incomplete strut apposition, %†	5.1 (1.5-10.6)	5.1 (1.5-10.8)	5.0 (1.7-10.5)	1.00
Follow-Up	**(N = 117)**	**(n = 58)**	**(n = 59)**	
Mean reference vessel area, mm^2	6.6 (5.1-8.9)	7.4 (5.7-10.5)	5.9 (4.3-7.8)	0.001
Minimum lumen area, mm^2	5.18 (3.7-6.9)	5.9 (4.3-7.4)	5.0 (3.6-5.8)	0.01
Percentage net volume obstruction, %	10.3 (6.0-15.8)	10.6 (6.7-16.1)	10.3 (5.9-13.7)	0.76
Incomplete strut apposition, %†	0.6 (0.0-4.8)	0.9 (0.0-6.4)	0.3 (0.0-3.5)	0.13

Values are n/N (%), mean ± SD, or median (interquartile range). *Stent expansion index refers to minimum stent area/reference lumen area. †Incomplete struts apposition percentage has been estimated only when applicable.
OCT = optical coherence tomography.

DISCUSSION

We reported on the first prospective controlled study designed to assess in vivo sex differences in the mechanisms of STEMI and vascular response to primary PCI with current-generation drug-eluting stents. The main findings are that men and women with STEMI, when matched for age, shared similar plaque morphology, cellular composition, and immunohistochemistry of thrombus, as well as biomarker substrates. Moreover, the immediate- and long-term vascular response to EES implantation was similar in both sexes.

Autopsy studies have suggested differences in morphology of the underlying plaque associated with acute MI in women versus men (8-10). Although plaque rupture of a thin-cap fibroatheroma has been recognized as the most prevalent pathologic substrate of STEMI, coronary thrombosis arising from nonruptured/eroded plaques was frequently reported, especially in women and young individuals. However, no systematic investigation in vivo of sex differences in culprit lesions phenotypes in the setting of STEMI is currently available. In accordance with previous post-mortem investigations, we found ruptured plaques to be the most frequent cause of coronary thrombosis, with approximately two-thirds of the classified culprit lesions being ruptured atherosclerotic plaques with thrombus, and the remaining one-third being represented by nonruptured/eroded plaques (Figure 2). Differently from previous reports, however, our study showed no sex gap in the prevalence of ruptured and eroded plaques. A possible explanation for this finding is that the age-matching algorithm might

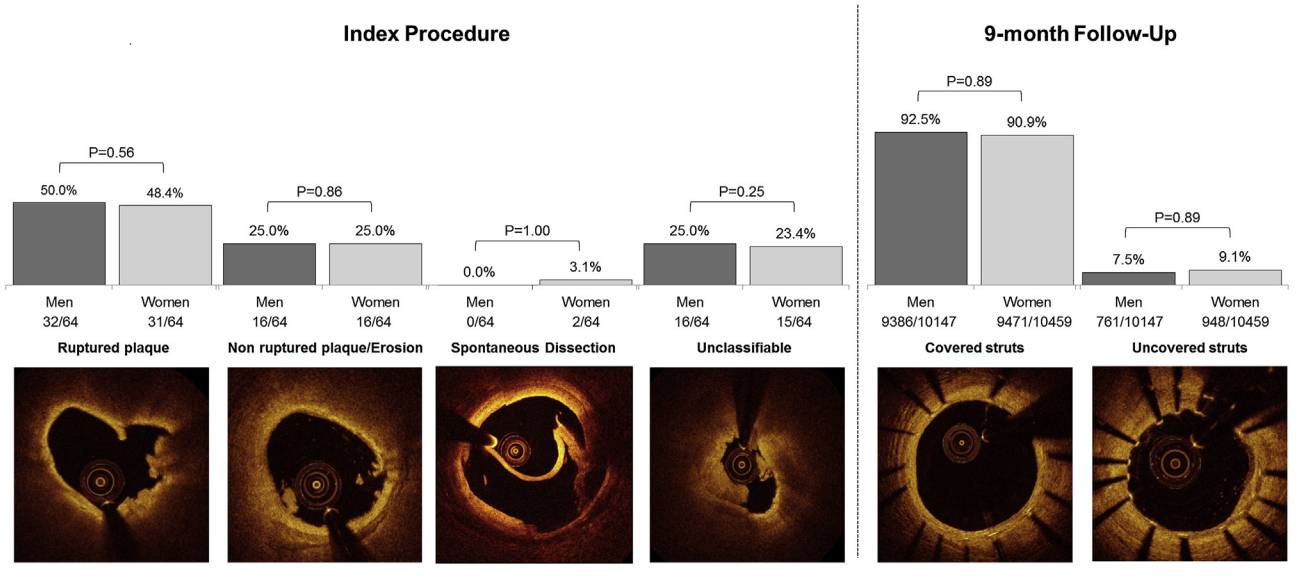

FIGURE 2 Study Endpoints

Nature of culprit plaque underlying coronary thrombosis (index procedure) and vascular healing response to everolimus-eluting stent (9-month follow-up) stratified by sex.

have significantly reduced the differences in clinical risk profile between sexes. Indeed, modifiable risk factors have been shown to account for 90% of MI in both sexes (18) and are clearly linked to different plaque morphologies in patients with coronary thrombosis (19,20). Moreover, in this study, very few women <50 years of age, a group with known higher prevalence of plaque erosion, were included (21).

We found similar cellular composition and immunohistochemistry of thrombus aspirates between men and women, along with comparable levels of systemic biomarkers of inflammation, immune response, and platelet activation. These findings support the validity of OCT imaging results for culprit plaque morphology. Notably, one-third of the patients had evidence of thrombus organization despite restricting enrollment only to patients within 6 h from symptom onset, in keeping with previous observations (16).

The coprimary objective of our trial was to investigate whether there are sex-related differences in vascular response to drug-eluting stents in the setting of STEMI. The relevance of this problem has been highlighted by the U.S. Food and Drug Administration, which issued a statement recommending the analysis of sex-specific outcomes in trials with novel implantable medical devices (22). Despite finding that women have significantly smaller coronary vessels, all measured OCT and angiographic parameters of stent performance and vascular response were similar between men and women. Specifically, rates of covered, uncovered, and incompletely apposed struts were remarkably similar, as was the percentage of in-stent lumen obstruction and binary restenosis.

The potential for a different outcome in women after STEMI has been described for many years (23). In our study, where patients and treatment strategies were comparable between sexes, 30-day and 1-year outcomes were similar. These findings suggest that disparities in age, risk factors, timing of presentation, and management rather than different biological mechanisms and response to treatment might be more relevant in affecting clinical outcome (24). However, the study was not powered to detect differences in clinical outcomes, and therefore, this result must be interpreted with caution.

STUDY LIMITATIONS. First, the entry criteria limited the enrollment to a low-risk, selected population. This was necessary to perform all of the study-required evaluations, including multiple OCT pullbacks. Second, the core laboratory was unable to classify the culprit plaque in one-quarter of the cases,

TABLE 4 Histologic Assessment of Aspirated Thrombus and Inflammatory/Platelet Activation Biomarkers

	Overall	Men	Women	p Value
Aspirated thrombus, n	79	40	39	
Thrombus volume, mm^3	6 (3–15)	6 (3–18)	6 (2–15)	0.70
Platelets presence	79/79 (100)	40/40 (100)	39/39 (100)	1.00
Average WBC, cells/5HPF	75 (50–150)	75 (50–200)	75 (50–150)	0.22
Plaque material	40/79 (50.6)	20/40 (50.0)	20/39 (51.2)	0.91
Thrombus age				1.00
Early	56 (70.9)	28 (70.0)	28 (69.8)	
Organized	23 (29.1)	12 (30.0)	11 (28.2)	
Immunohistochemistry analysis				
MPO, cells/5HPF	39 (26–90)	38 (24–86)	41 (26–91)	0.93
CD68, cells/5HPF	20 (10–40)	20 (10–50)	20 (10–30)	0.73
Interleukin-5, cells/5 HPF	0 (0–1)	0 (0–1)	0 (0–1)	0.93
CD42B score*	2 (2–3)	2 (2–3)	2 (2–3)	0.18
Blood biomarkers, n	129	65	64	
CRP, mg/l	2.08 (1.00–4.11)	1.64 (0.88–4.77)	2.21 (1.01–4.02)	0.49
MPO, ng/ml	604.2 (290.5–1,496.9)	512.7 (271.4–1,308.7)	956.7 (303.7–1,658.7)	0.09
ECP, µg/l	5.0 (2.8–9.1)	5.1 (2.5–10.5)	4.5 (2.9–7.9)	0.65
TBX_2, pg/ml	117.2 (60.6–256.1)	117.2 (58.5–189.1)	117.3 (62.9–261.6)	0.63

Values are median (interquartile range), n/N (%), or n (%). *The CD42B score employed a scale of 0 to 3 where 0 = no platelets, 1 ≤ one-third of the thrombus area, 2 ≤ one- to two-thirds of the thrombus area, and 3 ≥ two-thirds of the thrombus area.

5HPF = 5 high-power field; CRP = C-reactive protein; ECP = eosinophil cationic protein; MPO = myeloperoxidase; TBX_2 = thromboxane-B_2; WBC = white blood cells.

which is consistent with the latest OCT investigations revealing significant residual thrombus after thrombectomy, undetected by angiography (25,26). This potential bias might be mitigated by the equal distribution of unclassifiable plaques in both sexes and the similar clinical characteristics of patients with classified or nonclassified plaques. Third, manual thrombectomy was used in patients with TIMI flow grade 0/1 to recanalize the vessel and allow for a safer and diagnostic OCT pullback. A role of the thromboaspiration catheter in modifying the plaque etiology when crossing the culprit lesion cannot be entirely ruled out; however, it is likely that this effect, if any, was equally distributed in men and women. Fourth, whereas OCT criteria for plaque rupture are largely accepted, less explicit criteria apply for nonruptured/eroded plaques (12). Fifth, the study was not powered for clinical endpoints. Finally, although age matching controlled a proportion of baseline differences between men and women, a role for residual confounding factors cannot be excluded.

CONCLUSIONS

The present study shows that in age-matched men and women presenting with STEMI, there are no evident differences in culprit plaque morphology and local or systemic factors associated with acute

TABLE 5 Clinical Outcomes at 30 Days and 1 Year

	Overall	Men	Women	p Value
30 days				
MACCE	5/140 (3.6)	4/70 (5.7)	1/70 (1.4)	0.37
Death	2/140 (1.4)	1/70 (1.4)	1/70 (1.4)	1.00
Cardiac	2/140 (0.7)	1/70 (0.0)	1/70 (1.4)	1.00
Noncardiac	0/140 (0.7)	0/70 (1.4)	0/70 (0.0)	1.00
Reinfarction	2/140 (1.4)	2/70 (2.9)	0/70 (0.0)	0.50
Stroke	1/140 (0.7)	1/70 (1.4)	0/70 (0.0)	1.00
Stent thrombosis	3/140 (2.1)	2/70 (2.9)	1/70 (1.4)	1.00
Definite	2/140 (1.4)	2/70 (2.9)	0/70 (0.0)	0.50
Probable	1/140 (0.7)	0/70 (0.0)	1/70 (1.4)	1.00
Ischemia-driven target lesion revascularization*	2/140 (1.4)	2/70 (2.9)	0/70 (0.0)	0.50
Target vessel revascularization	2/140 (1.4)	2/70 (2.9)	0/70 (0.0)	0.50
1 year†				
MACCE	9/140 (6.4)	5/70 (7.1)	4/70 (5.7)	0.69
Death	6/140 (4.3)	3/70 (4.3)	3/70 (4.3)	1.00
Cardiac	3/140 (1.4)	1/70 (1.4)	2/70 (2.9)	0.57
Noncardiac	3/140 (2.9)	2/70 (2.9)	1/70 (1.4)	0.56
Reinfarction	2/140 (1.4)	2/70 (2.9)	0/70 (0.0)	0.16
Stroke	1/140 (0.7)	1/70 (1.4)	0/70 (0.0)	0.31
Stent thrombosis	3/140 (2.1)	2/70 (2.9)	1/70 (1.4)	0.55
Definite	2/140 (1.4)	2/70 (2.9)	0/70 (0.0)	0.16
Probable	1/140 (0.7)	0/70 (0.0)	1/70 (1.4)	0.32
Ischemia-driven target lesion revascularization*	5/140 (3.6)	3/70 (4.3)	2/70 (2.9)	0.69
Target vessel revascularization	9/140 (6.4)	5/70 (7.1)	4/70 (5.7)	0.72

Values are n/N (%). *Ischemia-driven target lesion revascularization refers to a procedure to treat recurrent ischemia occurring within or just outside the stent. †The p values are based on the log-rank test.

MACCE = major adverse cerebral and cardiovascular events (a composite of cardiac death, reinfarction, stroke, and target lesion revascularization for ischemia, in hierarchical order).

coronary thrombosis. A favorable vascular response to EES implantation with similar high rates of complete stent strut coverage is observed in both sexes.

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A full list of the investigators involved in the OCTAVIA Study appears online in the Online Appendix.

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KEY WORDS etiology, myocardial infarction, myocardial revascularization, sex differences

APPENDIX For supplemental data, including tables, please see the online version of this paper.

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