Sex Differences in Nonculprit Coronary Plaque Microstructures on Frequency-Domain Optical Coherence Tomography in Acute Coronary Syndromes and Stable Coronary Artery Disease

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Background—Numerous reports suggest sex-related differences in atherosclerosis. Frequency-domain optical coherence tomography has enabled visualization of plaque microstructures associated with disease instability. The prevalence of plaque microstructures between sexes has not been characterized. We investigated sex differences in plaque features in patients with coronary artery disease.

Methods and Results—Nonculprit plaques on frequency-domain optical coherence tomography imaging were compared between men and women with either stable coronary artery disease (n=320) or acute coronary syndromes (n=115). A greater prevalence of cardiovascular risk factors was observed in women. Nonculprit plaques in women with stable coronary artery disease were more likely to exhibit plaque erosion (8.6% versus 0.3%; *P*=0.03) and a smaller lipid arc (163.1±71.4° versus 211.2±71.2°; *P*=0.03), and less likely to harbor cholesterol crystals (17.2% versus 27.5%; *P*=0.01) and calcification (15.4% versus 34.4%; *P*=0.008), whereas fibrous cap thickness (105.2±62.1 versus 96.1±40.4 μm; *P*=0.57), the prevalence of thin-cap fibroatheroma (26.5% versus 25.2%; *P*=0.85), and microchannels (19.2% versus 20.5%; *P*=0.95) were comparable. In women with acute coronary syndrome, a smaller lipid arc (171.6±53.2° versus 235.8±86.4°; *P*=0.03), a higher frequency of plaque erosion (11.4% versus 0.6%; *P*=0.04), and a lower prevalence of cholesterol crystal (28.6% versus 38.2%; *P*=0.03) and calcification (10.0% versus 23.7%; *P*=0.01) were observed. These differences persisted after adjusting clinical demographics. Although thin-cap fibroatheromas in men clustered within proximal arterial segments, thin-cap fibroatheromas were evenly distributed in women.

Conclusions—Despite more comorbid risk factors in women, their nonculprit plaques exhibited more plaque erosion, and less cholesterol and calcium content. This distinct phenotype suggests sex-related differences in the pathophysiology of atherosclerosis. **(*Circ Cardiovasc Imaging*. 2016;9:e004506. DOI: 10.1161/CIRCIMAGING.116.004506.)**

Key Words: acute coronary syndrome ■ atherosclerosis ■ coronary artery disease ■ optical coherence tomography ■ women

Despite widespread use of established medical therapies, coronary artery disease (CAD) is the leading cause of mortality in women in most developed countries.[1,2] More than a quarter of a million women die each year in the United States because of CAD, with projections that this will rise during the next few decades.[1,2] This highlights the need to better understand the factors promoting atherosclerotic events and to establish more effective therapeutic approaches in women.

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See Clinical Perspective

Considerable evidence has demonstrated sex differences in the clinical presentation of CAD. Women have a greater symptom burden and a higher rate of functional disability but a lower prevalence of obstructive CAD.[3–5] Histology studies have reported that culprit lesions causing acute coronary syndrome (ACS) or sudden cardiac death in women harbor less extensive atherosclerosis and evidence of rupture, with a higher prevalence of plaque erosion.[6–9] These observations suggest a potentially distinct form of pathophysiology of atherosclerosis in women. Given the systemic nature of coronary atherosclerosis, we hypothesized that nonculprit plaques in women undergoing percutaneous coronary intervention (PCI) might also exhibit distinct plaque features in vivo. High-resolution intravascular imaging with frequency-domain optical coherence tomography (FD-OCT) permits visualization

Received January 4, 2016; accepted June 23, 2016.

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The Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.116.004506/-/DC1.

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of plaque morphologies, components, and microstructures associated with instability in vivo.[10,11] Therefore, we sought to compare FD-OCT–derived nonculprit plaque features in women and men with stable CAD and ACS.

Methods

Study Population

We retrospectively analyzed FD-OCT imaging data in patients with CAD who underwent PCI at the Cleveland Clinic from May 2011 to April 2013 (Figure 1). FD-OCT imaging use was decided based on operators' discretion to guide their PCI procedure. Of 3108 PCI cases during the study period, 2497 cases were ineligible for FD-OCT imaging because of the following reasons: left main disease, chronic total occlusion within target vessel, vessel size ≥4 mm, patients with chronic kidney disease, congestive heart failure, and cardiogenic shock. In the remaining 611 eligible patients, FD-OCT imaging was performed in in 456 cases (74.8%). After exclusion of 21 patients because of poor image quality (n=16) or imaging within a bypass graft (n=5), 435 patients with CAD (stable CAD: n=320 and ACS: n=115) were included into the current analysis. The current study complies with the Declaration of Helsinki. The institutional review board committee of the Cleveland Clinic approved this retrospective audit of FD-OCT images and clinical data from patients who had undergone FD-OCT imaging in the context of clinically indicated PCI procedures.

FD-OCT Data Acquisition

FD-OCT imaging of the entire target vessel was performed before PCI as previously described.[12] Briefly, a FD-OCT (C7-XRTM OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN) was advanced to the distal site of the target artery for PCI after intracoronary administration of nitroglycerin (100–300 μg). Contrast media was continuously injected through the guiding catheter during FD-OCT pullback (20 mm/s). Multiple FD-OCT pullbacks were undertaken to investigate the entire of target vessel. FD-OCT imaged segments were overlapped by using a side branch as a landmark for analysis. When patients had multiple target vessels requiring PCI, all of these vessels were imaged and included into the analysis. The raw FD-OCT data were deidentified and transferred to open-source software, ImageJ (National Institutes of Health, Bethesda, MD). All FD-OCT images were analyzed at Atherosclerosis Imaging Core Laboratory of Cleveland Clinic by two experienced investigators who were blinded to the clinical presentations. When there was discordance between investigators, a consensus reading was obtained from a third independent investigator.

FD-OCT Image Analysis

Nonculprit plaque with diameter stenosis 20% to 70% on quantitative coronary angiography and culprit plaques receiving PCI were analyzed. Nonculprit plaque was defined as a coronary artery stenosis with diameter stenosis 20% to 70%, which PCI has not been undertaken. Individual plaques within a vessel were separated by at least 5-mm from each other. Each nonculprit plaque was evaluated for the presence of rupture, erosion, and calcified nodules according to the previously established definition. Plaque rupture was defined as the presence of fibrous cap discontinuity and cavity formation in the plaque.[13,14] Plaque erosion was defined as the presence of attached thrombus overlying an intact and visualized plaque, luminal surface irregularity without thrombus, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus.[13,14] Calcified nodule was defined as protruding, superficial, and nodular calcium with disrupted fibrous cap.[13,14] Lesions that did not meet the above criteria were classified as others.

Individual plaque components and microstructures were further analyzed. Lipid was defined as a low signal region with diffuse border.[12] The lipid arc was measured in every frame through the entire length of lipid-containing plaques and lipid length measured on the longitudinal view. The fibrous cap thickness was defined as the minimum distance from the coronary artery lumen to inner border of lipid.[12] The average of 3 measurements at its thinnest part was used for the analysis. Thin-cap fibroatheroma (TCFA) was defined as a plaque with lipid content in ≥2 quadrants and the thinnest part of fibrous cap ≤65 μm.[12] A microchannel was defined as a signal-poor void without connection to the lumen, recognized on ≥3 consecutive cross-sectional images.[12,15] Intracoronary thrombus was defined as a mass protruding into the vessel lumen from the surface of the vessel wall.[12] Cholesterol crystal was defined as a thin, linear region of high signal intensity within a lipidic plaque.[12,16]

Quantitative Coronary Angiography Analysis

Quantitative coronary angiography (CMS-QCA ver 7.0; Medis, Leiden, The Netherlands) was used for analyzing reference

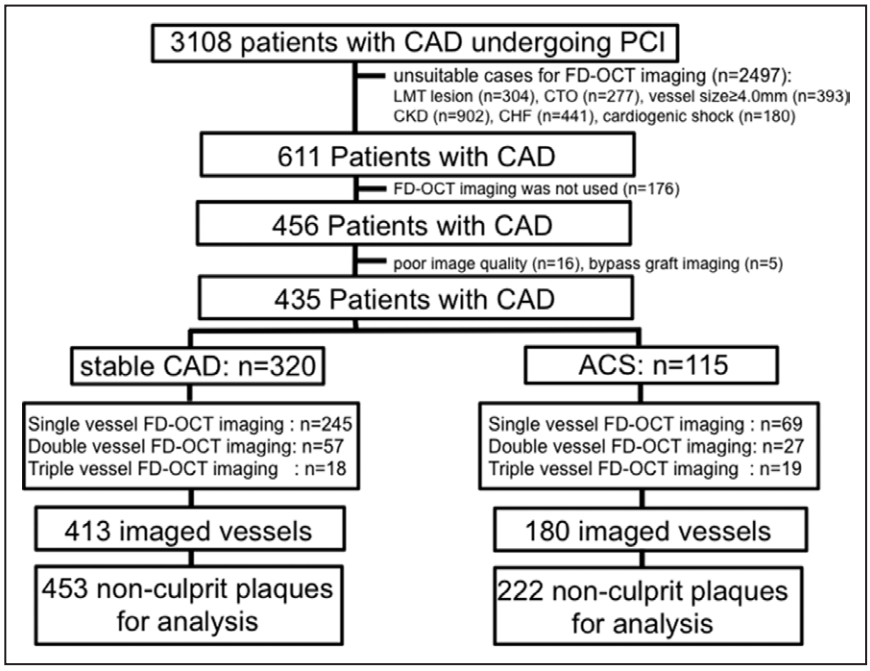

Figure 1. Study population. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CTO, chronic total occlusion; FD-OCT, frequency-domain optical coherence tomography; LMT, left main trunk; and PCI, percutaneous coronary intervention.

Table 1. Clinical Characteristics in Stable CAD

	Men (n=217)	Women (n=103)	*P* Value
Age, y	60.4±9.4	63.1±11.2	0.08
Body mass index, kg/m^2	29.4±5.2	31.3±7.1	0.18
Hypertension, n (%)	147 (67.7)	82 (79.6)	0.02
Hyperlipidemia, n (%)	161 (74.1)	75 (72.8)	0.82
Type 2 diabetes mellitus, n (%)	68 (31.3)	43 (41.7)	0.03
Current smoker, n (%)	28 (12.9)	17 (16.5)	0.51
Metabolic syndrome, n (%)	80 (36.8)	55 (53.4)	0.02
Angina pectoris, n (%)	161 (74.2)	71 (68.9)	0.28
Silent myocardial ischemia, n (%)	56 (25.8)	32 (31.1)	
Single vessel disease, n (%)	156 (71.9)	81 (78.6)	0.04
Multivessel disease, n (%)	61 (28.1)	22 (21.4)	
Left ventricular ejection fraction, (%)	52±10	51±9	0.38
Medication on admission			
Aspirin, n (%)	215 (99.1)	102 (99.0)	0.95
β-Blockers, n (%)	158 (72.8)	81 (78.6)	0.28
ACE inhibitor, n (%)	118 (54.4)	60 (58.2)	0.48
Statin, n (%)	186 (85.7)	87 (84.5)	0.83
Biochemistry data			
LDL-C, mmol/L	2.3±0.8	2.9±1.0	0.008
HDL-C, mmol/L	1.1±0.2	1.2±0.4	0.04
Triglyceride, mmol/L (interquartile range)	1.1 (0.7–1.8)	1.3 (1.0–3.1)	0.01
CRP, mg/L	2.8 (1.0–4.7)	4.0 (1.8–6.3)	0.04

ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; CRP, c-reactive protein; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

Table 2. Clinical Characteristics in ACS

	Men (n=80)	Women (n=35)	*P* Value
Age, y	61.4±9.6	65.5±12.2	0.33
Body mass index, kg/m^2	29.9±5.7	33.4±4.7	0.21
Hypertension, n (%)	55 (68.7)	29 (82.9)	0.04
Hyperlipidemia, n (%)	64 (80.0)	25 (71.4)	0.76
Type 2 diabetes mellitus, n (%)	19 (23.7)	15 (42.8)	0.04
Current smoker, n (%)	17 (21.2)	9 (25.7)	0.85
Metabolic syndrome, n (%)	29 (36.2)	21 (60.0)	0.02
Previous angina, n (%)	20 (25.0)	8 (22.9)	0.93
STEMI, n (%)	24 (30.0)	8 (22.9)	0.79
NSTEMI, n (%)	51 (63.8)	24 (68.6)	0.81
Unstable angina pectoris, n (%)	5 (6.2)	3 (8.5)	0.92
Single vessel disease, n (%)	49 (61.2)	25 (71.4)	0.09
Multivessel disease, n (%)	31 (38.8)	10 (28.6)	
Left ventricular ejection fraction, (%)	41±16	43±18	0.51
Medication on admission			
Aspirin, n (%)	2 (2.5)	1 (2.8)	0.97
β-Blockers, n (%)	15 (18.7)	6 (17.1)	0.94
ACE inhibitor, n (%)	25 (31.2)	11 (31.4)	0.98
Statin, n (%)	13 (16.2)	6 (17.1)	0.90
Biochemistry data			
LDL-C, mmol/L	2.4±0.8	3.0±1.1	0.03
HDL-C, mmol/L	1.0±0.2	1.2±0.5	0.12
Triglyceride, mmol/L (interquartile range)	2.4 (1.8–3.6)	3.0 (2.1–5.5)	0.04
CRP, mg/L	3.1 (1.9–6.0)	5.1 (2.4–7.5)	0.10

ACE, angiotensin-converting enzyme, ACS, acute coronary syndrome; CRP, c-reactive protein, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST elevation myocardial infarction; and STEMI, ST-elevation myocardial infarction.

diameter, minimum lumen diameter, and diameter stenosis of coronary artery stenosis.

Statistical Analysis

Continuous variables are expressed as mean±SD or median, and categorical variables as percentage. The χ^2 test was used to test for differences in categorical variables between groups and continuous data were compared using unpaired *t* test or Mann–Whitney test when the variable was not normally distributed. Generalized estimating equations approach was used to take into account the intraclass correlation because of the multiple plaques analyzed within a single patient's data. FD-OCT measures were analyzed by an analysis of covariance adjusting for clinical characteristics (age, hypertension, diabetes mellitus, body mass index, and metabolic syndrome), the degree of risk control (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and c-reactive protein), and statin use. Cardiovascular outcomes (a composite of death, nonfatal myocardial infarction, and revascularization) were summarized as Kaplan–Meier percentages and compared using log-rank tests. $P<0.05$ was considered significant.

To assess the reproducibility of measurements, randomly selected 200 nonculprit plaques were analyzed by the 2 experienced investigators. With regard to intraobserver variability, the investigator repeated a blind analysis at least 2 weeks after the initial one, and these 2 measurements were compared. Interobserver and intraobserver reliabilities were estimated by means of κ coefficient for binary outcomes and intraclass correlation coefficient for continuous measurements. The intraobserver and interobserver differences in fibrous cap thickness and lipid arc were determined as mean±SD.

For the primary outcome, the prevalence of plaque erosion, a sample of 230 nonculprit lesions will be required for 90% power at a 2-sided α level of 0.05 to detect a nominal difference of 1.5%, assuming a SD of 3.5%. All statistical analyses were performed using SPSS (version 17.0; SPSS Inc, Chicago, IL).

Results

Clinical Demographics

Tables 1 and 2 summarize clinical characteristics in patients with stable CAD (n=320) and ACS (n=115), respectively. Women with stable CAD were more likely to have a history of hypertension (79.6% versus 67.7%; *P*=0.02), type 2 diabetes mellitus (41.7% versus 31.3%; *P*=0.03), and metabolic

syndrome (53.4% versus 36.8%; *P*=0.02). Women had a lower prevalence of multivessel disease (21.4% versus 28.1%; *P*=0.04). Despite similar statin use between sexes (84.5% versus 85.7%; *P*=0.83), women were more likely to have a higher level of low-density lipoprotein (2.9±1.0 versus 2.3±0.8 mmol/L; *P*=0.008), high-density lipoprotein (1.2±0.4 versus 1.1±0.2 mmol/L; *P*=0.04), triglyceride (median: 1.3 versus 1.1 mmol/L; *P*=0.01), and C-reactive protein (median: 4.0 versus 2.8 mg/L; *P*=0.04). These differences in clinical features were similarly observed in women with ACS (Table 2).

Location and Quantitative Coronary Angiography Data of Imaged Plaques

Of 320 patients with stable CAD, single-, double-, and triple-vessel FD-OCT imaging were conducted in 245, 57, and 18 cases, respectively, identifying 453 nonculprit plaques within 413 imaged vessels. Similarly, 222 nonculprit plaques were identified within 180 imaged vessels in ACS patients (single-, double-, and triple-vessel imaging: 69, 27, and 19 cases, respectively; Figure 1). There was no significant difference in the imaged length of coronary artery between men and women (81±17 versus 76±14 mm; *P*=0.52). The anatomic distribution and angiographic features of plaques are shown in Table 3. More than 40% of nonculprit plaques were located within the left descending artery in both sexes. Reference diameter was smaller in women (stable CAD: 2.9±0.2 versus 3.2±0.3 mm; *P*=0.04 and ACS: 2.9±0.3 versus 3.3±0.4 mm; *P*=0.04; Table 3, stable CAD and ACS).

Table 3. Location of Nonculprit Plaques and QCA Data

Stable CAD	Men (n=302)	Women (n=151)	*P* Value
Plaque location			
LAD, n (%)	123 (40.7)	62 (41.1)	0.83
LCX, n (%)	69 (22.8)	39 (25.8)	
RCA, n (%)	110 (36.5)	50 (33.1)	
QCA data			
Reference diameter, mm	3.2±0.3	2.9±0.2	0.04
Minimum lesion diameter, mm	1.9±0.2	2.0±0.2	0.81
Percent diameter stenosis, %	39.9±17.4	35.1±15.7	0.63
ACS			
	Men (n=152)	Women (n=70)	*P* Value
Plaque location			
LAD, n (%)	63 (41.4)	31 (44.3)	0.70
LCX, n (%)	46 (30.3)	21 (30.0)	
RCA, n (%)	43 (28.3)	18 (25.7)	
QCA data			
Reference diameter, mm	3.3±0.4	2.9±0.3	0.04
Minimum lesion diameter, mm	2.0±0.3	2.1±0.4	0.79
Percent diameter stenosis, %	37.1±15.2	34.0±12.8	0.69

ACS indicates acute coronary syndrome; CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery; QCA, quantitative coronary angiography; and RCA, right coronary artery.

Plaque-Based Analysis of FD-OCT Measures in Patients With Stable CAD

Table 4 shows FD-OCT measures of nonculprit plaques in patients with stable CAD. Different features of plaque classification at nonculprit lesions were observed in women (*P*=0.03). Nonculprit plaques in women were less likely to exhibit plaque rupture (0.7% versus 5.6%) and more likely to demonstrate plaque erosion (8.6% versus 0.3%). There were no significant differences in the prevalence of fibrous (35.1% versus 32.8%; *P*=0.82) and lipidic plaques (64.9% versus 67.2%; *P*=0.82) between sexes. Women demonstrated a smaller lipid arc (163.1±71.4° versus 211.2±71.2°; *P*=0.03). There were no significant differences in fibrous cap thickness (105.2±62.1 versus 96.1±40.4 μm; *P*=0.57) and the prevalence of TCFA (26.5% versus 25.2%; *P*=0.85), microchannel (19.2% versus 20.5%; *P*=0.95), and thrombus (2.6% versus 2.6%; *P*=0.98), whereas women were less likely to harbor cholesterol crystal (17.2% versus 27.5%;

Table 4. Nonculprit Plaque Features in Stable CAD

FD-OCT measures in patients with stable CAD	Men (n=302)	Women (n=151)	*P* Value
Plaque classification			
Plaque rupture, n (%)	17 (5.6)	1 (0.7)	0.03
Plaque erosion, n (%)	1 (0.3)	13 (8.6)	
Calcified nodule, n (%)	11 (3.6)	7 (4.6)	
Others, n (%)	273 (90.5)	130 (86.1)	
Plaque components			
Fibrous, n (%)	99 (32.8)	53 (35.1)	0.82
Lipid, n (%)	203 (67.2)	98 (64.9)	
Lipid content			
Averaged lipid arc, °	211.2±71.2	163.1±71.4	0.03
Lipid length, mm	6.7±6.8	5.3±5.2	0.07
Plaque microstructures			
Fibrous cap thickness, μm	96.1±40.4	105.2±62.1	0.57
TCFA, n (%)	76 (25.2)	40 (26.5)	0.85
Microchannel, n (%)	62 (20.5)	29 (19.2)	0.95
Thrombus, n (%)	8 (2.6)	4 (2.6)	0.98
Cholesterol crystal, n (%)	83 (27.5)	26 (17.2)	0.01
Calcification, n (%)	104 (34.4)	23 (15.2)	0.008
Comparison of FD-OCT measures adjusting for clinical characteristics	Men	Women	*P* Value
Averaged lipid arc, °*	187.6±36.1	144.2±31.6	0.04
Plaque rupture, %*	10.3	2.6	0.03
Plaque erosion, %*	0.9	6.6	0.03
Cholesterol crystal, %*	29.1	20.5	0.02
Calcification, %*	35.4	17.9	0.02

ACS indicates acute coronary syndrome; CAD, coronary artery disease; FD-OCT, frequency-domain optical coherence tomography; and TCFA, thin-cap fibroatheroma.

*The presented values are adjusted for differences in clinical characteristics, medication use, and the degree of risk factor control.

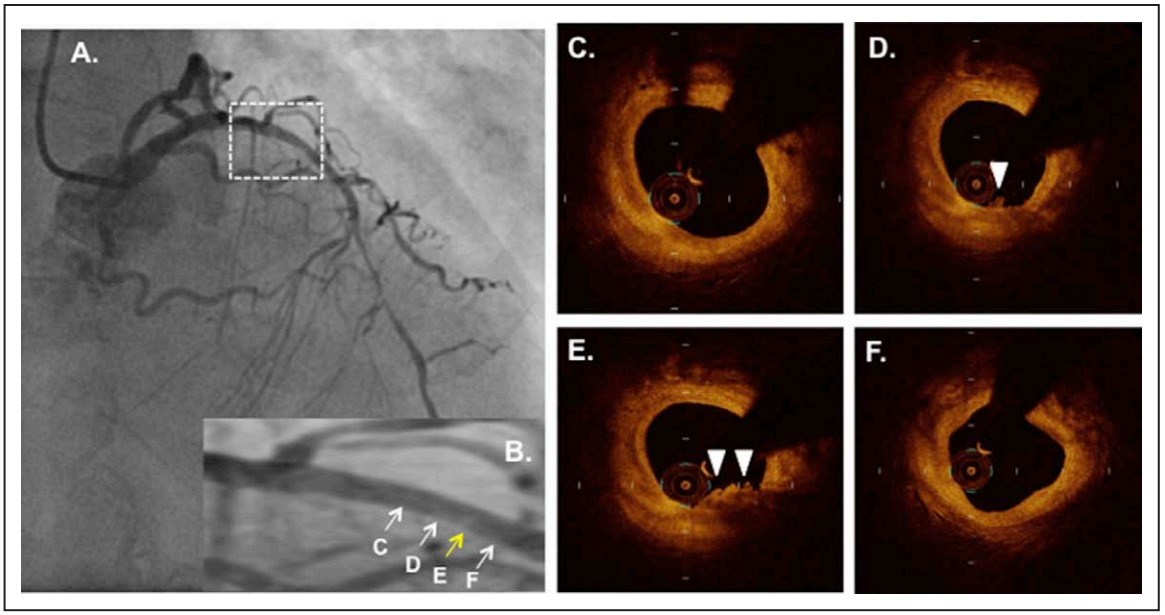

Figure 2. Representative frequency-domain optical coherence tomography (FD-OCT) images in women. A 52-y-old woman presented stable coronary artery disease. Coronary angiography demonstrated a mild (nonculprit lesion) and a tight stenosis (culprit lesions) at proximal and mid of the left anterior descending artery, respectively (**A**). Haziness within the vessel (yellow arrow) was observed (**B**). FD-OCT imaging visualized fibrous plaque (**C**–**F**). **D** and **E**, An irregular lumen surface with attached mural thrombus, indicating plaque erosion.

P=0.01) and calcification (15.4% versus 34.4%; *P*=0.008). After adjustment for differences in clinical characteristics, nonculprit plaques in women still continued to exhibit a smaller lipid arc (*P*=0.04), less plaque rupture (*P*=0.03), cholesterol crystals (*P*=0.02) and calcification (*P*=0.02), and more plaque erosion (*P*=0.03; Table 4, comparison of FD-OCT measures adjusting for clinical characteristics). Representative FD-OCT images in women and men were shown in Figures 2 and 3.

FD-OCT measures at culprit lesions in patients with stable CAD were summarized in the Table I in the Data Supplement. Of 428 culprit lesions within 413 target vessels, 139 lesions were excluded because of the inability to cross FD-OCT catheter through the lesions (n=35) and suboptimal imaging of culprit lesions (n=104). In the remaining 289 culprit lesions, a higher frequency of plaque erosion (9.3% versus 0.9%) was observed in women, although this comparison did not meet statistical significance (*P*=0.08). Smaller lipid arc (165.0±72.6° versus 225.2±78.4°; *P*=0.04) and lower prevalence of cholesterol crystal (13.9% versus 27.5%; *P*=0.03) and calcification (16.3% versus 34.4%; *P*=0.009) were observed in women (Table I in the Data Supplement).

Plaque-Based Analysis of FD-OCT Measures in Patients With ACS

FD-OCT measures in patients with ACS are summarized in Table 5. Similar to patients with stable CAD, there were significant differences in plaque classification in men and women (*P*=0.04). Plaque rupture was less frequently observed (2.8% versus 13.1%), and the prevalence of plaque erosion in women was higher compared with men (11.4% versus 0.6%). Smaller lipid arc (171.6±53.2° versus 235.8±86.4°; *P*=0.03) and a lower frequency of cholesterol crystal (28.6% versus 38.2%; *P*=0.03) and calcification (10.0% versus 23.7%; *P*=0.01) were identified in women (Table 5, FD-OCT measures in patients with ACS). Multivariate analysis demonstrated that sex differences were observed with regard to the prevalence of plaque rupture (*P*=0.04), its erosion (*P*=0.04), cholesterol crystal (*P*=0.03), and calcification (*P*=0.02; Table 5, comparison of FD-OCT measures adjusting for clinical characteristics). Lipid arc within nonculprit lesions was smaller in women, but this comparison failed to meet statistical significance (*P*=0.08).

Table II in the Data Supplement summarizes features of culprit lesions in ACS patients. Of 184 culprit lesions in 180 target vessels, FD-OCT catheter could not cross 18 severely calcified lesions, and another 67 lesions were not clearly visualized. Analysis of the remaining 99 culprit lesions has demonstrated more frequent plaque erosion (35.7% versus 18.3%) and a lower proportion of cholesterol crystal (25.0% versus 40.8%) and calcification (7.1% versus 30.9%) in women, although these comparison were not statistically significant (*P*=0.10, 0.07, and 0.05, respectively; Table II in the Data Supplement). Lipid arc was significantly smaller in women compared with men (189.2±68.1° versus 261.2±88.2°; *P*=0.04).

Spatial Distribution of TCFA

The location of TCFA in men and women with stable CAD or ACS was shown in Table 6. TCFAs in men were more likely to be located at proximal segment (<40 mm from the ostium of each major coronary artery) in the left anterior descending (76.0% versus 26.0%; *P*=0.03) and right coronary arteries (80.4% versus 19.6%; *P*=0.03). In contrast, TCFAs in women evenly distributed within the coronary arteries (left anterior

Table 5. Nonculprit Plaque Features in ACS

FD-OCT measures in patients with ACS	Men (n=152)	Women (n=70)	*P* Value
Plaque classification			
Plaque rupture, n (%)	20 (13.1)	2 (2.8)	0.04
Plaque erosion, n (%)	1 (0.6)	8 (11.4)	
Calcified nodule, n (%)	13 (8.6)	5 (7.1)	
Others, n (%)	101 (66.4)	49 (70.0)	
Plaque components			
Fibrous, n (%)	33 (21.7)	16 (22.9)	0.90
Lipid, n (%)	119 (78.3)	54 (77.1)	
Lipid content			
Averaged lipid arc, °	235.8±86.4	171.6±53.2	0.03
Lipid length, mm	7.8±6.2	6.5±4.8	0.38
Plaque microstructures			
Fibrous cap thickness, μm	90.9±67.9	100.9±51.2	0.84
TCFA, n (%)	70 (46.1)	32 (45.7)	0.94
Microchannel, n (%)	48 (31.6)	18 (25.7)	0.35
Thrombus, n (%)	15 (9.9)	6 (8.6)	0.89
Cholesterol crystal, n (%)	58 (38.2)	20 (28.6)	0.03
Calcification, n (%)	36 (23.7)	7 (10.0)	0.01
Comparison of FD-OCT measures adjusting for clinical characteristics	Men	Women	*P* Value
Averaged lipid arc, °*	201.8±30.8	164.1±34.5	0.08
Plaque rupture, %*	11.1	1.4	0.04
Plaque erosion, %*	0.6	10.0	0.04
Cholesterol crystal, %*	32.8	21.4	0.03
Calcification, %*	26.3	10.0	0.02

ACS indicates acute coronary syndrome; FD-OCT, frequency-domain optical coherence tomography; and TCFA, thin-cap fibroatheroma.

*The presented values are adjusted for differences in clinical characteristics, medication use, and the degree of risk factor control.

descending artery: 60.0% versus 40.0%; *P*=0.63; left circumflex artery: 40.9% versus 59.1%; *P*=0.63; and right coronary artery: 52.0% versus 48.0%; *P*=0.63).

Cardiovascular Outcomes Between Sexes

In patients with stable CAD or ACS, there was no significant difference in major adverse cardiovascular event rate between sexes during observational period (median follow-up period: 2.2 years; stable CAD: 8.1% versus 9.5% at 2.2-year follow-up; log-rank test *P*=0.71 and ACS: 11.5% versus 12.2% at 2.2-year follow-up; log-rank test *P*=0.83; Figure I in the Data Supplement).

Interobserver and Intraobserver Variability

Interobserver and intraobserver variability were summarized in Table III in the Data Supplement. Intraobserver variability yielded acceptable concordance for plaque classification, components, and microstrctures. Interobserver variability showed slightly lower concordance for these measures. Intraclass correlations were 0.92 and 0.98 for fibrous cap thickness, and 0.95 and 0.97 for lipid arc. Intraobserver and interobserver differences in measurements of fibrous cap thickness and lipid arc were 18±16 and 13±11 μm, and 23±14° and 12±10°, respectively (Table III in the Data Supplement).

Table 6. Distribution of TCFAs

	Number of TCFA=146		
Men	Proximal*	Nonproximal†	*P* Value
LAD, n (%)	38/50 (76.0)	12/50 (26.0)	0.03
LCX, n (%)	21/40 (52.5)	19/40 (47.5)	
RCA, n (%)	45/56 (80.4)	11/56 (19.6)	
Women			
	Number of TCFA=72		
	Proximal*	Nonproximal†	*P* Value
LAD, n (%)	15/25 (60.0)	10/25 (40.0)	0.63
LCX, n (%)	9/22 (40.9)	13/22 (59.1)	
RCA, n (%)	13/25 (52.0)	12/25 (48.0)	

LAD indicates left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; and TCFA, thin-cap fibroatheroma.

*Proximal=<40 mm from the ostium of each major coronary artery.

†Nonproximal=≥40 mm from the ostium of each major coronary artery.

Discussion

The superior imaging resolution of FD-OCT enables elucidation of detailed plaque characteristics in vivo. Our analysis demonstrates that nonculprit plaques in women were more likely to exhibit plaque erosion. Despite more prevalent coronary risk factors, smaller amounts of lipid and a lower frequency of cholesterol crystals and calcifications were observed in women.

Pathological studies have already demonstrated differences in plaque morphologies between men and women. Plaque erosion was more frequently observed at culprit lesions associated with sudden coronary death or acute myocardial infarction in women.[6–9,17] Additionally, the amount of plaque burden and the extent of calcification at culprit sites were smaller in women compared with that in men.[8,9,18–20] In the current study, nonculprit lesions in women exhibited more frequent plaque erosion and less calcific and lipidic plaques in both stable and unstable patients. These observations extend previous reports from histology studies of culprit lesions in female ACS patients.[6] Importantly, they underscore the increasing recognition of the potential role that erosion plays in precipitating subsequent cardiovascular events, particularly in women with CAD, and present an additional target for the development of novel biomarkers and therapies.

The volume of atherosclerotic plaques might associate with sex differences in plaque compositions. Although FD-OCT imaging in our study does not have enough capabilities to evaluate the extent of plaque burden because of its limited imaging depth, grayscale intravascular ultrasound imaging has demonstrated greater amount of coronary atheroma volume within nonculprit segments in men with stable CAD or ACS.[21,22] These lesions in men harbored a variety of

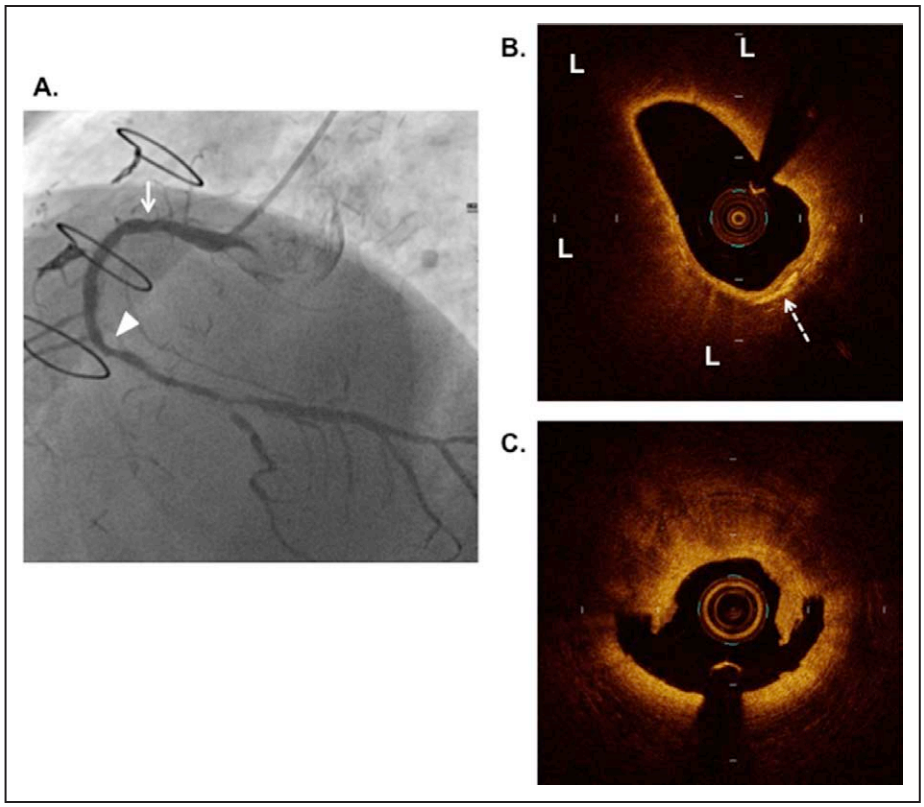

Figure 3. Representative frequency-domain optical coherence tomography (FD-OCT) images in men. A 65-y-old man presented acute coronary syndrome. Coronary angiography demonstrated several coronary artery stenosis within the right coronary artery (**A**). FD-OCT visualized mild (arrow) and moderate (arrow head) stenosis in the proximal and the mid segments (**A**). Proximal lesion exhibited lipid plaque (L) with cholesterol crystal (dashed arrow) (**B**). In another moderate stenosis, plaque rupture was observed (**C**).

plaque components including necrotic core, fibrous tissue, fibrofatty, and calcium on virtual histology intravascular ultrasound imaging, whereas the amount of each composition was smaller in women who contained less atherosclerotic plaque.[22] These observations support the extent of plaque burden as a potential contributor to differences in FD-OCT–derived plaque components between sexes in our study.

Despite more risk factors and less optimal lipid control in women, their nonculprit plaques contained smaller amounts of both lipid and calcium and were less likely to harbor cholesterol crystals. These observations, however, did not translate into differences in fibrous cap thickness and the frequency of TCFAs between sexes. Whether this reflects differential effects of risk factor exposure on the artery wall in women requires further investigation. The observation that women undergo greater disease regression in response to high-intensity statins,[23] despite smaller baseline plaque burden, also suggests potential sex differences in the response of the artery wall to risk factor modification.

Previous imaging studies have demonstrated a predilection for vulnerable plaques within the more proximal regions of the coronary vasculature.[24–26] We observed a similar distribution in men, whereas TCFAs seemed to be located in proximal and more distal segments with a similar frequency in women. Although more proximally located TCFAs in men may promote more extensive myocardial damage, it remains to be determined whether a different distribution pattern of TCFAs in women in our analysis would ultimately translate into differences in cardiovascular outcomes.

Several caveats of the present analysis should be noted. FD-OCT imaging was used based on clinical indication. This could be a bias to select study patients, which might affect our findings. Given the shallow penetration depth of the infrared light beam, FD-OCT does not reliably image the full burden of plaque in the artery wall of all patients. All patients had presented for PCI for a clinical indication, and it is unknown whether the current findings apply to asymptomatic individuals. Study population, especially the number of ACS patients, is relatively small, limiting statistical power to detect significant differences in cardiovascular outcomes between sexes.

In summary, nonculprit plaques in women were more likely to harbor plaque erosion on FD-OCT. Despite more comorbid risk factors than men, plaque rupture, large lipid arcs, cholesterol crystals, and calcifications were less frequently observed within nonculprit plaques in women. Sex-related differences were also observed with regard to the distribution pattern of TCFAs. These findings highlight distinct pathophysiology of atherosclerosis between sexes, potentially leading to differences in clinical presentation.

Acknowledgments

We are grateful for the technical expertise of the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic.

Disclosures

Dr Nissen has received research support to perform clinical trials through the Cleveland Clinic Coordinating Center for Clinical Research from Pfizer, AstraZeneca, Novartis, Roche, Daiichi-Sankyo, Takeda, Sanofi-Aventis, Resverlogix, and Eli Lilly and is a consultant/advisor for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. Dr Nicholls is a consultant for AstraZeneca, Amgen, Boehringer Ingelheim, CSL Behring, Merck, Takeda, Novartis, Pfizer, Sanofi-Regeneron, Eli Lilly, and Roche and has received research support from AstraZeneca, Amgen, Cerenis, Novartis, Resverlogix, Eli Lilly, InfraReDx, Anthera, Roche, Sanofi-Regeneron, and Lipid Sciences. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Considerable evidence has demonstrated sex differences in the clinical presentation of coronary artery disease (CAD). Women have a greater symptom burden but a lower prevalence of obstructive CAD compared with men. Pathohistological studies have reported that culprit lesions causing acute coronary syndrome or sudden cardiac death in women harbor less extensive atherosclerosis and evidence of rupture, with a higher prevalence of plaque erosion. Given the systemic nature of coronary atherosclerosis, nonculprit lesions in women might also harbor distinct plaque features in vivo compared with men. The current study analyzed 320 patients with stable CAD and 115 patients with acute coronary syndrome by using frequency-domain optical coherence tomography, a high-resolutional intravascular imaging modality enabling detailed visualization of atherosclerotic plaques in vivo. In women with stable CAD, plaque erosion was more frequently observed at nonculprit plaques (8.6% versus 0.3%; P=0.03), accompanied with smaller lipid arc (163.1±71.4 versus 211.2±71.2°; P=0.03) and a lower frequency of cholesterol crystals (17.2 versus 27.5%; P=0.01) and calcification (15.4 versus 34.4%; P=0.008). These plaque features were similarly observed at nonculprit lesions in women with acute coronary syndrome. Although thin-cap fibroatheromas in men clustered within proximal arterial segments, thin-cap fibroatheromas were evenly distributed in women. These findings highlight distinct pathophysiology of atherosclerosis between sexes, potentially leading to differences in clinical presentation. Because erosion is recognized as the potential plaque feature precipitating subsequent cardiovascular events, particularly in women with CAD, our observation might suggest plaque erosion at nonculprit segment as a therapeutic target to further improve cardiovascular outcomes in women with CAD.