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Relation of Gender to Atherosclerotic Plaque Characteristics by Differing Angiographic Stenosis Severity

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It is unknown whether gender influences the atherosclerotic plaque characteristics (APCs) of lesions of varying angiographic stenosis severity. This study evaluated the imaging data of 303 symptomatic patients from the derivation arm of the CREDENCE (Computed TomogRaphic Evaluation of Atherosclerotic Determinants of Myocardial IsChEmia) trial, all of whom underwent coronary computed tomographic angiography and clinically indicated nonemergent invasive coronary angiography upon study enrollment. Index tests were interpreted by 2 blinded core laboratories, one of which performed quantitative coronary computed tomographic angiography using an artificial intelligence application to characterize and quantify APCs, including percent atheroma volume (PAV), low-density noncalcified plaque (LD-NCP), noncalcified plaque (NCP), calcified plaque (CP), lesion length, positive arterial remodeling, and high-risk plaque (a combination of LD-NCP and positive remodeling ≥1.10); the other classified lesions as obstructive (≥50% diameter stenosis) or nonobstructive (<50% diameter stenosis) based on quantitative invasive coronary angiography. The relation between APCs and angiographic stenosis was further

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Funding: none.

See page 282 for Declaration of Competing Interest.

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https://doi.org/10.1016/j.amjcard.2023.07.004

examined by gender. The mean age of the study cohort was 64.4 ± 10.2 years (29.0% female). In patients with obstructive disease, men had more LD-NCP PAV (0.5 ± 0.4 vs 0.3 ± 0.8, p = 0.03) and women had more CP PAV (11.7 ± 1.6 vs 8.0 ± 0.8, p = 0.04). Obstructive lesions had more NCP PAV compared with their nonobstructive lesions in both genders, however, obstructive lesions in women also demonstrated greater LD-NCP PAV (0.4 ± 0.5 vs 1.0 ± 1.8, p = 0.03), and CP PAV (17.4 ± 16.5 vs 25.9 ± 18.7, p = 0.03) than nonobstructive lesions. Comparing the composition of obstructive lesions by gender, women had more CP PAV (26.3 ± 3.4 vs 15.8 ± 1.5, p = 0.005) whereas men had more NCP PAV (33.0 ± 1.6 vs 26.7 ± 2.5, p = 0.04). Men had more LD-NCP PAV in nonobstructive lesions compared with women (1.2 ± 0.2 vs 0.6 ± 0.2, p = 0.02). In conclusion, there are gender-specific differences in plaque composition based on stenosis severity. **(Am J Cardiol 2023;204:276−283)**

Large-scale clinical trials leveraging quantitative coronary computed tomographic angiography (CCTA) suggest that atherosclerotic plaque characteristics (APCs), like percent atheroma volume (PAV; plaque volume normalized for vessel volume), noncalcified plaque (NCP), low-density NCP (LD-NCP), calcified plaque (CP) and positive arterial remodeling (≥1.10), can provide important insights into a patient's disease progression and outcomes.[1−5] Consistently, several assessments of gender-based differences in atherosclerosis have attempted to explain the clinical progression of cardiac disease in women, who typically present later in life than men and suffer worse outcomes after an event.[6−10] However, it remains unclear whether specific plaque phenotypes exist in lesions based on angiographic stenosis severity and furthermore, whether phenotypes are gender specific. Consequently, this retrospective analysis of the CREDENCE (Computed TomogRaphic Evaluation of Atherosclerotic Determinants of Myocardial IsChEmia) trial employs an evaluation of APCs by quantitative CCTA to identify the relation of APCs, angiographic stenosis severity, and gender.

Methods

The study population was comprised 303 consecutively enrolled patients from the derivation arm of the prospective, multicenter, derivation-validation, CREDENCE trial. The CREDENCE trial enrolled stable patients with suspected coronary artery disease (CAD) referred for nonemergent invasive coronary angiography (ICA) by American College of Cardiology/American Heart Association clinical practice guidelines. After enrollment, patients underwent CCTA followed by quantitative ICA within 60 days. The institutional review board of each enrolling site approved the study protocol and all patients provided written informed consent. Patient demographics, cardiovascular risk factors, laboratory values, and medications were prospectively collected and recorded at the time of CCTA. All index tests were interpreted in blinded fashion by separate core laboratories.[3,11]

Sites performed CCTA using either a single or dual source computed tomography (CT) scanner with ≥64-detector rows and by protocols consistent with Society of Cardiovascular CT guidelines.[11,12] Nitroglycerin was administered immediately before CCTA acquisition and patients received β blockers as needed. The resulting image quality was acceptable in 99% of patients.

The core laboratory responsible for interpreting noninvasive imaging data for this substudy performed quantitative CCTA in a blinded manner using a United States Food and Drug Administration-cleared artificial intelligence software (Cleerly LABS, Denver, Colorado) that leverages validated convolution neural network models to perform automated analysis of plaque characteristics on CCTA.[13−17] In this approach, neural networks are used to optimize image series, contour the lumen and outer vessel wall, and identify the length of each lesion and the point of maximum stenosis. These parameters are subsequently used to automatically characterize and quantify vascular remodeling, plaque volumes, and percent diameter stenosis. Once the artificial intelligence algorithm completes all operations, a quality control cardiac CT-trained technician reviews the results and provides any necessary manual adjustments.[18−20] Figure 1 provides an example of the software analysis output.

Coronary segments with a diameter ≥2 mm were included in the analysis using a modified 18-segment Society of Cardiovascular CT model.[21,22] Each segment was evaluated for the presence or absence of coronary atherosclerosis, defined as any tissue structure >1 mm^2 within the coronary artery wall that was differentiated from the surrounding epicardial tissue, epicardial fat, or the vessel lumen itself. Coronary plaque burden was normalized to vessel volume to account for gender variations in coronary artery volume. Plaque length referred to the measurement of uninterrupted plaque along the length of a vessel whereas plaque diffusivity was the percent plaque along the length of a vessel divided by the total vessel length. Plaque burden was reported as PAV, which was calculated as ([Plaque Volume/Vessel Volume] × 100%).[22] Plaque volumes (mm^3) were calculated for each coronary vessel and then summated to compute the total plaque volume at the patient level.

Plaque components were characterized based on Hounsfield unit (HU) ranges with LD-NCP defined as plaques 30 HU (commonly associated with lipid-rich plaque), NCP between 30 and 350 HU; a more fibrous plaque form and CP, the most dense plaque form defined as >350 HU.[23] Positive remodeling was defined as a ratio ≥1.10 when dividing the lesion luminal diameter by the normal reference

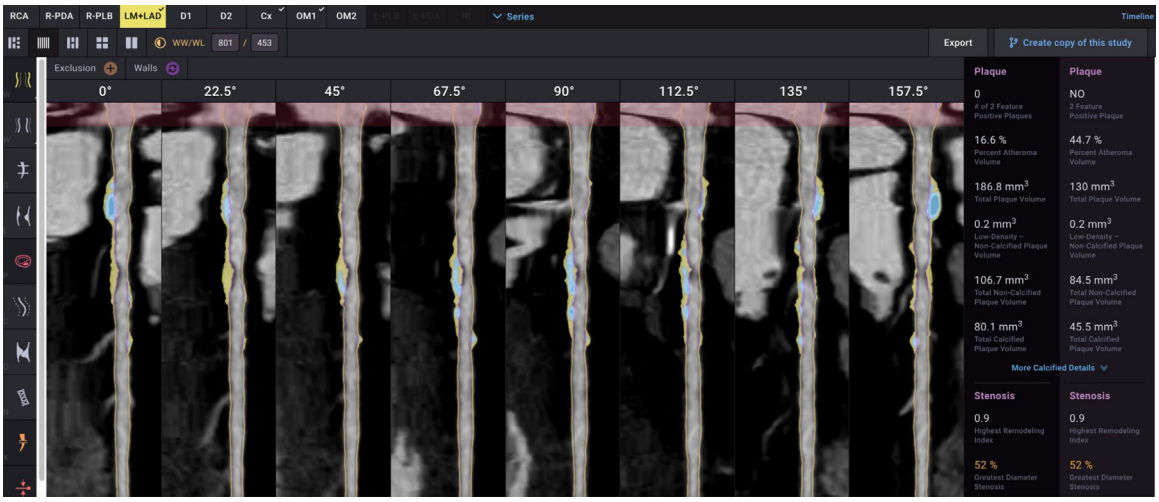

Figure 1. Example of AI characterization of APCs in an obstructive lesion.
This image provides multiple views of a vessel segment along with the AI software itemized output analyzing the lesion contours and plaque content. The contour of the vessel's outer wall is outlined in *yellow*; the luminal wall is outlined in *purple*. The vessel segment contains an obstructive lesion with a 52% diameter stenosis and a total plaque volume of 186.8 mm^3. The plaque is comprised a combination of LD-NCP (0.2 mm^3), NCP (106.7 mm^3), and CP (80.1 mm^3). This lesion exhibits negative remodeling with a remodeling index of 0.9. AI = artificial intelligence.

diameter. The reference diameter was defined by an average of the vessel diameters at each end of the lesion to correct for changes in vessel structure because of remodeling.[24] High-risk plaque was defined by lesions with both LD-NCP and positive remodeling.[3]

All statistical analyses were performed using SAS version 9.4 (SAS, Cary, North Carolina). Continuous data are reported as mean ± SD and categorical variables are presented as absolute numbers with corresponding frequencies. Student's *t* test, Mann−Whitney test, chi-square, and Fisher's exact tests were used to compare the distribution of continuous and categorical variables, respectively. All analyses that directly compared the male cohort to the female cohort were controlled for demographic differences between the genders.

Results

There was a high prevalence of CAD risk factors in the study cohort, 29% of which were women (mean age 65.3 ± 9.0 years), and 71% men (mean age 64.1 ± 10.6 years, p = NS). Overall, women had higher low-density lipoprotein (LDL) levels (101.0 ± 36.4 vs 89.0 ± 35.8, p = 0.01) whereas men used tobacco more commonly (61.4% vs 15.9%, p <0.0001), a trend that remained consistent across subanalyses of men with both obstructive (63.5% vs 15.5%, p <0.0001) and nonobstructive disease (57.7% vs 16.0%, p <0.0001). In patients with nonobstructive disease, women had higher high-density lipoprotein (54.6 ± 16.2 vs 46.3 ± 12.7, p = 0.004) and LDL levels (102.8 ± 33.3 vs 87.6 ± 31.1, p = 0.02). There were no differences in the prevalence of hypertension, dyslipidemia, diabetes mellitus, or family history of CAD identified based on gender or stenosis severity. Additionally, there was also no difference in statin use between the 2 genders (Table 1). Subsequent analyses were controlled for distinctions in high-density lipoprotein and LDL levels and tobacco use.

When comparing all patients with obstructive and nonobstructive disease, obstructive disease was associated with

Table 1
Baseline demographics by sex and angiographic stenosis

Variable	Females (N=88)	Males (N=215)	*P*-Values	Non-obstructive			Obstructive (≥50%)		
				Females (N=50)	Males (N=78)	P-Value	Females (N=38)	Males (N=137)	*P*-Value
Age, mean (SD), y	65.3 (9.0)	64.1 (10.6)	0.3311	64.5 (10.4)	61.1 (10.1)	0.8353	66.4 (6.9)	64.1 (11.0)	0.1074
Hypertension (%)	57 (64.8%)	138 (64.2%)	0.9229	29 (58.0%)	50 (64.1%)	0.4883	28 (73.7%)	88 (64.2%)	0.2755
Dyslipidemia (%)	45 (51.1%)	90 (41.9%)	0.1403	24 (48.0%)	32 (41.0%)	0.4377	21 (55.3%)	58 (42.3%)	0.1565
Diabetes (%)	25 (28.4%)	70 (32.6%)	0.4798	12 (24.0%)	26 (33.3%)	0.2595	13 (34.2%)	44 (32.1%)	0.8460
Family history (%)	18 (20.5%)	41 (19.1%)	0.7823	8 (16.0%)	10 (12.8%)	0.6137	10 (26.3%)	31 (22.6%)	0.6348
Tobacco use, ever (%)	14 (15.9%)	132 (61.4%)	<0.0001	8 (16.0%)	45 (57.7%)	<0.0001	6 (15.8%)	87 (63.5%)	<0.0001
Statin Use (%)	56.8% (50)	55.3% (215)	0.8152	28 (56.0%)	57.7% (45)	0.8503	22 (57.9%)	54.0% (74)	0.6706
HDL, mg/dl	52.7 (13.7)	46.8 (39.8)	0.2006	54.6 (16.2)	46.3 (12.7)	0.0035	50.4 (9.3)	47.0 (48.4)	0.6850
LDL, mg/dl	101.0 (36.4)	89.0 (35.8)	0.0137	102.8 (33.3)	87.6 (31.1)	0.0171	98.8 (40.2)	89.7 (38.2)	0.2228
TG, mg/dl	130.5 (81.9)	131.0 (88.7)	0.9664	123.1 (73.2)	115.7 (56.6)	0.5520	139.8 (92.0)	139.0 (100.85)	0.9645
SBP (SD), y	139.1 (18.2)	139.7 (16.5)	0.7907	139.7 (20.2)	137.8 (15.7)	0.5398	138.4 (15.4)	140.8 (16.9)	0.4227
DBP (SD), y	78.6 (11.8)	80.8 (10.1)	0.1051	78.8 (12.9)	81.8 (10.5)	0.1557	78.3 (10.5)	80.3 (10.0)	0.3036

SBP: systolic blood pressure DBP: diastolic blood pressure.

Table 2
Per-patient atherosclerotic plaque characteristics by sex and angiographic stenosis severity

Variable	Non-obstructive (N=128)	Obstructive ≥50% (N=175)	P-value	Males*			Females		
				Non-obstructive (N=78)	Obstructive (N=137)	P-Value	Non-obstructive (N=50)	Obstructive (N=38)	P-value
PAV, Total	14.1 (10.6)	21.3 (13.0)	<0.0001	15.7 (1.4)	20.6 (1.1)	0.0029	11.6 (1.6)	22.6 (1.8)	<0.0001
PAV, LD-NCP	0.3 (0.3)	0.4 (0.4)	0.0024	0.3 (0.1)	0.5 (0.04)	0.0155	0.2 (0.04)	0.3 (0.04)	0.2851
PAV, NCP	8.7 (5.5)	12.4 (7.2)	<0.0001	9.4 (0.8)	12.9 (0.6)	0.0005	7.5 (0.8)	11.1 (0.9)	0.0044
PAV, CP	5.4 (7.1)	8.9 (9.3)	<0.0001	6.3 (1.0)	8.0 (0.8)	0.1510	4.1 (1.1)	11.6 (1.2)	<0.0001
Remodeling Index	1.3 (0.2)	1.4 (0.2)	0.0384	1.3 (0.03)	1.4 (0.02)	0.0829	1.3 (0.03)	1.4 (0.03)	0.1343
PR >1.10	103 (80.5%)	155 (88.6%)	0.0501	79.9%	90.9%	0.0238	41 (82.0%)	31 (81.6)%	0.9595
HRP, %	94 (73%)	140 (80%)	0.1785	57 (73.1%)	112 (81.8%)	0.1170	37 (74%)	28 (73.7%)	0.9734
Lesion length	27.8 (18.4)	33.7 (18.1)	0.0010	32.2 (2.4)	34.3 (1.6)	0.4384	21.1 (2.2)	32.2 (2.6)	0.0015

* Results reflect data controlled for differences in smoking in men.
CP = calcified plaque; HRP = high risk plaque (LD-NCP + PR); LD-NCP = low-density non-calcified plaque; NCP = non-calcified plaque; PAV = percent atheroma volume; PR = positive remodeling.

greater amounts of each type of plaque including LD-NCP PAV (0.4 ± 0.4 vs 0.3 ± 0.3, p = 0.002), NCP PAV (12.4 ± 7.2 vs 8.7 ± 5.5, p <0.0001), and CP PAV (8.9 ± 9.3 vs 5.4 ± 7.1, p <0.0001). When comparing patients with nonobstructive and obstructive disease within each gender, similarities and differences emerged. Both men and women with obstructive disease had greater amounts of PAV (20.6 ± 1.1 vs 15.7 ± 1.4, p = 0.003 and 22.6 ± 1.8 vs 11.6 ± 1.6, p <0.0001) and NCP PAV (12.9 ± 0.6 vs 9.4 ± 0.8, p = 0.001 and 11.1 ± 0.9 vs 7.5 ± 0.8, p = 0.004, respectively). However, obstructive disease in men was also associated with more LD-NCP PAV (0.5 ± 0.04 vs 0.3 ± 0.1, p = 0.02), whereas obstructive disease in women was associated with more CP PAV (11.6 ± 1.2 vs 4.1 ± 1.1, p <0.0001), and longer lesion lengths (32.2 ± 2.6 vs 21.1 ± 2.2, p = 0.002; Table 2). Consistently, when comparing men and women with obstructive disease, men had more LD-NCP PAV (0.5 ± 0.4 vs 0.3 ± 0.8, p = 0.03) whereas women had more CP PAV (11.7 ± 1.6 vs 8.0 ± 0.8, p = 0.04). There were no observed gender-based differences in the plaque composition of men and women with nonobstructive disease (Table 3).

On the lesion level, the composition of obstructive and nonobstructive stenoses differed by gender (Table 4). Within the male cohort, obstructive stenoses demonstrated higher PAV (51.7 ± 17.9 vs 44.5 ± 17.6, p = 0.003) and NCP PAV (35.4 ± 18.6 vs 28.0 ± 13.6, p = 0.0001). In contrast, obstructive stenoses within the female cohort demonstrated higher amounts of all forms of plaque including total PAV (55.4 ± 16.5 vs 40.6 ± 15.6, p <0.0001), LD-NCP PAV (1.0 ± 1.8 vs 0.4 ± 0.5, p = 0.03), NCP PAV (29.5 ± 16.5 vs 23.1 ± 12.3, p = 0.007), and CP PAV (25.9 ± 18.7 vs 17.4 ± 16.5, p = 0.03). Figure 2 provides an image of a stenotic lesion in a man and a woman.

When comparing plaque composition of the obstructive lesions in men to women (Table 5), findings were like those observed on the patient level. Obstructive lesions in women demonstrated greater CP PAV (26.3 ± 3.4 vs 15.8 ± 1.5, p = 0.005) than obstructive lesions in men, whereas obstructive lesions in men demonstrated greater NCP PAV (33.0 ± 1.6 vs 26.7 ± 2.5, p = 0.04), and positive remodeling (1.1 ± 0.03 vs 1.0 ± 0.03, p = 0.02). The nonobstructive lesions in men had greater LD-NCP PAV (1.2 ± 0.2 vs 0.6 ± 0.2, p = 0.02) than nonobstructive lesions in women.

Table 3
Per-patient atherosclerotic plaque characteristics by angiographic stenosis severity and sex

Variable	Obstructive ≥50%*			Non-obstructive <50%†		
	Males (N=137)	Females (N=38)	P-Value	Males (N=78)	Females (N=50)	P-value
PAV, Total	21.0 (1.1)	22.3 (2.2)	0.4689	16.0 (1.2)	13.3 (1.8)	0.2339
PAV, LD-NCP	0.5 (0.04)	0.3 (0.08)	0.0295	0.3 (0.04)	0.2 (0.1)	0.1164
PAV, NCP	13.0 (0.6)	10.6 (1.2)	0.0962	9.9 (0.7)	8.2 (1.0)	0.1822
PAV, CP	8.0 (0.8)	11.7 (1.6)	0.0407	6.2 (0.8)	5.2 (1.1)	0.4793
Remodeling Index	1.4 (0.02)	1.4 (0.04)	0.5621	1.3 (0.03)	1.4 (0.04)	0.8989
PR >1.10	86.8%	80.7%	0.2340	79.6%	81.6%	0.8006
HRP, %	79.2%	72.0%	0.2278	73.8%	71.7%	0.8178
Lesion length	34.4 (1.6)	31.5 (3.2)	0.4316	33.8 (2.1)	23.5 (3.1)	0.0094

* Results reflect data controlled for differences in smoking.
† Results reflect data controlled for HDL/LDL levels between men and women.
CP = calcified plaque; HRP = high risk plaque (LD-NCP + PR); LD-NCP = low-density non-calcified plaque; NCP = non-calcified plaque; PAV = percent atheroma volume; PR = positive remodeling.

Table 4
Per-lesion atherosclerotic plaque characteristics of obstructive and non-obstructive lesions by sex

Variable	Non-obstructive (N=187)	Obstructive ≥50% (N=175)	*P*-value	Males			Females		
				Non-obstructive (N=132)	Obstructive ≥50% (N=132)	*P*-Value	Non-obstructive (N=55)	Obstructive ≥50% (N=43)	*P*-value
PAV, Total	43.4 (17.0)	52.6 (17.6)	<0.0001	44.5 (17.6)	51.7 (17.9)	0.0032	40.6 (15.6)	55.4 (16.5)	<0.0001
PAV, LD-NCP	0.980 (2.31)	1.570 (2.93)	0.0318	1.2 (2.7)	1.8 (3.2)	0.1450	0.4 (0.5)	1.0 (1.8)	0.0271
PAV, NCP	0.266 (0.13)	0.340 (0.18)	<0.0001	28.0 (13.6)	35.4 (18.6)	0.0001	23.1 (12.3)	29.5 (16.5)	0.0066
PAV, CP	0.168 (0.17)	0.186 (0.18)	0.6732	16.5 (17.8)	16.2 (17.0)	0.4834	17.4 (16.5)	25.9 (18.7)	0.0338
Remodeling Index	1.088 (0.21)	1.070 (0.28)	0.4754	1.1 (0.2)	1.1 (0.3)	0.5067	1.1 (0.2)	1.0 (0.3)	0.5900
PR >1.10	63 (33.7%)	54 (30.9%)	0.4671	48 (36.4%)	40 (30.3%)	0.0735	15 (27.3%)	14 (32.6%)	0.1789
HRP, %	76 (40.6%)	64 (36.6%)	0.4318	60 (45.5%)	52 (39.4%)	0.3527	16 (29.1%)	12 (27.9%)	0.7922
Lesion length	16.482 (13.99)	18.240 (15.21)	0.2402	17.6 (14.5)	18.1 (15.4)	0.8771	13.7 (12.2)	18.6 (14.8)	0.0537

CP = calcified plaque; HRP = high risk plaque (LD-NCP + PR); LD-NCP = low-density non-calcified plaque; NCP = non-calcified plaque; PAV = percent atheroma volume; PR = positive remodeling.

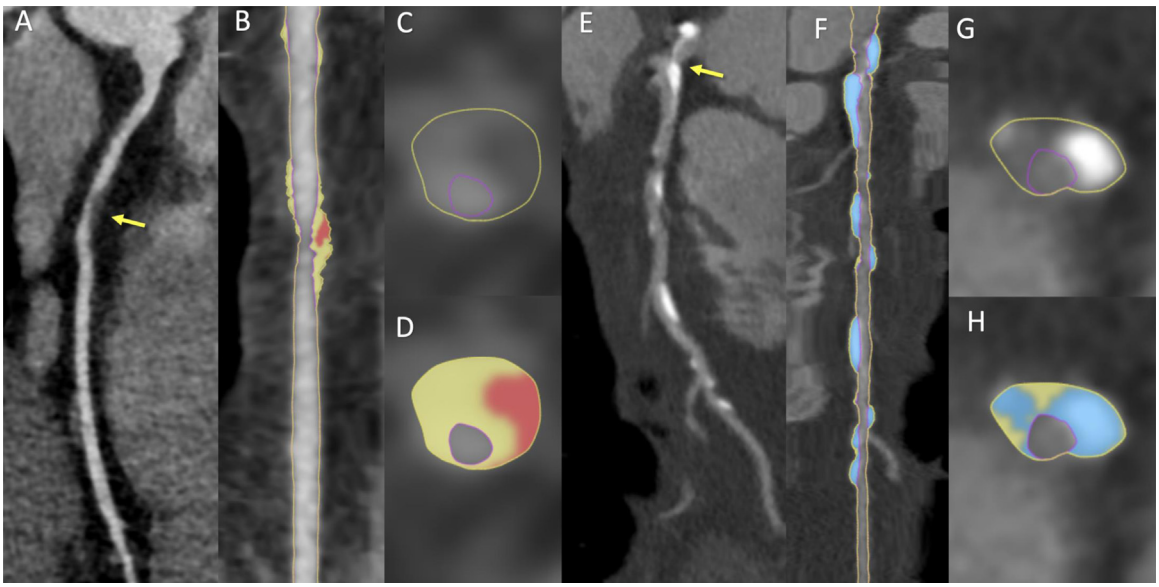

Figure 2. Example of stenotic plaques in a man and a woman.
Panels *(A to D)*: A 58-year-old man with new chest pain and a positive SPECT exam demonstrates a 50% to 69% stenosis of the proximal to mid RCA *(A, arrow)*. AI-QCT depicts a NCP with both low-density (red overlay) and noncalcified (yellow overlay) components on SMPR *(B)* and cross-sectional image with and without overlay *(C,D)*. Panels *(E)*: A 65-year-old woman with stable angina and a 50% to 69% stenosis of the left main coronary artery *(E, arrow)*. AI-QCT depicts a predominantly CP with calcified *(blue overlay)* and noncalcified *(yellow overlay)* components by SMPR *(F)* and a cross-sectional image with and without overlay *(G,H)*.
AI-QCT = artificial intelligence-quantitative computed tomography; RCA = right coronary artery; SMPR = straightened multiplanar reconstruction; SPECT = single photon emission computed tomography.

Discussion

This study compared the plaque composition and stenosis severity of 303 patients who underwent blinded quantitative CCTA and quantitative ICA to determine whether specific plaque phenotypes exist based on stenosis severity and gender. The results indicate that there are gender-based differences in plaque composition based on stenosis severity present at both the patient and lesion levels. Firstly, men with obstructive disease have more LD-NCP PAV than women with obstructive disease, whereas women have more CP PAV. Additionally, within the female cohort, obstructive lesions were comprised a heterogeneous combination of accumulated plaque including total PAV, LD-NCP PAV, NCP PAV, and CP PAV, whereas within the male cohort, the plaque composition of obstructive lesions was differentiated from nonobstructive lesions by more PAV and NCP PAV alone. Finally, the distinguishing gender-specific features of obstructive lesions and nonobstructive lesions mirrored patient-level findings with men demonstrating greater LD-NCP PAV in nonobstructive lesions and greater NCP PAV in obstructive lesions compared with women, whereas women had more CP PAV in obstructive lesions than men.

To our knowledge, this is the first study to examine plaque composition by coronary stenoses severity and gender,

Table 5
Per-lesion atherosclerotic plaque characteristics stratified by angiographic stenosis severity and sex

Variable	Obstructive ≥50%			Non-obstructive <50%*		
	Males (N=132)	Females (N=43)	P-Value	Males (N=132)	Females (N=55)	P-value
PAV, Total	51.9 (1.6)	54.9 (2.4)	0.3078	43.9 (1.8)	43.2 (2.7)	0.8356
PAV, LD-NCP	1.8 (0.03)	0.8 (0.03)	0.0573	1.2 (0.2)	0.6 (0.2)	0.0220
PAV, NCP	33.0 (1.6)	26.7 (2.5)	0.0401	26.8 (1.2)	23.1 (2.3)	0.1680
PAV, CP	15.8 (1.5)	26.3 (3.4)	0.0047	15.8 (1.6)	19.1 (2.9)	0.3374
Remodeling Index	1.1 (0.03)	1.0 (0.03)	0.0185	1.1 (0.02)	1.1 (0.03)	0.4272
PR >1.10	31.4%	27.9%	0.6532	38.6%	30.9%	0.4668
HRP, %	40.1%	25.4%	0.0735	44.7%	29.9%	0.1763
Lesion length	18.0 (1.2)	19.8 (2.1)	0.4401	14.7 (1.4)	13.2 (1.7)	0.0544

* All results reflect data controlled for differences in HDL/LDL and smoking between men and women.
CP = calcified plaque; HRP = high risk plaque (LD-NCP + PR); LD-NCP = low-density non-calcified plaque; NCP = non-calcified plaque; PAV = percent atheroma volume; PR = positive remodeling.

and in doing so, has identified unique lesion and patient-level gender-based plaque phenotypes. First, this study identified that men with obstructive disease have greater LD-NCP PAV than women, a pattern that extended to the lesion level where obstructive stenoses in men also had comparatively greater NCP PAV than obstructive stenoses in women. The significance of this distinction is reinforced by the findings of APC-focused outcomes trials like ICONIC (Incident Coronary EveNts Identified by Computed Tomography), SCOT-HEART (Scottish Computed Tomography of the HEART) and PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) which each link nonCP forms, particularly, LD-NCP to an increased risk for major adverse cardiac events (MACEs). In the ICONIC study, comprised patients who experienced acute coronary syndrome (ACS) between baseline and follow-up CCTA, LD-NCP was identified as the strongest discriminant of future ACS risk when compared with non-ACS controls.[2] This observation was echoed by the SCOT-HEART trial which identified a significant increase in ACS risk based on prevalence of LD-NCP, whereas the PROMISE trial quantified a twofold to threefold increase in MACE based on the presence of high-risk plaque, defined by the presence of both LD-NCP and positive remodeling.[1,5] High levels of NCP forms suggest one source of elevated risk for men[25] with advanced disease and may present a marker for screening and intervention.

In contrast, women with obstructive disease demonstrated comparatively greater CP PAV at both the patient and lesion levels, despite similar use of statins between the genders. One explanation for this pattern is provided by El Mahdiui et al[7] who observed a rapid reduction in fibrous and NCP in women compared with age-matched men in the perimenopausal stage, suggesting a possible hormonal role in plaque stabilization. However, whereas the presence of higher amounts of CP in obstructive lesions in women may represent a more efficient process of plaque stabilization,[4] it may also contribute to delayed clinical presentation. Based on the findings of the CREDENCE trial, which showed that specific APCs are associated with (and can therefore be used to help discriminate) ischemic lesions and vessels, NCPs were in the APCs most strongly associated with vessel-level ischemia alongside stenosis severity.[3] Furthermore, gender-based comparisons of ischemia by invasive fractional flow reserve have demonstrated that even when men and women are matched by stenosis severity, women in the category with the highest atherosclerotic burden had greater risk of MACE than men whereas women maintained greater fractional flow reserve readings than men.[10,26] It follows that women with greater amounts of CP PAV in stenotic lesions may be more adept at minimizing flow disparities than men whse plaque profile has comparatively more NCP PAV. This provides rationale for early plaque-based screening as the composition of obstructive lesions in women may dissociate the presence of advanced disease from symptom onset.

Finally, this study identified that the plaque profile of obstructive lesions in women included not only more CP but more of each NCP form compared with their nonobstructive lesions. Although men had greater LD-NCP PAV in nonobstructive lesions than women, obstructive lesions had similar volumes of LD-NCP PAV between the genders. This finding is especially important because of outcome disparities in how each gender manages this vulnerable plaque form. Although studies in the literature support a pattern of rapid NCP regression in women, Plank et al[8] show that when present, women with LD-NCP have a greater odds ratio for MACE than men. Although stenotic and nonstenotic lesions alike can pose risk of ACS,[2] this plaque signature identifies specific risk associated with obstructive lesions in women. Furthermore, the disproportional nature of the outcomes for similar measures between men and women reinforces the importance of early screening.

This study has limitations. Although the cohort evaluated was prospectively enrolled from a large, multicenter clinical trial, this substudy represents a retrospective evaluation, and consequently, all study results should be considered hypothesis-generating. Additionally, the study enrolled a symptomatic cohort, and results should be interpreted in that context, as it is unclear whether these same results would apply to the general population. Furthermore, although lesion progression is dynamic, this substudy evaluated coronary artery stenoses at a single point in time rather than across a longitudinal period. Additionally, the

data did not stratify women based on menopausal status which may have obscured whether distinct plaque signatures are present in the stenotic lesions of women at different ages. Finally, although this study uses stenosis as a marker of disease severity, large-scale randomized controlled trials have not observed clinical benefit from the isolated treatment of high-grade stenoses, and consequently, the long-term clinical utility of using stenosis as the primary end point of CAD severity remains uncertain.[2,27]

In summary, the plaque composition of obstructive stenoses is gender specific. These findings lay the groundwork for additional studies that might investigate whether and how these unique plaque phenotypes influence gender-oriented differences in coronary outcomes.

Declaration of Competing Interest

Crabtree, Jennings, Earls, Hoffmann, and Min are employees of Cleerly Inc.; Earls, Marques, Choi, and Min have equity in Cleerly Inc. The remaining authors have no conflicts of interest to declare.

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