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CLINICAL RESEARCH

Sex Differences in Compositional Plaque Volume Progression in Patients With Coronary Artery Disease

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ABSTRACT

OBJECTIVES The study sought to explore sex-based differences in total and compositional plaque volume (PV) progression.

BACKGROUND It is unclear whether sex has an impact on PV progression in patients with coronary artery disease (CAD).

METHODS The study analyzed a prospective multinational registry of consecutive patients with suspected CAD who underwent 2 or more clinically indicated coronary computed tomography angiography (CTA) at ≥2-year intervals. Total and compositional PV at baseline and follow-up were quantitatively analyzed and normalized using the analyzed total vessel length. Multivariate linear regression models were constructed.

RESULTS Of the 1,255 patients included (median coronary CTA interval 3.8 years), 543 were women and 712 were men. Women were older (62 ± 9 years of age vs. 59 ± 9 years of age; $p < 0.001$) and had higher total cholesterol levels (195 ± 41 mg/dl vs. 187 ± 39 mg/dl; $p = 0.002$). Prevalence of hypertension, diabetes, and family history of CAD were not different (all $p > 0.05$). At baseline, men possessed greater total PV (31.3 mm^3 [interquartile range (IQR): 0 to 121.8 mm^3] vs. 56.7 mm^3 [IQR: 6.8 to 152.1 mm^3] $p = 0.005$), and there was an approximately 9-year delay in women in developing total PV than in men. The prevalence of high-risk plaques was greater in men than women (31% vs. 20%; $p < 0.001$). In multivariate analysis, after adjusting for age, clinical risk factors, medication use, and total PV at baseline, despite similar total PV progression rates, female sex was associated with greater calcified PV progression ($\beta = 2.83$; $p = 0.004$) but slower noncalcified PV progression ($\beta = -3.39$; $p = 0.008$) and less development of high-risk plaques ($\beta = -0.18$; $p = 0.049$) than in men.

CONCLUSIONS The compositional PV progression differed according to sex, suggesting that comprehensive plaque evaluation may contribute to further refining of risk stratification according to sex. (NCT02803411).
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ABBREVIATIONS AND ACRONYMS

CACS = coronary artery calcification score

CAD = coronary artery disease

CTA = computed tomography angiography

CVD = cardiovascular disease

HRP = high-risk plaque

HU = Hounsfield unit

IQR = interquartile range

PV = plaque volume

Cardiovascular disease (CVD) remains a leading cause of mortality and morbidity in both women and men, but the overall CVD mortality has dramatically declined over recent decades as a result of preventive strategies (1). However, the decline in CVD mortality has been far less significant for women (1-3), and they continue to have higher mortality rates than men, although women generally present with smaller plaque burden and less obstructive coronary artery disease (CAD) (4-9). Pathologic and invasive angiographic evidence has also suggested sex-specific differences in atherosclerotic plaque profiles, with plaque erosion more frequently observed in women and plaque rupture more frequent in men (4,5,9). Overall, these findings indicate that sex may have an influence on both the development and progression of CAD and on the pattern of compositional plaque progression. Therefore, a better understanding of the sex differences in the pathogenesis of coronary atherosclerosis would help to identify patients at higher risk earlier and offer them appropriate preventive measures to improve both quality of life and clinical outcomes.

To address these issues, evaluation of the atherosclerotic burden and its changes over the entire coronary artery, instead of visualizing a few selected lesions or segments, is mandatory, as CAD is a dynamic disease with plaques at various stages that can coexist in a single patient, whereby 1 plaque may just be developing while another is stabilizing or even regressing (10). In this regard, coronary computed tomography angiography (CTA) may represent an optimal imaging modality, as it allows not only simplified detection of the presence of CAD, but also quantification of the composition within plaques and detection of its changes across the entire coronary vasculature (11). Recent studies have also demonstrated a direct association between the overall atherosclerotic burden and characteristics of individual plaques assessed by coronary CTA and clinical outcomes (12-14).

Hence, we explored the sex differences in overall and compositional atherosclerotic burden according to age group and evaluated whether the total and compositional plaque volume (PV) progression rate also differed according to sex in patients with CAD from a large multicenter registry of serial coronary CTAs.

METHODS

STUDY DESIGN AND POPULATION. The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study is a dynamic multinational observational registry that prospectively collected clinical, procedural, and follow-up data on 2,252 consecutive patients who underwent clinically indicated serial coronary CTA at an interscan interval of ≥2 years from 13 sites in 7 countries between 2003 and 2015 (15). Patients with

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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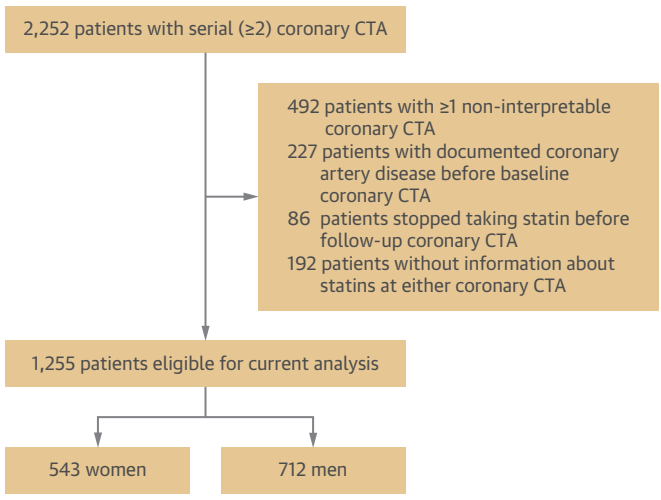
no data at baseline (coronary CTA-1) or at follow-up (coronary CTA-2) were excluded. The study protocol was approved by the Institutional Review Boards of all participating centers.

For the current analysis, patients with either coronary CTA results uninterpretable for quantitative assessment (n = 492), those with documented prior CAD (defined as myocardial infarction or revascularization before coronary CTA-1 (n = 227), those lacking information on statin use at either coronary CTA (n = 192), and those who discontinued statins following coronary CTA-1 (n = 86) were also excluded. Overall, 1,255 patients (543 women and 712 men) were ultimately included in the final analysis (**Figure 1**).

FIGURE 1 CONSORT Diagram



Selection of patient for the current analysis. CTA = computed tomography angiography.

CORONARY CTA ANALYSIS PROTOCOL. All acquisition and analysis of coronary CTAs were performed in accordance with the guidelines provided by the Society of Cardiovascular Computed Tomography (16,17). Coronary CTA datasets were transferred to a core laboratory for analysis by Level III experienced readers using semi-automated plaque analysis software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands) with manual correction as described previously (18,19).

Briefly, for the determination of atherosclerotic plaque burden across the entire coronary tree, all coronary segments and lesions with diameters ≥2 mm were evaluated for every coronary artery and its branches using a modified 17-segment American Heart Association model (17,20). The presence of an atherosclerotic plaque was defined as any tissue ≥1 mm^3 within or adjacent to the lumen that could be discriminated from the surrounding pericardial tissue, epicardial fat, or lumen, and identified in ≥2 planes (17,20). For serial comparisons of coronary CTAs, coronary segments and lesions were co-registered between the coronary CTA-1 and coronary CTA-2 evaluations using fiduciary landmarks, including the distance from the ostium and the branch vessels.

To determine the overall atherosclerotic plaque burden of a patient, total PV (mm^3) was determined by summing the PVs of each segment (21). Total PV was further subclassified automatically by the software into compositional PVs using predefined Hounsfield unit (HU) cutoff values (21): 1) non-calcified (−30 to 350 HU) PV encompassing necrotic core (−30 to 30 HU), fibrofatty (30 to 130 HU), and fibrous (131 to 350 HU) PV; and 2) calcified PV (≥351 HU) (11,22).

On the lesion level, stenosis severity was determined based on the % diameter stenosis. The presence of high-risk plaque (HRP) features defined as coronary lesions with evidence of ≥2 of positive arterial remodeling, low-attenuation plaque, or spotty calcification, were also determined based on qualitative assessment (20,23).

STATISTICAL ANALYSIS. Categorical variables are presented as absolute counts and percentages, and continuous variables are expressed as mean ± SD or median (interquartile range [IQR]) as appropriate. Differences between categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate, while differences between continuous variables were assessed using Student's *t* test.

To account for the difference in the total vessel length between patients, particularly between women and men, and to provide equal weighting of each patient in the calculation of PV, normalized PVs were defined as [(absolute PV/the total length of analyzed coronary arteries) × the mean total analyzed vessel length of the study population] (21,24-26). Total and compositional PV progressions were defined as the difference of each value between baseline and follow-up coronary CTAs annualized by dividing with the interscan interval ([ΔPV]/[coronary CTA intervals]) (mm^3/year) (24).

To explore the association between female sex and progression of total and compositional coronary PVs at the per-patient level, multivariate linear regression models adjusted for age, smoking history, hypertension, diabetes mellitus, hyperlipidemia, family history of CAD, body mass index, change in low-density

TABLE 1 Clinical Characteristics of the Study Population

	Women (n = 543)	Men (n = 712)	p Value
Clinical characteristics at baseline			
Age, yrs	61.9 ± 9.0	59.2 ± 9.3	<0.001
Coronary CTA interval, yrs	3.7 ± 1.5	3.9 ± 1.6	0.015
Body mass index, kg/m^2	24.8 ± 3.3	25.5 ± 3.1	<0.001
Systolic blood pressure, mm Hg	128 ± 17	131 ± 18	0.029
Hypertension	297 (54.8)	357 (50.4)	0.113
Diabetes mellitus	119 (22.0)	142 (20.0)	0.392
Family history of CAD	142 (26.2)	195 (27.4)	0.624
Smoking	109 (20.1)	358 (50.6)	<0.001
Total cholesterol, mg/dl	194.5 ± 40.9	187.0 ± 39.3	0.002
LDL level, mg/dl	117.5 ± 36.1	114.8 ± 33.9	0.178
HDL level, mg/dl	52.9 ± 14.3	49.3 ± 13.8	<0.001
Triglycerides, mg/dl	143.7 ± 87.9	149.9 ± 90.3	0.236
Typical chest pain	24 (4.4)	36 (5.1)	0.689
Atypical chest pain	421 (77.5)	482 (68.0)	<0.001
Noncardiac chest pain	60 (11.0)	67 (9.4)	0.395
Referral reason for coronary CTA			0.018
Cardiac symptoms	497 (98.2)	565 (95.4)	
Further evaluation of CAD	9 (1.8)	27 (4.6)	
Antiplatelets	207 (38.1)	273 (38.3)	0.953
Beta-blockers	143 (26.4)	206 (29.0)	0.304
Statin use at coronary CTA-2	329 (60.6)	452 (63.5)	0.295
Follow-up duration after coronary CTA-2, yrs	4.6 ± 2.1	4.0 ± 2.2	<0.001
Clinical outcomes after coronary CTA-2	50 (10.2)	64 (11.4)	0.619
Revascularization	44 (9.0)	62 (11.0)	0.271
Nonfatal myocardial infarction	1 (0.2)	1 (0.2)	
Cardiac mortality	5 (1.0)	1 (0.2)	

Values are mean ± SD or n (%).

ACC = American College of Cardiology; CAD = coronary artery disease; CTA = computed tomography angiography; CTA-2 = follow-up coronary computed tomography angiography; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

lipoprotein levels, and statin use, and baseline PVs were constructed for both sexes. For lesion level analysis, multivariate linear regression models were repeated using cluster analysis to account for effects of common clinical factors in clustered lesions within a single patient. The statistical significance of the beta coefficients (β) of female sex in each model was assessed using the likelihood ratio test, according to recent recommendations (27).

Propensity score matching between women and men in 1:1 manner using same variables used in the multivariate linear regression analysis was performed to assess the contribution of each plaque compositions to every 100 mm^3 total PV progression (28).

A 2-tailed p value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. Overall, 543 women and 712 men were included in the study (Table 1). Women were about 3 years older and had a lower body mass index than men (61.9 ± 9.0 years of age vs. 59.2 ± 9.3 years of age and 24.8 ± 3.3 kg/m^2 vs. 25.5 ± 3.1 kg/m^2, respectively; all p < 0.001). Except for the lower proportion of smoking history in women (20.1% vs. 50.6%; p < 0.001), the prevalence of other clinical risk factors including hypertension, diabetes mellitus, and family history of CAD were similar. Further, there was no difference in medication use at coronary CTA-2 including statins, antiplatelets, and beta-blockers (all p > 0.05). The intensity of statins used was also not different between sexes (p = 0.636) (Supplemental Table 1). The total cholesterol level was higher in women than in men (194.5 ± 40.9 mg/dl vs. 187.0 ± 39.3 mg/dl; p = 0.002), driven by a higher level of high-density lipoprotein levels in women (52.9 ± 14.3 mg/dl vs. 49.3 ± 13.8 mg/dl; p < 0.001). There was no difference in the levels of low-density lipoprotein and triglycerides between sexes (all p > 0.05).During the mean follow-up of 4.3 years, clinical outcomes, mostly coronary revascularization, were similar between sexes (10.2% vs. 11.4%; p = 0.619).

CORONARY CTA FINDINGS AT BASELINE. At baseline, women possessed fewer coronary lesions than men (1.9 ± 2.0 vs. 2.3 ± 2.2; p < 0.001) (Table 2). The prevalence of HRP lesions including positive remodeling, low-attenuation plaques, and spotty calcification was also lower in women than in men (all p < 0.05).

As the total vessel length was shorter in women than in men (383.3 mm [IQR: 316.3 to 474.5 mm] vs. 420.0 mm [IQR: 343.3 to 484.2 mm]; p = 0.004), PVs were normalized using the average of the total vessel length of the study population. After normalization, women had smaller total PV than men (31.3 mm^3 [IQR: 0 to 121.8 mm^3] vs. 56.7 mm^3 [IQR: 6.8 to 152.1 mm^3]; p = 0.005), driven by smaller noncalcified PV (20.54 mm^3 [IQR: 0 to 74.93 mm^3] vs. 39.09 mm^3 [IQR: 3.99 to 109.14 mm^3]; p < 0.001) and all of its constituents. There was no difference in calcified PV (p = 0.106).

Total and compositional PVs showed an exponential increase in both women and men when stratified according to age group (Figure 2). Across all age deciles, women had lower total PVs. A total PV of 100 mm^3 was reached at about 63 years of age for women and at 54 years of age for men, representing an 8- to 10-year delay. When compositional PVs of

TABLE 2 Coronary CTA Findings at Baseline and the Impact of Female Sex

	Univariate Analysis			Female Sex in Multivariable Analysis		
	Women (n = 543)	Men (n = 712)	p Value	Coefficient	SE	p Value
Total vessel length, mm	383.3 (316.3-474.5)	420.0 (343.3-484.2)	0.004	−10.784	7.563	0.154
Number of lesions	1.9 ± 2.0	2.3 ± 2.2	0.0006	−0.146	0.117	0.215
Presence of high-risk plaque* features at baseline						
High-risk plaque*	111 (20.4)	220 (30.9)	<0.001	−0.201	0.081	0.012
Positive remodeling	321 (59.1)	493 (69.2)	<0.001	−0.198	0.077	0.010
Low-attenuation plaque	89 (15.8)	158 (22.2)	0.005	−0.153	0.088	0.080
Spotty calcification	81 (14.9)	146 (20.5)	0.011	−0.138	0.091	0.129
Quantitative coronary CTA measures: normalized PVs (mm^3) at baseline						
Total PV	31.3 (0.0-121.8)	56.7 (6.8-152.1)	0.005	5.488	6.668	0.411
Calcified PV	4.42 (0.00-34.33)	6.96 (0.00-37.70)	0.106	5.208	4.117	0.206
Noncalcified PV†	20.54 (0.00-74.93)	39.09 (3.99-109.14)	<0.001	0.28	5.214	0.957
Fibrous PV	15.93 (0.00-51.23)	25.00 (2.91-67.95)	0.009	2.452	4.081	0.548
Fibrous-fatty PV	1.62 (0.00-13.41)	6.64 (0.00-29.46)	<0.001	−2.218	1.975	0.262
Necrotic core PV	0.00 (0.00-0.62)	0.06 (0.00-1.91)	0.048	0.107	0.428	0.803

Values are median (interquartile range) or n (%). *High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification. †Noncalcified PV is the summation of fibrous, fibrofatty, and necrotic core PV.

CTA = computed tomography angiography; PV = plaque volume.

women were compared with those of 54-year-old men, women had the same amount of calcified PV at 59 years of age, and noncalcified PV at about 71 years of age, representing a more prominent delay in noncalcified PV progression than calcified PV in women (p = 0.001).

ANNUAL PROGRESSION OF TOTAL AND COMPOSITIONAL PVs AND IMPACT OF FEMALE SEX. When the annual PV changes were compared, the total PV progression was significantly slower in women than in men (5.62 mm^3/year [IQR: 0 to 20.80 mm^3/year] vs. 8.29 mm^3/year [IQR: 1.38 to 22.39 mm^3/year]; p = 0.026) (**Table 3**), driven by the slower progression of the noncalcified PV (0.02 mm^3/year [IQR: -0.58 to 6.95 mm^3/year] vs. 2.43 mm^3/year [IQR: 0 to 10.68 mm^3/year]; p < 0.001) and all of its components. The progression rate of calcified PV did not differ between sexes (p = 0.670).

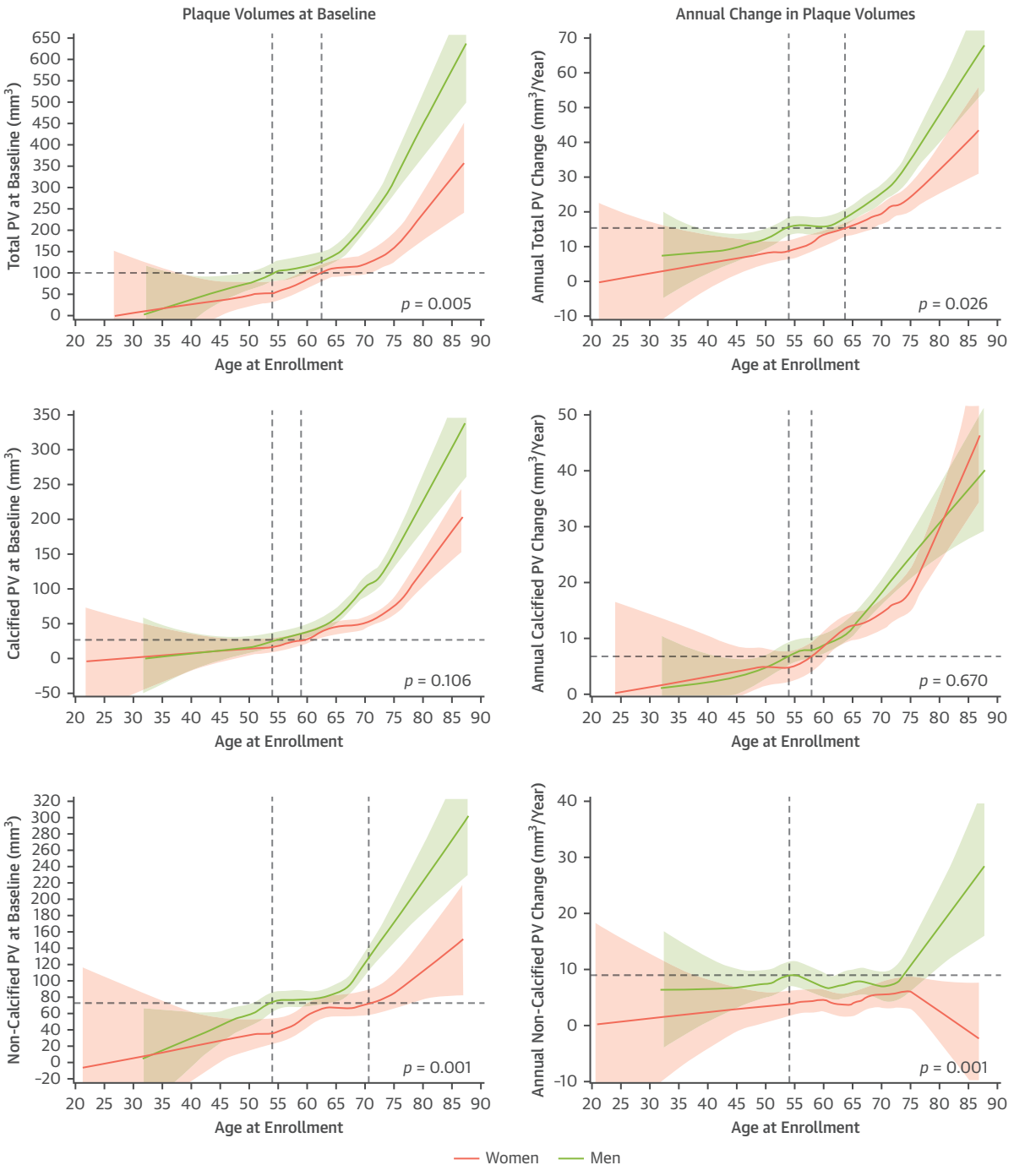
Upon stratifying according to age groups (**Figure 2**), the progression rate of total PV was relatively parallel between women and men. The annual total PV change rate of men at 54 years of age, in which the total PV reached 100 mm^3, was similar to women at 64 years of age, demonstrating a similar age gap as that of the total PV. The progression rate of calcified PV was similar for women and men throughout the age group, but the noncalcified PV progression rate continued to be higher in men.

In multivariate analysis adjusting for age, risk factors, lipid level, statin use, and total PV at baseline, there was no effect of female sex on the total PV progression rate (p = 0.677) (**Table 3**). However, women were associated with greater calcified PV progression (β = 2.832; p = 0.004) but slower noncalcified PV progression (β = -3.387; p = 0.008) than men. Women were also associated with less development of HRP features (β = -0.176; p = 0.049), including low-attenuation plaques and spotty calcification (β = -0.217 and β = -0.217, respectively; all p < 0.05).

When PVs were stratified according to age group after propensity score matching using the same variables adjusted for in the multivariate linear regression analysis, including total PV at baseline (Supplemental Table 2), the progression rates of compositions remained significantly different. The progression of the total and calcified PV became similar, while the noncalcified PV progression became faster in men, and female sex was independently associated with the slower progression of noncalcified PV (Supplemental Table 3 and Supplemental Figure 1). The 100-mm^3 increase in total PV included a 62.8-mm^3 increase in calcified PV and a 37.2-mm^3 increase in noncalcified PV in women, while men exhibited a 40.9-mm^3 increase in calcified PV and a 59.1-mm^3 increase in noncalcified PV (**Central Illustration**).

LESION-LEVEL ANALYSIS OF THE IMPACT OF FEMALE SEX IN CHANGES OF TOTAL AND COMPOSITIONAL PV. On lesion level analysis, 1,411 lesions in women and 2,164 lesions in men were compared (**Table 4**). The prevalence of obstructive lesions (diameter stenosis ≥50%) did not differ (p = 0.196), but HRP features were more frequently observed in lesions in men (11.1% vs. 13.6%;

FIGURE 2 **Differences in Baseline PV and Annual PV Changes Between Women and Men According to Age Group**



Women exhibited less total and noncalcified plaque volume (PV) at baseline, and the slower progression rate of total and noncalcified PV than men. **Lines** are moving averages of PVs and annual changes in PVs across ages for women and men. PVs are normalized. The shading represents 95% confidence intervals.

TABLE 3 Per-Patient Analysis of the Annual Changes of Coronary CTA Findings and the Impact of Female Sex

	Univariate Analysis			Female Sex in Multivariable Analysis		
	Women (n = 543)	Men (n = 712)	p Value	Coefficient	SE	p Value
Newly developed high-risk plaque* features at follow-up						
High-risk plaque*	86 (15.8)	139 (19.5)	0.092	−0.176	0.09	0.049
Positive remodeling	264 (48.6)	337 (47.3)	0.651	0.045	0.069	0.516
Low-attenuation plaque	51 (9.4)	68 (9.6)	0.924	−0.217	0.102	0.034
Spotty calcification	60 (11.1)	105 (14.8)	0.055	−0.217	0.102	0.034
Annualized change in normalized PVs (mm^3/year): per patient						
Total PV	5.62 (0.00 to 20.80)	8.29 (1.38 to 22.39)	0.026	−0.555	1.331	0.677
Calcified PV	2.99 (0.00 to 12.18)	3.08 (0.22 to 10.38)	0.670	2.832	0.977	0.004
Noncalcified PV†	0.02 (-0.58 to 6.95)	2.43 (0.00 to 10.68)	<0.001	−3.387	1.283	0.008
Fibrous PV	0.73 (0.00 to 6.59)	2.68 (0.00 to 8.99)	0.009	−1.882	0.909	0.039
Fibrous-fatty PV	0.00 (-0.61 to 0.69)	0.00 (-0.82 to 2.32)	0.015	−1.135	0.589	0.054
Necrotic core PV	0.00 (-0.01 to 0.02)	0.00 (-0.02 to 0.15)	0.008	−0.379	0.133	0.004

Values are n (%) or median (interquartile range). *High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification. †Noncalcified PV is the summation of fibrous, fibrofatty, and necrotic core PV.

Abbreviations as in Table 2.

p = 0.026). The total PV of each lesion was smaller in women than in men at the baseline (11.02 mm^3 [IQR: 0 to 24.52 mm^3] vs. 11.96 mm^3 [IQR: 0.8 to 28.94 mm^3]; p = 0.002), and likely comprised smaller noncalcified PVs (5.38 mm^3 [IQR: 0 to 15.79 mm^3] vs. 6.73 mm^3 [IQR: 0 to 19.12 mm^3]; p < 0.001). The calcified PV did not differ between sexes (p = 0.644).

When annualized, the total PV progression rate showed no sex differences, but lesions in women exhibited faster calcified PV progression and slower progression of noncalcified PV than did the lesions in men (2.11 mm^3/year [IQR: 0.81 to 4.21 mm^3/year] vs. 1.45 mm^3/year [IQR: 0.45 to 3.47 mm^3/year] and 0.95 mm^3/year [IQR: -0.15 to 3.60 mm^3/year] vs. 1.46 mm^3/year [IQR: 0.08 to 4.32 mm^3/year], respectively; all p < 0.001). On multivariate analysis, women were associated with a faster progression of calcified PV (β = 4.96; p < 0.001) and a slower progression of noncalcified PV (β = -3.41; p < 0.001).

DISCUSSION

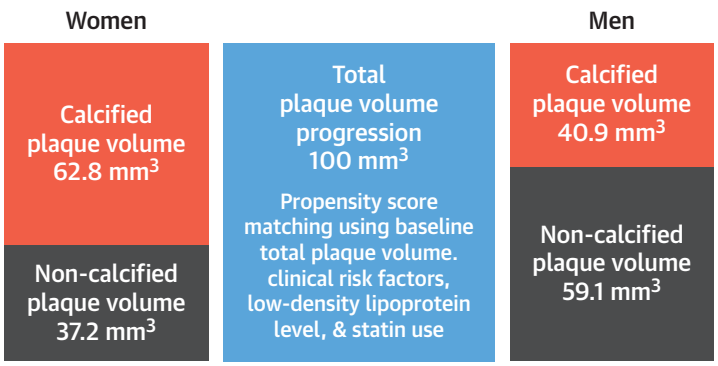
The analysis of the PARADIGM registry showed that the total and compositional PV progression rate differed between sexes at both the patient and lesion levels. At baseline, women displayed less overall coronary atherosclerotic burden than did men of the same age in all age deciles. Once the baseline total PVs were matched, the progression rate of the total PV did not differ between sexes, but progression was driven mainly by calcified PV progression in women while noncalcified PV progression was predominant in men. Female sex was independently associated with faster calcified PV progression and slower noncalcified PV progression, as observed in the multivariate analysis. Accordingly, more sophisticated evaluation of plaque progression including plaque compositions may contribute to further refine the risk stratification according to sex.

Before adjustment with age, clinical risk factors, and total PV at baseline, we observed an approximately 9-year delay in women in developing total coronary atherosclerotic burden compared with that in men in this study. At both the per-patient and per-lesional level, women had a smaller atherosclerotic overall burden over all age ranges, after the differences in total vessel length was normalized and despite older age and similarities in clinical risk factors, which is in line with current evidence exploring sex-specific atherosclerotic profiles (4-6,9,29).

Moreover, once the total PV was matched in women and men, the progression rate of total PV showed no sex differences, and female sex had no effect on total PV progression rate in multivariate analysis. These findings support previous observations wherein total PV, either at the patient or lesion level, or the coronary artery calcium score (CACS) at baseline was the most important independent predictor of risk for rapid plaque progression and clinical outcomes (12,14,30,31), and where the CACS increased exponentially (32). Together, these observations might suggest that the progression of coronary atherosclerosis accelerates exponentially, rather than in linearly.

In pathological and invasive studies of patients with acute coronary syndrome, nonculprit lesions in women possessed lesser total PV including less amount of both calcified and noncalcified PV (9,33). In the evaluation of patients with CAD who underwent

CENTRAL ILLUSTRATION Sex Differences in Compositional PV Progression



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Differences in compositional plaque volume (PV) change between women and men for every 100-mm^3 progression of total PV after propensity score matching by age; body mass index; hypertension; diabetes mellitus; family history of coronary artery disease; smoking history; low-density lipoprotein (LDL); use of statins, aspirin, and beta-blockers; and baseline total PV. PVs are normalized. Noncalcified PV is the summation of fibrous, fibrofatty, and necrotic core PV.

repeated coronary CTA in the current analysis, the total PV at baseline was smaller in women and was driven only by significantly smaller noncalcified PV, but not by calcified PV at both the per-patient and per-lesion levels. Most importantly, compositional PV progression constituting a given total PV change significantly differed between the sexes although female sex had no effect on the progression rate of total PV once the total PV at baseline was adjusted. Female sex was independently associated with faster calcified PV progression, slower noncalcified PV progression, and reduced development of HRP lesions in multivariate analysis. To our knowledge, this is the first description of the impact of sex differences in compositional PV progression in a CAD population using noninvasive measurements.

The protective effects of estrogen on the development and progression of coronary atherosclerosis have been suggested (9). Hormone replacement therapy in menopausal women retarded the progression of CACS in a randomized clinical trial (34), and estrogen inhibited vascular calcification in a molecular study (35). Therefore, the accelerated progression of calcified PV in women shown in this study may be partly associated with the mean age of 62 years of the women enrolled, which is an age by which most women would have reached menopause. Nonetheless, female sex was still independently associated with slower progression of the noncalcified PV and reduced development of HRP features. Therefore, whether the "protective" effects of the female sex are exhibited only through the inhibition of the coronary artery calcification by estrogen or whether genetic factors other than estrogen also directly affect the progression of coronary atherosclerosis, especially the noncalcified portion, requires further clarification.

Studies have consistently reported that same extent of coronary atherosclerosis or CACS or the presence of multivessel CAD increases cardiovascular risk more for women than men (8,36,37), and women with acute coronary syndrome are more likely to have plaque erosion, while men are more likely to have plaque ruptures (4,5,9,33). Our findings, at least in part, might provide evidence bridging these prior observations, as total PV progression was mainly driven by calcified PV, which supposedly is associated with more stable plaques as previously reported, in women and female sex was independently associated with reduced development of incident HRP features and noncalcified PV, which could result in women presenting less incidence of sudden plaque rupture, an event largely associated with greater burden of noncalcified (or lipid-rich) regions of plaques.

Recent guidelines have focused on the importance of sex-specific evidence to improve CVD risk prediction (38,39), but only incorporate CACS results and apply an identical CACS threshold for initiating statin treatment for both sexes (39). However, the progression of compositional PVs and adverse plaque characteristics could be widely different within a group sharing the same extent of total PV between women and men as shown in this study. Therefore, it may well be the time to initiate studies assessing the value of more comprehensive evaluation of coronary atherosclerosis for risk stratification, rather than simply focusing on overall plaque burden, especially for women at higher risk. In this regard, coronary CTA might offer better risk stratification as the direct association between noncalcified PV and HRP features identified by coronary CTA and clinical outcomes has been repeatedly proven in recent studies (13,14).

STUDY LIMITATIONS. First, selection bias was inevitable, as only patients with more than 2 coronary CTA scans were eligible for enrollment. It is plausible that patients who experienced worsening of symptoms may have been referred for invasive studies before the second coronary CTA was performed and were likely not enrolled in the registry. Hence, the study population was representative of patients with CAD that were generally at low risk, as reflected in the low rate of hard events. Thus, the generalizability of the

TABLE 4 Per-Lesion Analysis of Coronary CTA Findings and the Impact of Female Sex

	Univariate Analysis			Female Sex in Multivariable Analysis		
	Women (n = 1,411)	Men (n = 2,164)	p Value	Coefficient	SE	p Value
Diameter stenosis, %	9.62 (0.00 to 21.30)	11.1 (0.03 to 22.40)	0.049	−0.32	0.471	0.748
Diameter stenosis ≥50%	16 (1.1)	36 (1.7)	0.196	−0.153	0.175	0.382
Lesion length, mm	13.58 (0.00 to 20.8)	14 (5.49 to 22.38)	0.004	−0.16	0.344	0.873
The presence of high-risk plaque* features at baseline						
High-risk plaque	156 (11.1)	294 (13.6)	0.026	−0.066	0.062	0.280
Low-attenuation plaque	104 (7.4)	199 (9.2)	0.056	−0.08	0.072	0.267
Spotty calcification	117 (8.3)	210 (9.7)	0.152	−0.084	0.071	0.236
Positive remodeling	734 (52.0)	1,178 (54.4)	0.157	−0.01	0.041	0.805
Quantitative coronary CTA measures at baseline – normalized PVs (mm^3)						
Total PV	11.02 (0.00 to 24.52)	11.96 (0.80 to 28.94)	0.002	−0.64	0.482	0.520
Calcified PV	1.88 (0.00 to 8.23)	1.69 (0.00 to 7.54)	0.644	0.16	0.313	0.870
Noncalcified PV†	5.38 (0.00 to 15.79)	6.73 (0.00 to 19.12)	<0.001	−0.72	0.502	0.472
Fibrous PV	4.8 (0.00 to 11.17)	5.57 (0.00 to 13.46)	0.001	−0.78	0.286	0.438
Fibrous-fatty PV	0.05 (0.00 to 2.30)	0.24 (0.00 to 3.68)	<0.001	−0.55	0.282	0.584
Necrotic core PV	0.00 (0.00 to 00)	0.00 (0.00 to 0.04)	0.216	0.3	0.074	0.762
Newly developed high-risk plaque* features at follow-up						
High-risk plaque*	111 (7.9)	177 (8.2)	0.737	−0.053	0.073	0.468
Positive remodeling	61 (4.3)	80 (3.7)	0.347	0.124	0.102	0.223
Low-attenuation plaque	74 (5.2)	136 (6.3)	0.196	−0.136	0.086	0.112
Spotty calcification	433 (30.7)	570 (26.4)	0.005	0.074	0.044	0.094
Annualized change in normalized PVs: per lesion						
Diameter stenosis, %/yr	1.29 (−0.14 to 3.54)	1.21 (-0.22 to 3.28)	0.607	−0.61	0.149	0.543
Total PV, mm^3/yr	3.93 (1.93 to 7.38)	3.86(1.78 to 7.59)	0.187	−0.32	0.208	0.752
Calcified PV, mm^3/yr	2.11 (0.81 to 4.21)	1.45 (0.45 to 3.47)	<0.001	4.96	0.124	<0.001
Noncalcified PV, mm^3/yr†	0.95 (−0.15 to 3.60)	1.46 (0.08 to 4.32)	<0.001	−3.41	0.199	<0.001
Fibrous PV, mm^3/yr	1.07 (−0.04 to 3.15)	1.41 (0.18 to 3.57)	0.010	−1.84	0.136	0.066
Fibrous-fatty PV, mm^3/yr	0.00 (−0.06 to 0.26)	0.00 (-0.07 to 0.62)	<0.001	−3.31	0.104	<0.001
Necrotic core PV, mm^3/yr	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.002	−2.84	0.028	0.005

Values are n (%) or median (interquartile range). *High-risk plaque is defined as a lesion with ≥2 features indicative of positive arterial remodeling, low-attenuation plaque, or spotty calcification. †Noncalcified PV is the summation of fibrous, fibrofatty, and necrotic core PV.

CACS = coronary artery calcium score; other abbreviations as in Table 2.

results to high-risk populations and the direct association between observed sex differences in the compositional PV changes to the clinical outcomes is unknown. There were also some differences in baseline characteristics between women and men because of the observational design. However, this is the first study to describe differences in compositional PV progression between sexes in a lower-risk population not indicated for invasive studies. Furthermore, the main findings of this study remained consistent after adjusting all clinical risk factors, age, statin use, and baseline total PV in both multivariate analysis and propensity score matching. To overcome these limitations, large population-based prospective registries of serial coronary CTA would be ideal. However, as there are currently no recommendations on the use of serial coronary CTA for the evaluation of CAD (40), an observation registry such as the PARADIGM provides a unique opportunity to evaluate sex differences over the natural history of coronary atherosclerosis.

CONCLUSIONS

The development of coronary atherosclerosis was slower in women than that in men, while the progression of compositional PV was significantly different between sexes. Women experienced a similar progression rate of total PV once the baseline total PV were matched, but with significantly faster progression of calcified PV and slower progression of noncalcified PV than men. The direct association between observed sex differences in the compositional PV changes to future clinical outcomes needs to be further investigated.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Once the total PV has been reached, the progression rate of the total plaque burden does not differ between women and men, but compositional changes are markedly different between sexes. Women experience faster calcified but slower noncalcified PV progression than men.

TRANSLATIONAL OUTLOOK: Prospective studies should be used to investigate whether more comprehensive evaluation of the progression of coronary atherosclerosis incorporating compositional changes would provide improvement in risk stratification of patients with CAD.

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KEY WORDS coronary artery atherosclerosis, coronary artery disease, coronary computed tomography angiography, sex difference

APPENDIX For supplemental tables and a supplemental figure, please see the online version of this paper.