ORIGINAL RESEARCH

Differences in Plaque Characteristics and Myocardial Mass

Implications for Physiological Significance

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ABSTRACT

BACKGROUND The mechanism of the fractional flow reserve (FFR) difference according to sex has not been clearly
understood.

OBJECTIVES This study sought to evaluate sex differences in coronary stenosis, plaque characteristics, and left ven-
tricular (LV) mass and their implications for physiological significance.

METHODS This was a post hoc analysis of a pooled population of multicenter, international prospective cohorts. Pa-
tients (166 women and 489 men) underwent coronary computed tomography angiography (CCTA) within 90 days before
invasive FFR measurements were included. The minimal lumen area, percent of plaque burden, whole vessel plaque
volume by composition, high-risk plaque characteristics, and LV mass were analyzed from CCTA images.

RESULTS Among 1,188 vessels analyzed, the FFR value was higher in women than that in men (0.85 ± 0.13 vs $0.82 \pm
0.14$; $P = 0.001$) despite a similar percentage of diameter stenosis between the sexes ($45.9\% \pm 18.9\%$ vs $46.1\% \pm
17.7\%$; $P = 0.920$). The composition of fibrofatty plaque + necrotic core ($13.1\% \pm 16.9\%$ vs $21.2\% \pm 19.9\%$; $P < 0.001$)
and frequencies of low attenuation plaque (12.7% vs 24.5%; $P < 0.001$) and positive remodeling (33.8% vs 45.5%;
$P = 0.001$) were lower in women than in men. Vessel, plaque, and lumen volumes were significantly smaller in women
than that in men (all $P < 0.001$); however, no sex difference was observed in any of these parameters after adjustment
for LV mass (all $P > 0.10$). Sex was not an independent predictor of the FFR value after adjustment for stenosis severity,
plaque characteristics, and LV mass.

CONCLUSIONS Higher FFR values for the same stenosis severity in women can be explained by fewer high-risk plaque
characteristics and smaller myocardial mass in women than that in men. (CCTA-FFR Registry for
Risk Prediction; NCT04037163) (JACC: Asia 2022;2:157–167) © 2022 The Authors. Published by Elsevier on behalf of
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Daniel Berman, MD, served as the Guest Associate Editor for this paper. Nathan Wong, PhD, served as the Guest Editor in Chief for
this paper.

Because coronary atherosclerotic plaque formation and progression develop later in life in women, women present with coronary artery disease (CAD) approximately 1 decade later than men.[1,2] In addition, postmortem studies have reported that plaque erosion is more frequently observed than plaque rupture in younger women, distinct from men,[3] which suggests a different pathophysiology of CAD according to sex.

Fractional flow reserve (FFR), a physiological index that is regarded as a standard tool for assessing ischemia, has been reported to be higher in women than in men with the same stenosis severity.[4,5] Because plaque composition and characteristics are associated with the presence of ischemia independent of stenosis severity,[6-8] sex differences in plaque characteristics can be one reason for the difference in FFR value. In addition, a different myocardial mass according to sex can also affect FFR value because of its influence on the total amount of coronary flow.[9-11] Coronary computed tomography angiography (CCTA) is a widely used noninvasive imaging tool with high accuracy for the assessment of CAD[12,13]; it can provide various measurements of stenosis severity, plaque burden, composition, characteristics, and myocardial mass. Accordingly, comprehensive information on stenosis, plaque, and myocardial mass from CCTA may explain the sex difference in myocardial ischemia.

The present study sought to evaluate sex differences in coronary luminal narrowing, quantity and quality of atherosclerotic plaque, and myocardial mass and their implications for physiological significance.

METHODS

STUDY POPULATION. The study population was derived from the pooled population of the 3V FFR-FRIENDS study (3-Vessel Fractional Flow Reserve for the Assessment of Total Stenosis Burden and its Clinical Impact in Patients with Coronary Artery Disease; NCT01621438)[14] and the institutional registry of Tsuchiura Kyodo General Hospital. Of 1,136 patients in the 3V FFR FRIENDS study, 299 patients who underwent CCTA within 90 days before invasive FFR measurements were included in this study. On the

same basis, 448 patients from the institutional registry of Tsuchiura Kyodo General Hospital were included (Supplemental Figure 1). Because the 3V FFR-FRIENDS study was designed to assess clinical implications of 3-vessel FFR as an index of total physiological disease burden, FFR measurement was done for all 3 major epicardial vessels, except for vessels in which FFR measurement was not possible, such as small or totally occluded vessels.[14] In the institutional registry of Tsuchiura Kyodo General Hospital, FFR measurement was performed in vessels with an intermediate degree of stenosis according to the current guidelines. The study protocol was approved by the institutional review board or ethics committee of participating centers.

ANALYSIS OF CCTA IMAGES. CCTA images were analyzed at a core laboratory (Severance Cardiovascular Hospital) in a blinded fashion. Cross-sectional quantitative analysis of the target lesion, including the minimal lumen area (MLA) and percentage of plaque burden, was obtained as previously described.[15] For whole vessel analysis, 3-dimensional quantification of the vessel volume, plaque volume, lumen volume, and percentage of mean plaque burden (plaque volume/vessel volume × 100) of target vessels was performed using semi-automatic plaque analysis software (QAngioCT Research Edition, version 2.1.9.1, Medis Medical Imaging Systems).[16,17] Plaque composition was assessed by predefined Hounsfield unit (HU) thresholds: necrotic core (−30 to 30 HU); fibrofatty (30-130 HU), fibrous (131-350 HU); and calcified plaque (≥350 HU).[18] Qualitative plaque characteristics analysis was performed by the presence of the following properties: 1) low-attenuation plaque (average density ≤30 HU); 2) positive remodeling (remodeling index ≥1.1); 3) napkin-ring sign (peripheral high attenuation tissue surrounding a central lower attenuation portion); and 4) spotty calcification (average density >130 HU and diameter <3 mm).[15,19,20] Left ventricular (LV) mass was measured at an independent core laboratory (Samsung Medical Center) as previously described.[9]

INVASIVE CORONARY ANGIOGRAPHY AND PHYSIOLOGICAL MEASUREMENTS. Invasive coronary angiography was performed using standard techniques after an intracoronary bolus injection of 100-200 μg of nitroglycerin. Quantitative coronary angiography was performed at a core laboratory in all

included vessels, regardless of stenosis degree (Seoul National University Hospital), in a blinded fashion using validated software (CAAS II, Pie Medical System). In a vessel with >1 lesion, the most severe lesion was selected for quantitative and qualitative lesion characteristics. FFR measurements were performed after diagnostic angiography. The pressure sensor guidewire (Abbott Vascular) was equalized to aortic pressure at the tip of the guide catheter and then positioned at the distal segment of the target vessel. Hyperemic aortic pressure (Pa) and distal coronary arterial pressure (Pd) were obtained. The FFR was calculated as the mean Pd/Pa during maximum hyperemia.

STATISTICAL ANALYSIS. Continuous variables were compared using Student's *t*-test and categorical variables using the chi-square test. Analyses were performed on a per-patient basis for clinical characteristics and on a per-vessel basis for lesion characteristics, physiological indexes, and CCTA parameters. Comparisons of per-vessel measurements between sexes were performed with generalized estimating equations to account for clustering of vessel measurements from the same patient. Linear regression and logistic regression analyses were performed to establish the effect of patient sex on FFR. Covariates included in each model were as follows: model 1: clinical characteristics (age, sex, hypertension, diabetes, hypercholesterolemia, previous myocardial infarction, and acute coronary syndrome) and vessel and plaque volumes; model 2: model 1 + plaque composition and qualitative plaque characteristics; model 3: model 1 + LV mass; and model 4: model 1 + plaque composition and qualitative plaque characteristics + LV mass. For multivariate regression analysis, the variance inflation factor and tolerance for each variable were tested to exclude multicollinearity. In addition, mediation analysis was performed to demonstrate the direct and indirect effect of sex on FFR value when plaque characteristics and LV mass were set as moderators. Detailed information of mediation analysis was previously described.[21] Of the included variables for multivariable analysis, age, hypertension, diabetes, hyperlipidemia, previous myocardial infarction, acute coronary syndrome, left anterior descending artery, and vessel and plaque volumes did not have a significant mediating effect when fibrofatty + necrotic core (FFNC) volume and LV mass were included in the model. Therefore, we performed mediation analysis of sex for FFR, setting FFNC volume and LV mass as mediators, whereas other variables were set as covariates in the mediation models. A number of

**TABLE 1 Baseline Patient and Lesion Characteristics**

	Women	Men	P Value
Patient characteristics	(n = 166)	(n = 489)	
Age, y	69.8 ± 9.4	64.8 ± 9.9	<0.001
Hypertension	127 (76.5)	324 (66.3)	0.014
Diabetes mellitus	56 (33.7)	174 (35.6)	0.666
Hypercholesterolemia	98 (59.0)	275 (56.2)	0.529
Current smoking	13 (7.8)	152 (31.1)	<0.001
Previous myocardial infarction	3 (1.8)	30 (6.1)	0.028
Acute coronary syndrome	33 (19.9)	92 (18.8)	0.763
Vessel characteristics	(n = 308)	(n = 880)	
Vessel type			0.633
Left anterior descending artery	144 (46.8)	418 (47.5)	
Left circumflex artery	85 (27.6)	220 (25.0)	
Right coronary artery	79 (25.6)	242 (27.5)	
Lesion location			0.702
Proximal	154 (50.0)	430 (48.9)	
Mid	96 (31.2)	296 (33.6)	
Distal	58 (18.8)	154 (17.5)	
Quantitative coronary angiography			
Reference vessel diameter, mm	2.81 ± 0.59	2.96 ± 0.64	<0.001
Minimal lumen diameter, mm	1.54 ± 0.66	1.62 ± 0.68	0.077
% Diameter stenosis, %	45.9 ± 18.9	46.1 ± 17.7	0.920
Lesion length, mm	11.8 ± 9.5	12.3 ± 9.2	0.430
FFR	0.85 ± 0.13	0.82 ± 0.14	0.001
FFR ≤0.80	90 (29.2)	355 (40.3)	0.001

Values are mean ± SD or n (%).
FFR = fractional flow reserve.

TABLE 2 CCTA Parameters

	Women	Men	P Value
LV mass, g	102.4 ± 27.4	128.9 ± 34.4	<0.001
Cross-sectional analysis at the MLA site			
Vessel wall area, mm²	8.89 ± 4.54	10.25 ± 5.02	<0.001
MLA, mm²	3.07 ± 2.14	3.29 ± 2.21	0.162
% Lumen area stenosis, %	56.7 ± 21.2	59.2 ± 23.2	0.723
% Plaque burden, %	63.5 ± 17.9	65.0 ± 19.4	0.282
Whole vessel analysis			
Vessel length, mm	93.9 ± 38.5	107.5 ± 9.5	<0.001
Vessel volume, mm³	631.8 ± 337.7	778.1 ± 407.1	<0.001
Plaque volume, mm³	146.4 ± 119.7	195.3 ± 171.9	<0.001
Lumen volume, mm³	508.2 ± 282.1	609.2 ± 34.5	<0.001
% Mean plaque burden, %	22.3 ± 13.8	23.5 ± 14.8	0.246
Fibrofatty + necrotic core volume, mm³	19.3 ± 30.3	45.7 ± 64.3	<0.001
% Fibrofatty + necrotic core volume, %	13.1 ± 16.9	21.2 ± 19.9	<0.001
High-risk plaque characteristics			
Low attenuation plaque	33 (12.7)	187 (24.5)	<0.001
Positive remodeling	88 (33.8)	347 (45.5)	0.001
Spotty calcification	28 (10.8)	101 (13.2)	0.301
Napkin-ring sign	1 (0.4)	10 (1.3)	0.211

Values are mean ± SD or n (%).
CCTA = coronary computed tomography angiography; LV = left ventricle; MLA = minimal lumen area.

FIGURE 1   Distributions of CCTA Parameters
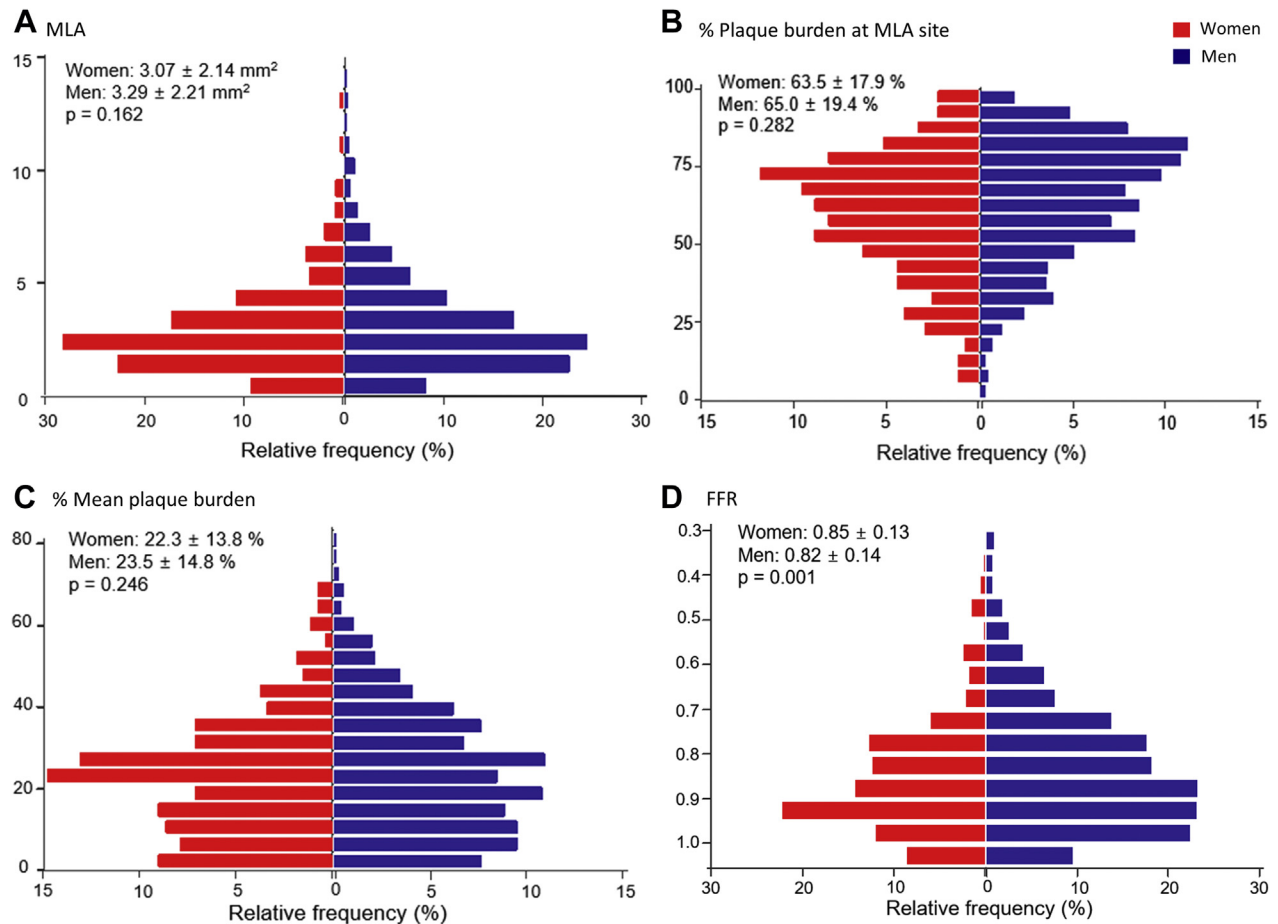
(A) Distributions of minimal lumen area (MLA), **(B)** percentage of plaque burden at the MLA site, **(C)** whole vessel plaque volume, and **(D)** fractional flow reserve (FFR). **Bars** indicate the frequencies among vessels. CCTA = coronary computed tomography angiography.

bootstrap samples for percentile bootstrap CIs was set as 5,000 when measuring the indirect effect. Two-sided P values <0.05 were considered statistically significant. All analyses were performed using SPSS version 22.0 (IBM Co).

RESULTS

PATIENT AND LESION CHARACTERISTICS. Of the 655 patients included in the analysis, 166 (25.3%) were women. The baseline patient and lesion characteristics are shown in **Table 1**. Women were older (69.8 ± 9.4 years vs 64.8 ± 9.9 years; $P < 0.001$) and had a more frequent prevalence of hypertension than that of men (76.5% vs 66.3%; $P = 0.014$). Regarding angiographic lesion characteristics, the reference vessel diameter was smaller (2.81 ± 0.59 mm vs 2.96 ±
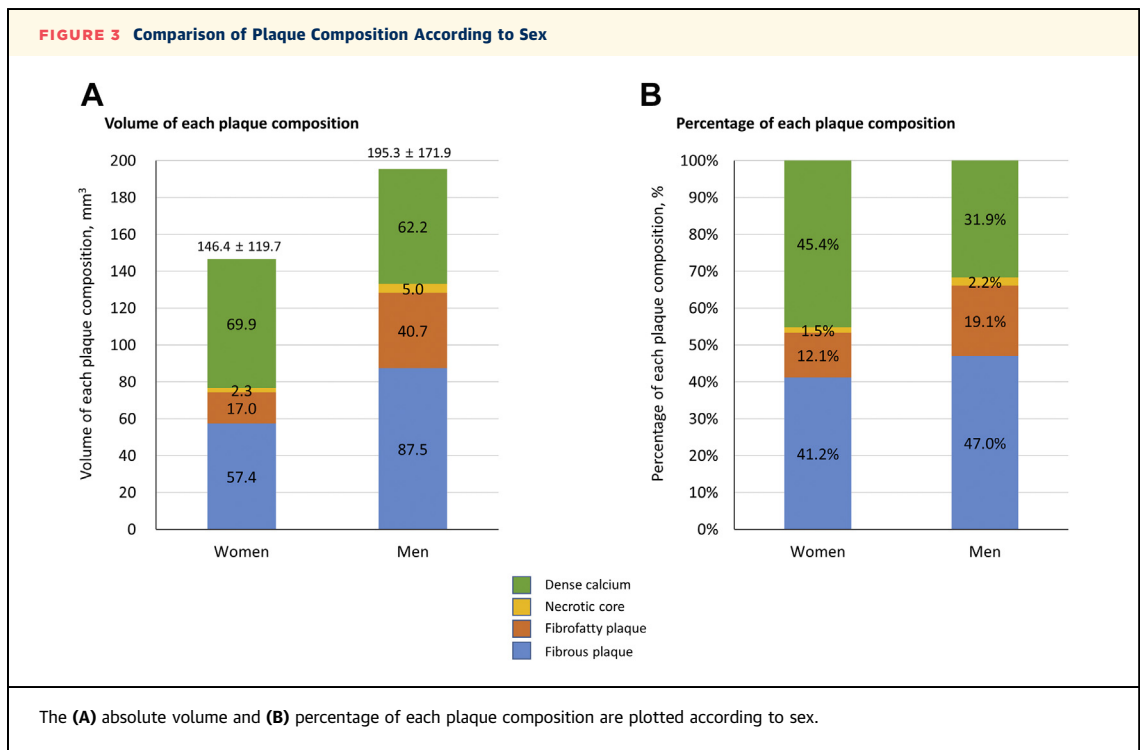
0.64 mm; $P < 0.001$), and minimal lumen diameter tended to be smaller in women than that in men (1.54 ± 0.66 mm vs 1.62 ± 0.68 mm; $P = 0.077$). Angiographic percent diameter stenosis was similar in women and men (45.9% ± 18.9% and 46.1% ± 17.7%, respectively; $P = 0.920$). However, the FFR value was higher (0.85 ± 0.13 vs 0.82 ± 0.14; $P = 0.001$) and the proportion of low FFR was lower in women than that in men (29.2% vs 40.3%; $P = 0.001$).

CCTA PARAMETERS. The CCTA parameters are shown in **Table 2**. The LV mass was smaller in women than that in men (102.4 ± 27.4 g vs 128.9 ± 34.4 g; $P < 0.001$). There were no differences in MLA (3.07 ± 2.14 mm² and 3.29 ± 2.21 mm², respectively; $P = 0.162$) and percentage of plaque burden (63.5% ± 17.9% and 65.0% ± 19.4%, respectively; $P = 0.282$)

FIGURE 2 Vessel, Plaque, and Lumen Volume After Adjustment for LV Mass
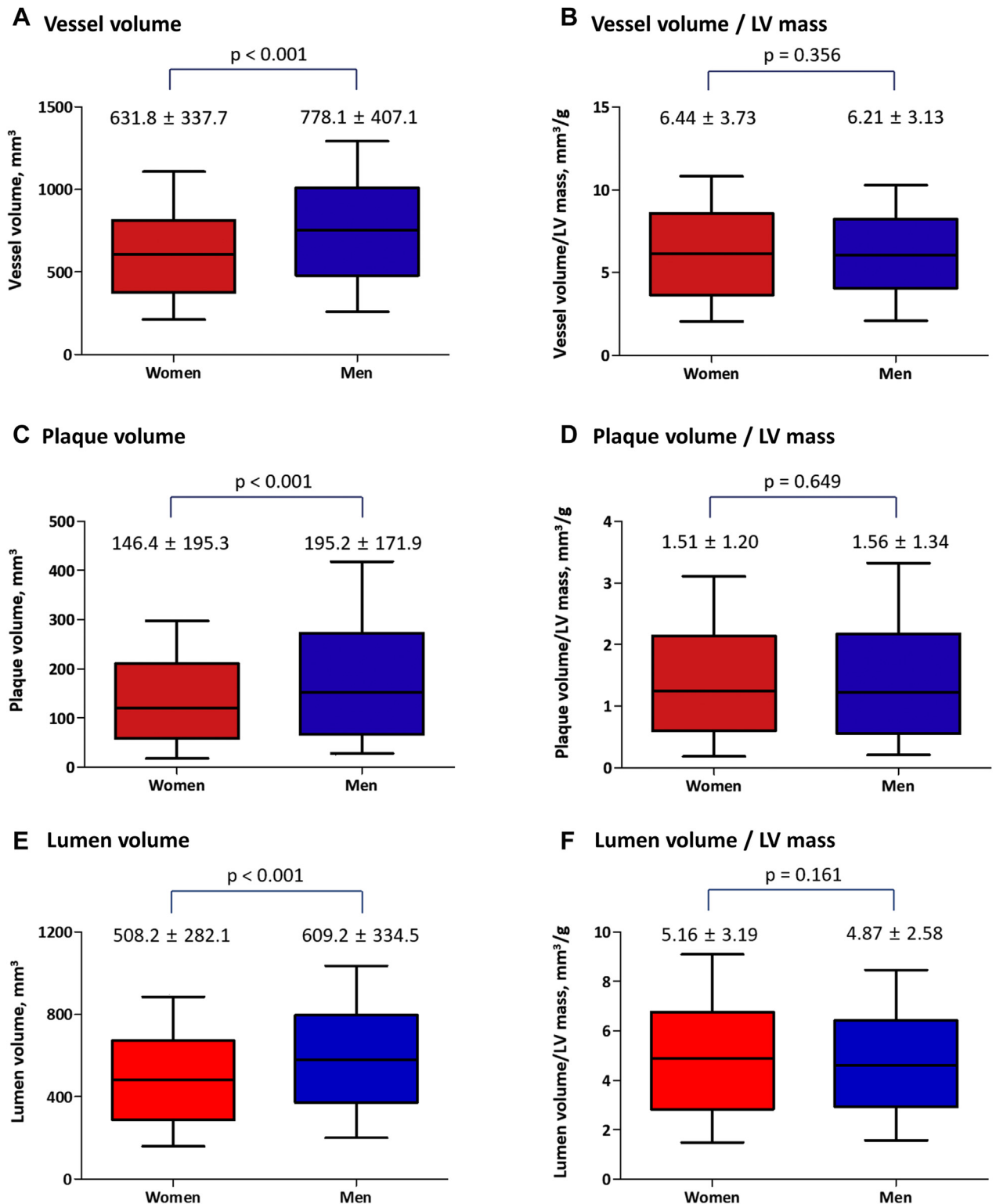
In whole vessel analysis, **(A, C, E)** vessel, plaque, and lumen volumes were significantly smaller in women than those in men. However, after adjustment for left ventricular (LV) mass, there were no differences in any of **(B, D, F)** vessel, plaque, and lumen volumes between women and men. **Box-and-whisker plots** indicate the median **(center line of the box)**, 25% and 75% ranges **(box edges)**, and 10% and 90% ranges **(whiskers)**.

FIGURE 3 Comparison of Plaque Composition According to Sex

The **(A)** absolute volume and **(B)** percentage of each plaque composition are plotted according to sex.

between women and men. Distributions of MLA, percentage of plaque burden at the MLA site, percentage of mean plaque burden, and FFR are shown in **Figure 1**. Among qualitative high-risk plaque characteristics, low attenuation plaque (12.7% vs 24.5%; $P < 0.001$) and positive remodeling (33.8% vs 45.5%; $P = 0.001$) were less frequent in women than that in men. In whole vessel analysis, vessel, plaque, and lumen volumes were significantly smaller in women than those in men (631.8 ± 337.7 mm^3 vs 778.1 ± 407.1 mm^3, 146.4 ± 119.7 mm^3 vs 195.3 ± 171.9 mm^3, and 508.2 ± 282.1 mm^3 vs 609.2 ± 334.5 mm^3, respectively; all $P < 0.001$) (**Figures 2A, 2C, and 2E**). However, after adjustment for LV mass, there were no differences in any of the vessel, plaque, and lumen volumes between women and men (6.44 ± 3.73 mm^3/g and 6.21 ± 3.13 mm^3/g, 1.51 ± 1.20 mm^3/g and 1.56 ± 1.34 mm^3/g, 5.16 ± 3.19 mm^3/g and 4.87 ± 2.58 mm^3/g, respectively; all $P > 0.10$) (**Figures 2B, 2D, and 2F**). With respect to plaque composition, percentages of fibrous plaque ($41.2\% \pm 21.5\%$ vs $47.0\% \pm 19.6\%$; $P < 0.001$), fibrofatty plaque ($12.1\% \pm 14.9\%$ vs $19.1\% \pm 18.0\%$; $P < 0.001$), and necrotic core ($1.5\% \pm 4.4\%$ vs $2.2\% \pm 5.1\%$; $P = 0.035$) were lower in women than those in men, in contrast to a higher dense calcium proportion in women ($45.4\% \pm 31.1\%$ vs $31.9\% \pm 27.9\%$; $P < 0.001$) (**Figure 3**). The percentage of FFNC was significantly lower in women ($13.1\% \pm 16.9\%$ vs $21.2\% \pm 19.9\%$; $P < 0.001$).

INDEPENDENT PREDICTORS OF FFR. **Table 3** shows independent predictors of FFR ≤0.80. In model 1, which included clinical characteristics and vessel and plaque volumes from CCTA as covariates, sex was an independent predictor of FFR. Lumen volume was not included in the final model because of multicollinearity. When plaque characteristics or LV mass were added into the analysis separately (model 2 and model 3), sex remained independent factor for FFR. However, in model 4, which included both plaque characteristics and LV mass, sex was not an independent determinant of FFR. These findings were consistently observed in linear regression models that predicted FFR as a continuous value (Supplemental Table 1).

In mediation analysis, when FFNC volume and LV mass were set as mediators separately, direct effect of sex on FFR was 81.2% (0.023; 95% CI: 0.006-0.039) and 67.7% (0.020; 95% CI: 0.003-0.038), respectively. However, when FFNC volume and LV mass were set as mediators simultaneously, the direct effect of sex became insignificant (0.016; 95% CI: −0.002 to 0.034; $P = 0.081$).

DISCUSSION

The main findings of the present study are as follows: 1) despite similar angiographic percentages of diameter stenosis, FFR values were higher in women than

those in men; 2) although the MLA, percentage of plaque burden, and percent mean plaque burden were similar between the sexes, the composition of fibrofatty plaque + necrotic core and frequencies of low attenuation plaque and positive remodeling were lower in women, which indicated more favorable plaque characteristics in women; and 3) sex was not an independent factor that affected the FFR value after adjusting for plaque characteristics and the LV mass (Central Illustration).

SEX DIFFERENCE IN CORONARY ATHEROSCLEROSIS. Initiation and progression of coronary atherosclerosis occurs later in life in women than in men.[1] Previous studies reported that plaque characteristics were more favorable in women than in men, although women usually have more risk factors for CAD. Sex-based analysis of intravascular ultrasound images from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial demonstrated less of a necrotic core and plaque rupture in women than that in men, despite similar plaque burden among patients with acute coronary syndrome.[22] A study that used near-infrared spectroscopy also showed a lower lipid core burden index in women than that in men.[23] However, in the OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity In Primary Angioplasty) study, no sex differences in culprit plaque morphology on optical coherence tomography images were observed.[24] With respect to plaque compositional progression, women showed slower non-calcified plaque progression but greater calcified plaque progression compared with men in a serial CCTA study.[25] In the present study, despite similar stenosis severity or plaque burden, lipid-rich plaque was less abundant and qualitative high-risk plaque characteristics were less frequent in women than those in men. In contrast, the proportion of dense calcium was higher in women than that in men, which possibly suggested greater plaque stability in women.[26] Our findings, together with those of previous studies, suggested that women might have more favorable plaque characteristics, despite their older age and a higher prevalence of hypertension. Therefore, distinctive pathophysiology according to sex should be considered when female patients present with symptomatic CAD.

Another interesting finding in our study was the relationship between heart size and plaque or vessel volume according to sex. Because there is a linear relationship between the coronary arterial volume and myocardial mass,[10] the question as to whether the difference in absolute volume of plaque or lumen is caused by patient sex versus heart size can be raised. In our study, vessel, plaque, and lumen volumes were significantly smaller in women than those in men. However, no sex difference was observed in any of those parameters after adjustment for LV mass. Therefore, sex differences in vessel or plaque volume might be explained more by the difference in heart size than by sex itself.

EFFECT OF SEX ON MYOCARDIAL ISCHEMIA. A higher FFR value for the same stenosis severity in women was observed in several previous studies.[4,5] One of the most frequently cited reasons for a higher FFR value in women than in men was microvascular dysfunction.[27] A blunted coronary hyperemic response in patients with microvascular dysfunction would lead to a smaller pressure gradient across a stenotic lesion and eventually a higher FFR value. However, according to recent invasive and positron emission tomography studies, hyperemic coronary flow was not different between women and men.[28,29] Different plaque characteristics between women and men could be a reason for the difference in myocardial ischemia according to sex. A substudy of the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial demonstrated that a low-density, noncalcified plaque volume significantly contributed to the low FFR value.[6] Furthermore, the presence of high-risk plaque characteristics, such as positive remodeling or low-attenuation plaque, was also associated with myocardial ischemia defined by a low FFR independent of stenosis severity.[7,8,30] Moreover, because vessel-specific myocardial mass determines coronary flow and FFR,[9] heart size can also be an independent determinant of FFR value. In our study, an increase in LV mass was an independent predictor of ischemia. even after adjustment for all variables. A recent CCTA-based study demonstrated that the CCTA-derived FFR was higher in women than in men for the same stenosis, and this was associated with a higher coronary volume to myocardial mass ratio.[11] Taken together, it can be inferred that different characteristics in plaque or myocardial mass in women may affect the FFR value. In the present study, the proportion of lipid-rich plaque or qualitative high-risk plaque characteristics was lower and LV mass was smaller in women than in men, acting in the direction of increasing the FFR value. Differences in plaque characteristics or LV mass separately could not explain sex differences in FFR values. Only

CENTRAL ILLUSTRATION Sex Differences in Coronary Computed Tomography Angiography Parameters and Fractional Flow Reserve

Kim CH, et al. JACC: Asia. 2022;2(2):157-167.
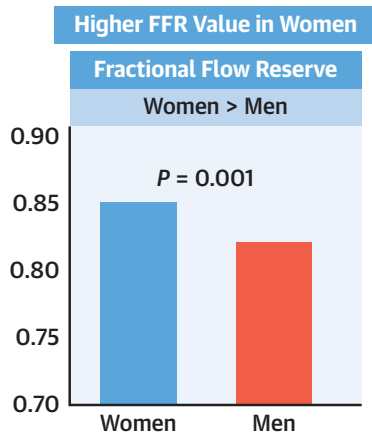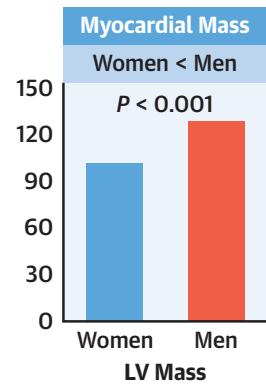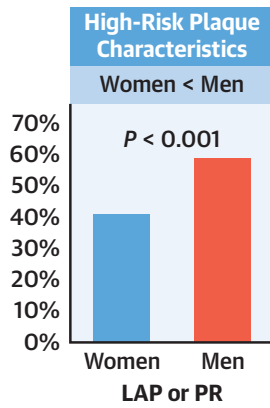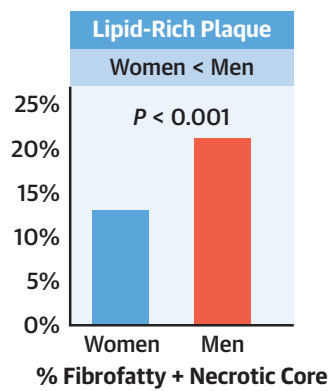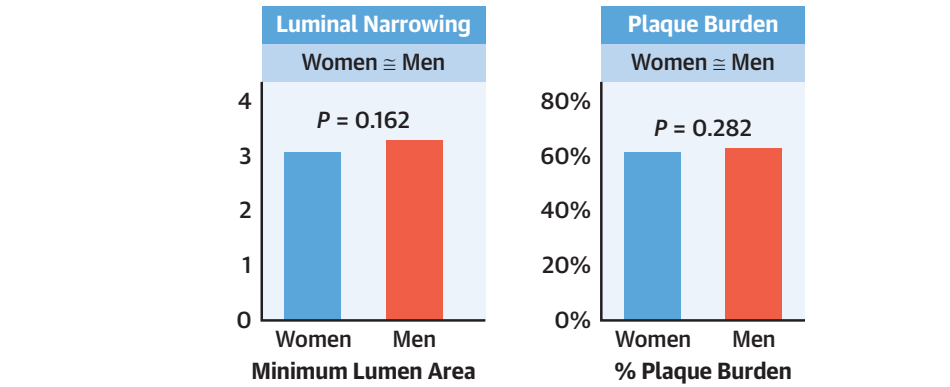
after adjusting for both plaque characteristics and LV mass, did patient sex show no effect on the FFR value. These results suggested that both plaque characteristics and LV mass contributed to the difference in myocardial ischemia between sexes.

STUDY LIMITATIONS. Some limitations of the present study should be considered. First, this was a post hoc analysis, so the potential influence of selection bias could not be excluded. Second, there was a limited number of women with abnormal FFR, so we might have lacked power to detect small differences caused by sex. Third, because the invasive measurement of microvascular function was not performed, sex differences in microvascular function could not be considered in the analysis. Fourth, plaque and lumen data from invasive imaging studies were not available. Fifth, information on angina status and body surface area was not collected.

CONCLUSIONS

The higher FFR value for the same stenosis severity in women can be explained by fewer high-risk plaque characteristics and a smaller myocardial mass in women than that in men.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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TABLE 3 Multivariate Logistic Regression Analysis for FFR ≤ 0.80

	Odds Ratio	95% CI	P Value
Model 1			
Sex (women)	0.539	0.383-0.759	<0.001
Age, by 10 yrs increase	0.930	0.797-1.086	0.361
Acute coronary syndrome	1.642	1.153-2.340	0.006
Left anterior descending artery	3.953	2.939-5.316	<0.001
Proximal lesion	1.362	1.027-1.808	0.032
Vessel volume, by 10 mm^3 increase	0.976	0.971-0.982	<0.001
Plaque volume, by 10 mm^3 increase	1.059	1.045-1.073	<0.001
Model 2			
Sex (women)	0.612	0.431-0.868	0.006
Age, by 10 yrs increase	0.971	0.828-1.139	0.717
Acute coronary syndrome	1.698	1.182-2.442	0.004
Left anterior descending artery	4.039	2.977-5.480	<0.001
Proximal lesion	1.311	0.981-1.752	0.067
Vessel volume, by 10 mm^3 increase	0.975	0.969-0981	<0.001
Plaque volume, by 10 mm^3 increase	1.048	1.032-1.064	<0.001
Low attenuation plaque	2.111	1.468-3.035	<0.001
Positive remodeling	1.528	1.136-2.055	0.005
Fibrofatty + necrotic core volume, by 10 mm^3 increase	1.041	1.003-1.080	0.036
Model 3			
Sex (women)	0.654	0.451-0.947	0.025
Age, by 10 yrs increase	0.940	0.798-1.108	0.463
Acute coronary syndrome	1.696	1.174-2.451	0.005
Left anterior descending artery	4.149	3.043-5.657	<0.001
Proximal lesion	1.361	1.013-1.828	0.041
Vessel volume, by 10 mm^3 increase	0.976	0.969-0.982	<0.001
Plaque volume, by 10 mm^3 increase	1.061	1.046-1.076	<0.001
LV mass, by 10 g increase	1.070	1.019-1.125	0.007
Model 4			
Sex (women)	0.743	0.509-1.086	0.125
Age, by 10 yrs increase	0.990	0.836-1.172	0.904
Acute coronary syndrome	1.758	1.206-2.563	0.003
Left anterior descending artery	4.267	3.097-5.879	<0.001
Proximal lesion	1.308	0.996-1.771	0.082
Vessel volume, by 10 mm^3 increase	0.974	0.968-0.980	<0.001
Plaque volume, by 10 mm^3 increase	1.048	1.032-1.065	<0.001
Low attenuation plaque	2.002	1.377-2.909	<0.001
Positive remodeling	1.511	1.108-2.059	0.009
Fibrofatty + necrotic core volume, by 10 mm^3 increase	1.051	1.009-1.094	0.016
LV mass, by 10 g increase	1.069	1.016-1.124	0.010

Model 1 includes clinical characteristics and vessel and plaque volumes as covariates. Model 2 added parameters on plaque composition and high-risk plaque characteristics to model 1. Model 3 added LV mass to model 1. Model 4 added LV mass to model 2. All models were adjusted with cardiac risk factors (hypertension, diabetes mellitus, hypercholesterolemia, previous myocardial infarction, and acute coronary syndrome). Lumen volume was not included in the final model because of multicollinearity.

Abbreviations as in **Table 2**.

CENTRAL ILLUSTRATION Continued

Despite similar luminal narrowing and plaque burden between women and men, the composition of lipid-rich plaque and frequencies of qualitative high-risk plaque characteristics were lower in women, indicating more favorable plaque characteristics in women. The fractional flow reserve (FFR) value was higher in women than in men despite similar stenosis severity; however, sex was not an independent factor that affected the FFR value after adjusting for plaque characteristics and the left ventricular (LV) mass. CCTA = coronary computed tomography angiography; LAP = low attenuation plaque; PR = positive remodeling.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The FFR value has been reported to be higher in women than in men with the same stenosis severity in previous studies. However, the mechanism of FFR difference according to sex has not been clearly understood. In our study, sex was not an independent predictor of FFR after adjustment for plaque characteristics and myocardial mass. This is the first study to demonstrate that different plaque characteristics can be a reason for different FFR values according to sex. Our study provided important insight into understanding CAD in women based on the comprehensive information of stenosis, plaque, and myocardial mass.

TRANSLATIONAL OUTLOOK: Further large-scale studies are needed to clarify the clinical implications of the influence of sex on plaque, myocardial mass, and FFR.

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KEY WORDS coronary artery disease, fractional flow reserve, myocardial mass, plaque, sex

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