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ORIGINAL RESEARCH

Sex Differences in Coronary Computed Tomography Angiography–Derived Fractional Flow Reserve



Lessons From ADVANCE

Timothy A. Fairbairn, MBChB, PhD,^a Rebecca Dobson, MD,^a Lyne Hurwitz-Koweek, MD,^b Hitoshi Matsuo, MD,^{c,d} Bjarne L. Norgaard, MD, PhD,^e Niels Peter Rønnow Sand, MD,^f Koen Nieman, MD, PhD,^g Jeroen J. Bax, MD, PhD,^h Gianluca Pontone, MD,ⁱ Gilbert Raff, MD,^j Kavitha M. Chinnaiyan, MD,^j Mark Rabbat, MD,^k Tetsuya Amano, MD,^c Tomohiro Kawasaki, MD,^l Takashi Akasaka, MD,^m Hironori Kitabata, MD,^c Sukumaran Binukrishnan, MD,^a Campbell Rogers, MD,ⁿ Daniel Berman, MD,^o Manesh R. Patel, MD,^b Pamela S. Douglas, MD,^b Jonathon Leipsic, MD^p

ABSTRACT

OBJECTIVES This study is to determine the management and clinical outcomes of patients investigated with coronary computed tomography angiography (CCTA)-derived fractional flow reserve (FFR_{CT}) according to sex.

BACKGROUND Women are underdiagnosed with conventional ischemia testing, have lower rates of obstructive coronary artery disease (CAD) at invasive coronary angiography (ICA), yet higher mortality compared to men. Whether FFR_{CT} improves sex-based patient management decisions compared to CCTA alone is unknown.

METHODS Subjects with symptoms and CAD on CCTA were enrolled (2015 to 2017). Demographics, symptom status, CCTA anatomy, coronary volume to myocardial mass ratio (V/M), lowest FFR_{CT} values, and management plans were captured. Endpoints included reclassification rate between CCTA and FFR_{CT} management plans, incidence of ICA demonstrating obstructive CAD (≥50% stenosis) and revascularization rates.

RESULTS A total of 4,737 patients (n = 1,603 females, 33.8%) underwent CCTA and FFR_{CT}. Women were older (age 68 ± 10 years vs. 65 ± 10 years; p < 0.0001) with more atypical symptoms (41.5% vs. 33.9%; p < 0.0001). Women had less obstructive CAD (65.4% vs. 74.7%; p < 0.0001) at CCTA, higher FFR_{CT} (0.76 ± 0.10 vs. 0.73 ± 0.10; p < 0.0001), and lower likelihood of positive FFR_{CT} ≤ 0.80 for the same degree stenosis (p < 0.0001). A positive FFR_{CT} ≤ 0.80 resulted in equal referral to ICA (n = 510 [54.5%] vs. n = 1,249 [56.5%]; p = 0.31), but more nonobstructive CAD (n = 208 [32.1%] vs. n = 354 [24.5%]; p = 0.0003) and less revascularization (n = 294 [31.4%] vs. n = 800 [36.2%]; p < 0.0001) in women, unless the FFR_{CT} was ≤ 0.75 where revascularization rates were similar (n = 253 [41.9%] vs. n = 715 [46.4%]; p = 0.06). Women have a higher V/M ratio (26.17 ± 7.58 mm³/g vs. 24.76 ± 7.22 mm³/g; p < 0.0001) that is associated with higher FFR_{CT} independent of degree stenosis (p < 0.001). Predictors of revascularization included stenosis severity, FFR_{CT}, symptoms, and V/M ratio (p < 0.001) but not female sex (p = 0.284).

CONCLUSIONS FFR_{CT} differs between the sexes, as women have a higher FFR_{CT} for the same degree of stenosis. In FFR_{CT}-positive CAD, women have less obstructive CAD at ICA and less revascularization, which is associated with higher V/M ratio. The findings suggest that CAD and FFR_{CT} variations by sex need specific interpretation as these differences may affect therapeutic decision making and clinical outcomes. (Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care [ADVANCE]; NCT02499679) (J Am Coll Cardiol Img 2020;13:2576–87) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Coronary artery disease (CAD) remains the major cause of mortality in women, responsible for 1 in 4 deaths (1). Despite significant advances against ischemic heart disease in recent years with falling death rates in both sexes, women have relatively higher cardiovascular death rates (2,3). Women present later in life, have different symptomatology, lower cardiovascular risk assessment scores, and lower incidence of obstructive CAD, yet a worse prognosis (4). Women are less likely to be referred for invasive coronary angiography (ICA) following a positive stress test, have lower rates of revascularization, and even receive fewer lifestyle interventions and medical treatments (5).

The explanation for this lower level of care and worse outcomes in women may stem in part from the intrinsic difficulties associated with the investigation of women with suspected CAD. Reduced peak exercise capacity, small body size, breast attenuation, and lower incidence of obstructive CAD are all confounding factors that limit the role of conventional noninvasive testing in the evaluation of women with suspected CAD. Sex-specific strategies and interpretation are therefore recommended in guidelines (6). Coronary computed tomography angiography (CCTA) has the advantage of being able to visualize coronary plaque and has been shown to improve outcomes versus ischemia testing through the intensification of medical treatments (7). However, CCTA also has the potential to miss physiologically important ischemia in nonobstructive coronary arteries that is readily detected by noninvasive stress testing and has important diagnostic and prognostic implications particularly in women who have a greater heterogeneity of heart disease (8,9).

Computed tomography-derived fractional flow reserve (FFR_{CT}) has been shown to improve the discrimination of ischemia versus other noninvasive tests (10), reduce the incidence of nonobstructive CAD at ICA (11), and increase the rates of coronary revascularization (12) with no sex-based

discrimination (13). FFR_{CT} also has the potential to improve the understanding of physiologic changes and diagnosis of microvascular disease through the calculation of coronary artery lumen volume and myocardial mass (14). The ADVANCE (Assessing Diagnostic Value of Non-invasive FFR_{CT} in Coronary Care) registry reported a change in patient management following FFR_{CT} in 2 of 3 patients across a broad variety of health care settings, geographic regions, and patient populations (15). The impact of a stable chest pain diagnostic strategy including FFR_{CT} on sex-specific diagnosis and clinical outcomes is unknown. We report the outcomes of a CCTA- and FFR_{CT}-determined strategy on patient management, rates of ICA, and revascularization according to sex.

METHODS

Clinically stable patients being investigated for suspected cardiac chest pain or symptoms suggestive of underlying CAD with evidence of coronary atherosclerosis on CCTA were prospectively enrolled as part of the ADVANCE registry study. Eligibility criteria included age older than 18 years, ability to provide informed consent, and CAD >30% degree stenosis (DS) on site based CCTA analysis. Exclusion criteria included no evidence of CAD on CCTA, inadequate CCTA image quality, life expectancy <1 year, and an inability to comply with follow-up. The study complied with the Declaration of Helsinki and all patients provided written informed consent following local institutional review board approval. Demographics, symptom status, CCTA and FFR_{CT} findings, treatment plans, and clinical outcomes through 90-days were recorded.

CCTA AND FFR_{CT} ASSESSMENT. CCTA was performed in accordance with local practice and international guidelines on a ≥ 64 -slice computed

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

DS = degree stenosis

FFR = fractional flow reserve

FFR_{CT} = coronary computed tomography angiography-derived fractional flow reserve

ICA = invasive coronary angiography

MT = medical treatment

PCI = percutaneous coronary intervention

From the ^aLiverpool Heart and Chest Hospital, Liverpool, United Kingdom; ^bDuke University School of Medicine, Durham, North Carolina, USA; ^cWakayama Medical University, Wakayama, Japan; ^dGifu Heart Center, Gifu, Japan; ^eAarhus University Hospital, Aarhus Skejby, Denmark; ^fHospital of South West Denmark, Esbjerg/University of Southern Denmark, Odense, Denmark; ^gStanford University Medical Center, Palo Alto, California, USA; ^hLeiden University Medical Center, Leiden, the Netherlands; ⁱCentro Cardiologico Monzino, IRCCS, University of Milan, Milan, Italy; ^jWilliam Beaumont Hospital, Royal Oaks, Michigan, USA; ^kLoyola University Medical Center, Maywood, Illinois, USA; ^lShin Koga Hospital, Fukuoka, Japan; ^mAichi Medical University, Aichi, Japan; ⁿHeartFlow, Redwood City, California, USA; ^oCedars Sinai Medical Centre, Beverly Hills, California, USA; and the ^pDepartment of Radiology, University of British Columbia, Vancouver, British Columbia, Canada. Edward Nicol, MD, served as Guest Editor for this paper.

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 [Author Center](#).

TABLE 1 Patient Demographics, Comorbidities, Symptom Status and CCTA Rejection Rate

	Female (n = 1,603)	Male (n = 3,134)	Total (N = 4,737)	p Value
Age, yrs	68.34 ± 9.79	65.01 ± 10.30	66.13 ± 10.26	<0.0001
Diamond Forrester CAD likelihood	36.24 ± 17.64	59.41 ± 16.76	51.62 ± 20.27	<0.0001
Comorbidities				
Diabetes mellitus	327 (20.4)	710 (22.7)	1037 (21.9)	0.0665
Hypertension	1,014 (63.3)	1,821 (58.1)	2,835 (59.8)	0.0006
Hyperlipidemia	974 (60.8)	1,779 (56.8)	2,753 (58.1)	0.0096
Tobacco use				
Current smoker	202 (12.6)	595 (19.0)	797 (16.8)	<0.0001
Ex-smoker	364 (22.7)	1,251 (39.9)	1,615 (34.1)	
Never smoked	915 (57.1)	1,058 (33.8)	1,973 (41.7)	
Angina status				
Typical	388 (22.4)	678 (20.2)	1,066 (21)	<0.0001
Atypical	666 (41.5)	1,061 (33.9)	1,727 (36.5)	
Dyspnea	178 (11.1)	294 (9.4)	472 (10.0)	
Noncardiac pain	111 (6.9)	186 (5.9)	297 (6.3)	
None	260 (16.2)	904 (28.8)	1164 (24.6)	
Canadian Cardiovascular Society angina class				
Grade I	83 (22.3)	171 (26.2)	254 (24.8)	0.4534
Grade II	217 (58.2)	344 (52.8)	561 (54.7)	
Grade III	36 (9.7)	75 (11.5)	111 (10.8)	
Grade IV	8 (2.1)	15 (2.3)	23 (2.2)	
Unknown	29 (7.8)	47 (7.2)	76 (7.4)	

Values are mean ± SD or n (%). Difference in means for continuous variables were tested using a Student's t-test using a Satterthwaite adjustment where the variances were statistically determined to be unequal; tests of general association were performed using a chi square test or Fisher exact test, as appropriate, for categorical variables. For categorical variables, observations with the value "unknown" were excluded in the calculation of p values.

CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

tomography scanner with the control of heart rate <60 beats/min recommended and administration of sublingual nitrates mandated in all patients. CCTA coronary stenosis severity was assessed in all vessels ≥ 2 mm and reported by the sites using a Coronary Artery Disease-Reporting and Data System categorization system for assessing CAD DS. The decision to request an FFR_{CT} analysis was made independent of the study by the clinician reporting the scan. All FFR_{CT} analyses were performed by a central core laboratory (HeartFlow, Redwood City, California) as previously described (16). A 3-dimensional model of the epicardial vessels is segmented using image algorithms that extract the luminal surface boundaries of all vessels >1 mm in size. Total coronary flow is computed and coronary resistance under hyperemia calculated. Once luminal boundaries are defined, total arterial lumen volume is calculated and the volume of myocardium extracted and multiplied by 1.05 to calculate left ventricular (LV) mass. The ratio of coronary lumen volume (mm³) and LV mass (g) was calculated (V/M ratio) (16). A 3-dimensional model and report were made available to the sites for local interpretation. The Duke Clinical Research Institute (Durham, North Carolina) acted as core laboratory

analyzing all CCTA and FFR_{CT} data, blinded to clinical information, symptom status, and outcomes. This included adjudication of vessel and stenosis-specific ischemia, defined as a value ≤ 0.80 . The stenosis-minimum FFR_{CT} was used for analysis and reporting.

MANAGEMENT STRATEGIES. Management plans following CCTA were determined for each subject by the enrolling site and by a core laboratory blinded to sex and actual care. Once the FFR_{CT} result was made available, the investigators were asked to re-determine the treatment strategy based on the new information of the CCTA combined with the FFR_{CT} result. Management options available for both site and core laboratory included medical treatment (MT), percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or additional diagnostic testing. Clinical management decisions rested with the referring physician. A positive FFR_{CT} was deemed to be a value ≤ 0.80 in accordance with the previously published invasive and noninvasive literature (17).

STUDY ENDPOINTS. The primary endpoint was the reclassification of management decisions between CCTA alone versus CCTA and FFR_{CT} according to sex.

TABLE 2 Anatomical Degree Stenosis Severity and FFR_{CT}

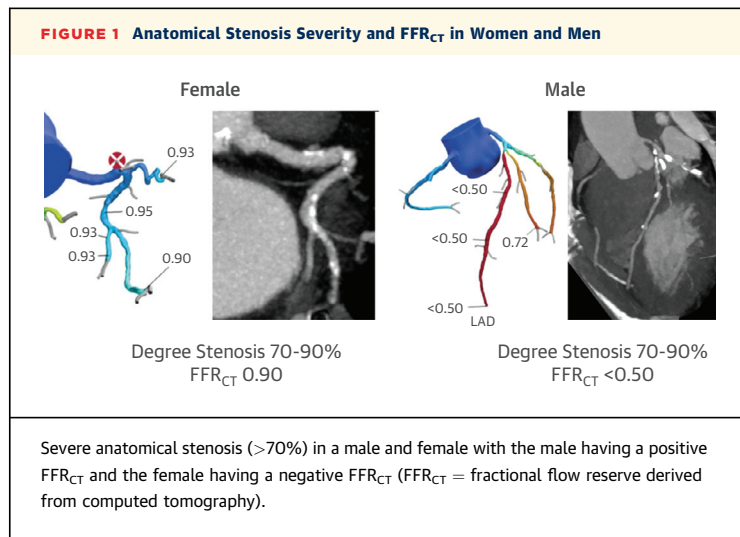
	Female (n = 1,603)	Male (n = 3,134)	Total (N = 4,737)	p Value
CCTA anatomical stenosis				
Obstructive stenosis ≥50%	1,049 (65.4)	2,340 (74.7)	3,389 (71.5)	<0.0001
Severe stenosis ≥70%	435 (27.1)	1,094 (34.9)	1,529 (32.3)	<0.0001
Degree stenosis				
Normal (0%)	14 (0.9)	12 (0.4)	26 (0.5)	<0.0001
Minimal (0%-30%)	125 (7.8)	165 (5.3)	290 (6.1)	
Mild (30%-50%)	410 (25.6)	613 (19.6)	1,023 (21.6)	
Moderate (50%-70%)	614 (38.3)	1,246 (39.8)	1,860 (39.3)	
Severe (70%-90%)	314 (19.6)	747 (23.8)	1,061 (22.4)	
Subtotal/occlusion (>90%/occluded)	121 (7.5)	347 (11.1)	468 (9.9)	
Missing	5 (0.3)	4 (0.1)	9 (0.2)	
Number of vessels with anatomically obstructive CAD (≥50% degree stenosis)				
0	549 (34.2)	790 (25.2)	1,339 (28.3)	<0.0001
1	690 (43.0)	1,399 (44.6)	2,089 (44.1)	
2	247 (15.4)	609 (19.4)	856 (18.1)	
3	112 (7.0)	332 (10.6)	444 (9.4)	
Missing	5 (0.3)	4 (0.1)	9 (0.2)	
Rate of obstructive CAD per vessel				
LAD stenosis ≥50%	836 (52.2)	1,876 (59.9)	2,712 (57.3)	<0.0001
LCx stenosis ≥50%	305 (19.0)	835 (26.6)	1,140 (24.1)	<0.0001
RCA stenosis ≥50%	379 (23.6)	902 (28.8)	1,281 (27.0)	0.0002
Coronary vessel FFR_{CT}				
LAD	0.78 (0.11)	0.75 (0.11)	0.76 (0.11)	<0.0001
LCx	0.87 (0.09)	0.84 (0.11)	0.85 (0.10)	<0.0001
RCA	0.85 (0.10)	0.84 (0.11)	0.84 (0.10)	<0.0001
Overall	0.76 (0.12)	0.73 (0.12)	0.74 (0.12)	<0.0001
Coronary volume and myocardial mass				
FFR _{CT}	(n = 1,049) 0.75 ± 0.11	(n = 2,061) 0.72 ± 0.11	(N = 3,110)* 0.73 ± 0.11	<0.0001
Volume, mm ³	2,548.1 ± 767.67	3,225.8 ± 977.41	2,997.2 ± 966.62	<0.0001
Mass, g	99.51 ± 23.11	133.19 ± 30.04	121.83 ± 32.12	<0.0001
V/M ratio	26.17 ± 7.58	24.76 ± 7.22	25.24 ± 7.37	<0.0001
V/M quartile 1	230 ± 21.9	547 ± 26.5	777 ± 25.0	<0.0001
V/M quartile 2	232 ± 22.1	546 ± 26.5	778 ± 25.0	
V/M quartile 3	271 ± 25.8	506 ± 24.6	777 ± 25.0	
V/M quartile 4	316 ± 30.1	462 ± 22.4	778 ± 25.0	

Values are n (%) or mean ± SD. Tests of general association were performed using chi square tests for categorical variables. *The coronary volume and myocardial mass is based on a smaller subpopulation.
 FFR_{CT} = fractional flow reserved derived by computed tomography; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery; V/M = volume to mass ratio; other abbreviations as in Table 1.

Secondary endpoints were to determine sex-based differences in the rate of ICA, incidence of non-obstructive CAD (no coronary stenosis ≥50%), and revascularization rates at 90 days.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or median (interquartile range); whereas categorical data are presented as frequency and percentage. Differences in mean for continuous variables were tested using a Welch t test and 1-way analysis of variance. For categorical variables, tests of general association were performed using a McNemar test (within sexes) and chi square test (between sexes) as appropriate. Odds ratios and

associated 95% confidence intervals (CIs) were calculated. When analyzing data where observations between factors are correlated (i.e., measured on the same subject), a generalized estimating equation approach was used to account for covariance between observations. Univariable and multivariable regression models were used to estimate the relationship between FFR_{CT} coronary volume, myocardial mass, and V/M. Stepwise logistic regression models were used to determine predictors of revascularization. A p value <0.10 was used for entry into multivariable models, a 2-sided level of p < 0.05 was considered significant.



RESULTS

Of 5,083 subjects enrolled, 190 (3.7%) CCTAs were not submitted (no significant CAD, n = 172; coronary stent, n = 9; CCTA not acquired as per protocol, n = 2; unknown, n = 7) and 156 (3.2%) CCTAs were rejected for FFR_{CT} analysis due to inadequate image quality. This left 4,737 (96.8%) subjects with CCTA and FFR_{CT}. There was no sex-related difference in the FFR_{CT} not being requested (women, n = 31 [1.8%] vs. men,

n = 47 [1.4%]) or CCTA rejection rate (females, n = 59 [3.4%] vs. males, n = 101 [3.0%]; p = 0.481).

CLINICAL CHARACTERISTICS. Baseline patient demographics and clinical characteristics are reported in Table 1. Of 4,737 patients with a successful FFR_{CT}, 1,603 (33.8%) were female. Women were older (age 68.3 ± 9.8 years vs. 65.1 ± 10.3 years; p < 0.0001) with greater prevalence of hypertension (63.3% vs. 58.1%; p = 0.0006) and hyperlipidemia (60.8% vs. 56.8%; p = 0.01), but less likely to have smoked cigarettes (never-smoked, 57.1% vs. smoked, 33.8%; p < 0.001) with a lower Diamond-Forrester pre-test likelihood of obstructive CAD (36.24 ± 17.6 vs. 59.41 ± 16.8; p < 0.001). Women were more likely to present with atypical angina (41.5% vs. 33.9%; p < 0.0001), but when typical angina was present there was no difference in the severity of the symptoms between the sexes.

CAD ON CCTA. Women had smaller coronary arteries by volume but less anatomically obstructive (≥50% DS) CAD (65.4% vs. 74.7%; p < 0.0001) and severe (≥70% DS) CAD (27.1% vs. 34.9%; p < 0.001) than men. Rates of single-vessel obstructive CAD was similar between the sexes (female, 43% vs. male, 44.6%; p > 0.05), but men had more multivessel CAD (2 vessels [women, 15.4% vs. men, 19.4%] and 3 vessels [female, 7% vs. male, 10.6%]; p < 0.0001). Obstructive CAD was most frequent in the left anterior descending (LAD) artery then the right coronary

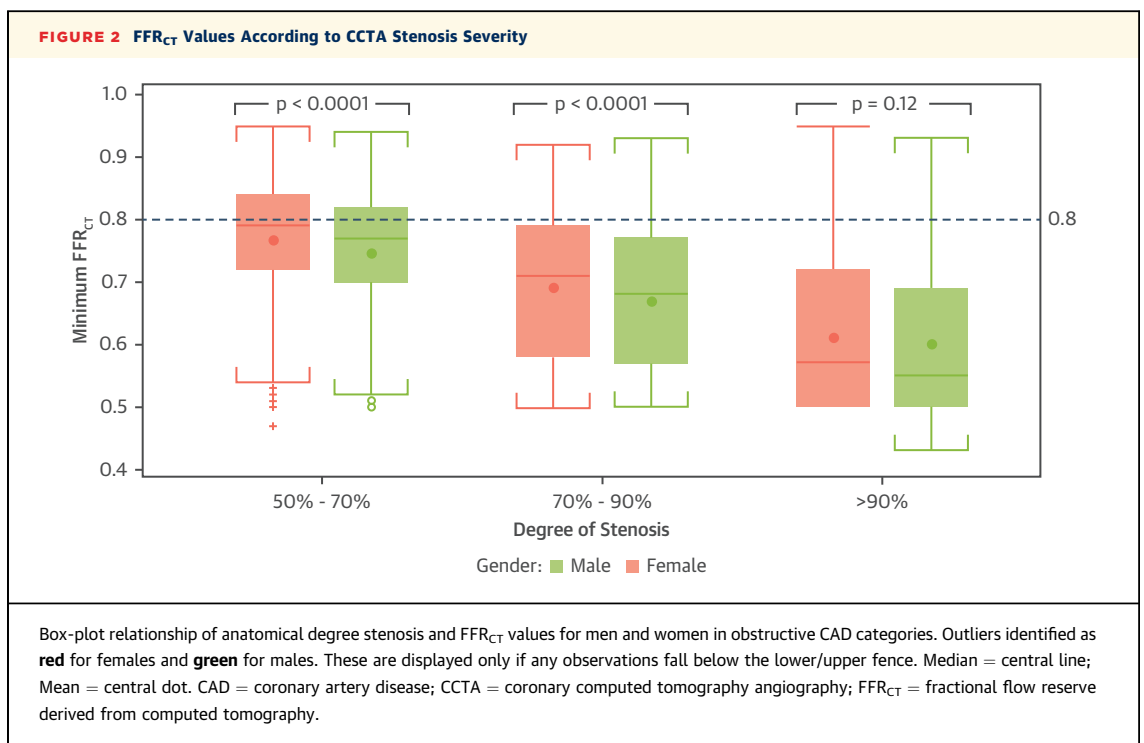
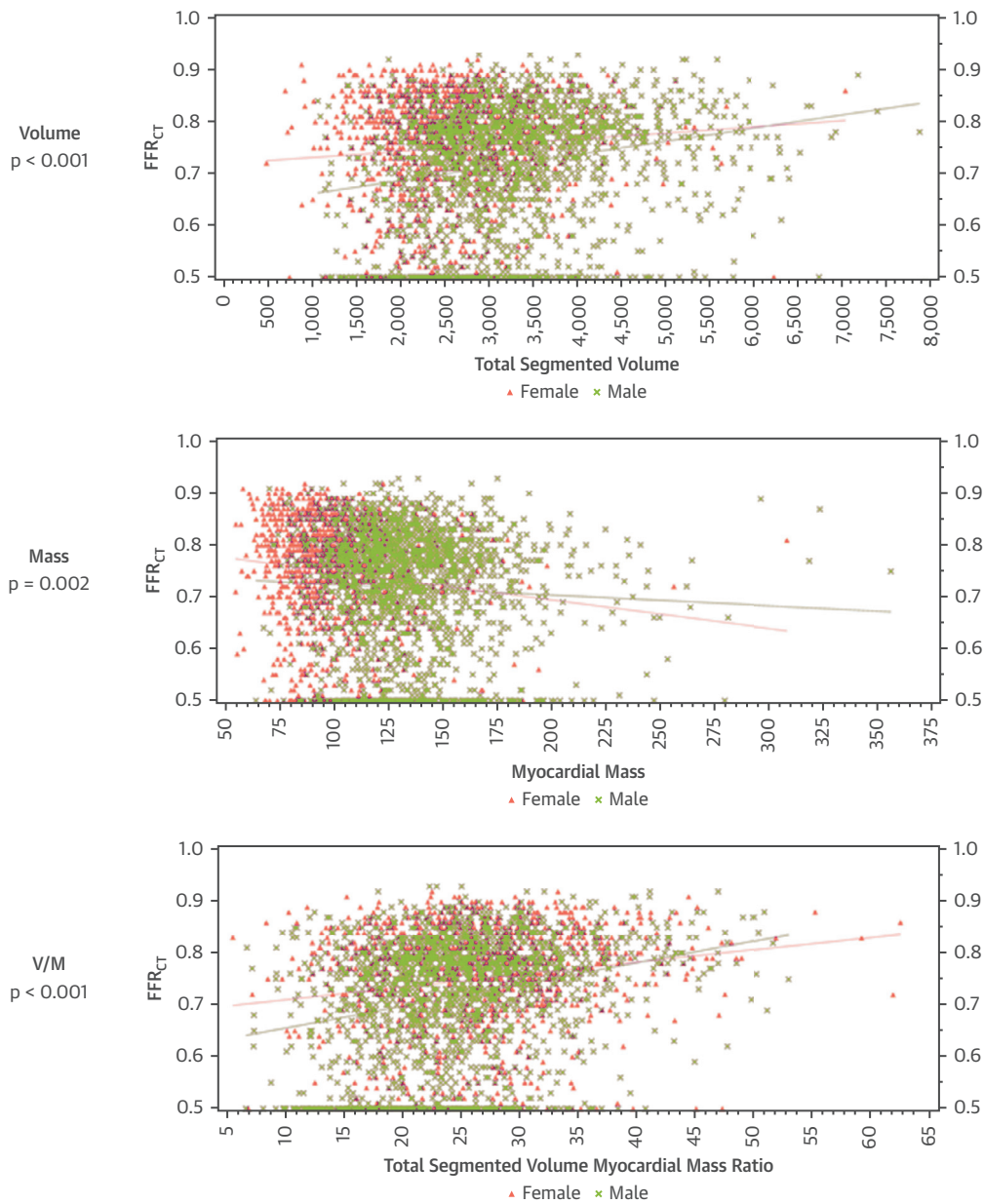


FIGURE 3 The Per-Patient Relationship of FFR_{CT} to Coronary Artery Volume, Left Ventricle Mass and V/M Ratio for Males and Females



Males are shown in green. Females are shown in red. Linear regression model with patient sex entered as a covariate. Sex remained significant in volume and V/M ratio: volume ($p = 0.0092$), mass ($p = 0.0505$), and V/M ratio ($p = 0.0017$). FFR_{CT} = fractional flow reserve derived from computed tomography; V/M = volume to mass ratio.

artery (RCA) and left circumflex (LCx) ($p < 0.001$ for both sexes), with no difference between men and women ($p = 0.15$) (Table 2).

FFR_{CT} FINDINGS. Minimum FFR_{CT} values were higher in women compared to men on a per-patient (0.76 ± 0.12 vs. 0.73 ± 0.12 ; $p < 0.0001$) and per-

vessel basis (LAD, 0.78 ± 0.11 vs. 0.75 ± 0.11 ; LCx, 0.87 ± 0.09 vs. 0.84 ± 0.11 ; and RCA, 0.85 ± 0.10 vs. 0.84 ± 0.11 ; all $p < 0.0001$) (Table 1). Women were thus less likely to have a positive FFR_{CT} ≤ 0.80 (women, $n = 935$ [58.3%] vs. men, $n = 2,210$ [70.5%]; $p < 0.0001$).

TABLE 3 Multiple Regression Analysis of the Predictors of Coronary Volume to Myocardial Mass Ratio*

	Estimate ± SD	95% CI	p Value
Intercept volume to mass ratio	25.90 ± 0.30	25.32 to 26.48	<0.0001
Female	0.94 ± 0.28	0.40 to 1.48	0.0006
Overall stenosis ≥50%	-0.83 ± 0.32	-1.45 to -0.21	0.0084
≥2 vessel disease	-2.77 ± 0.32	-3.39 to -2.15	<0.0001
FFR _{CT} >0.80	1.32 ± 0.30	0.72 to 1.91	<0.0001

Linear regression. *Reference categories are: male; overall stenosis <50%; <2 VD; FFR_{CT} ≤0.80.
CI = confidence interval; FFR_{CT} = fractional flow reserve derived from computed tomography; VD = vessel disease.

Men were more likely to have a positive FFR_{CT} ≤0.80 for the same degree of anatomical stenosis in the nonobstructive (0% to 49% DS; women, n = 224 [36.8%] vs. men, n = 369 [42.4%]; p = 0.03), moderate (50% to 69% DS; women, n = 353 [57.5%] vs. men, n = 856 [68.5%]; p < 0.0001), and severe (70% to 90% DS; women, n = 244 [77.7%] vs. men, n = 655 [87.7%]; p < 0.0001) stenosis categories (Figures 1 and 2). This per-patient analysis was consistent on a per-vessel basis for the LAD (women, n = 487 [62.8%] vs. men, n = 1,256 [72.9%]; p < 0.01) and LCx (women, n = 106 [39.1%] vs. men, n = 352 [49.5%]; p < 0.01). No sex-difference existed between DS and FFR_{CT} positivity (≤0.80) in the RCA (women, n=144 [44.9%] vs. men, n = 378 [49.4%]; p = 0.27).

VESSEL LUMEN VOLUME TO MYOCARDIAL MASS. A total of 3,110 (female, n = 1,049 [33.7%]) individuals had their coronary lumen volume and LV mass calculations performed. Women had significantly lower coronary lumen volume (2,548.1 ± 767.7 mm³ vs. 3,225.8 ± 977.4 mm³; p < 0.0001) and myocardial mass (99.5 ± 23.1 g vs. 133.2 ± 30.0 g; p < 0.0001) compared to men. Female LV mass was relatively lower, resulting in a higher V/M ratio compared to males (26.17 ± 7.58 mm³/g vs. 24.76 ± 7.22 mm³/g; p < 0.0001). When subdivided into quartiles, females were more likely to be in the higher V/M Q3-Q4 and males in the lower V/M Q1 to Q2 quartiles (p < 0.0001) (Table 2). Low coronary volume, high myocardial mass, and lower V/M ratio were all associated with a lower FFR_{CT} value on a per-vessel and per-patient basis (Q1 0.69 ± 0.12, Q2 0.72 ± 0.11, Q3 0.74 ± 0.11, Q4 0.76 ± 0.10; p < 0.0001) (Figure 3). Sex, stenosis severity, multivessel disease, and FFR_{CT} were independently associated with low V/M on multiple regression models (Table 3).

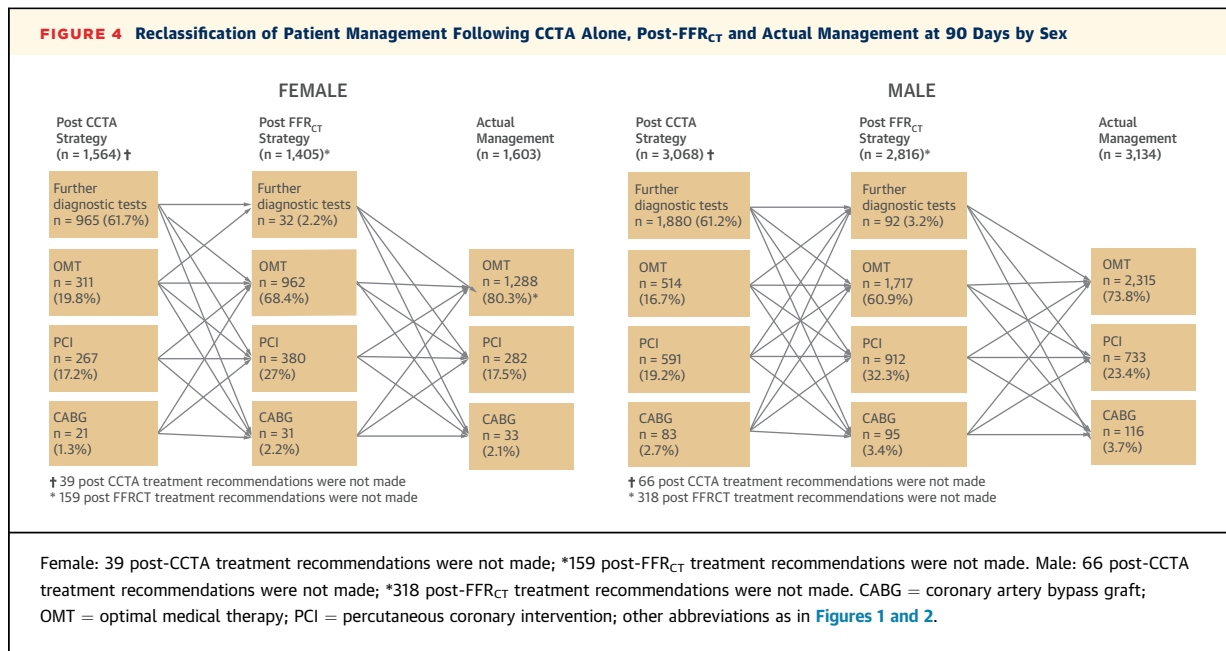
RECOMMENDED CLINICAL MANAGEMENT STRATEGIES AND RECLASSIFICATION FOLLOWING CCTA AND FFR_{CT}. The reclassification of recommended management

did not differ by sex (women = 63.13 [95% CI: 60.51 to 65.69]; men = 63.74 [95% CI: 61.91 to 65.53]; p = 0.70). Women were more frequently recommended for MT and less frequently for revascularization (PCI/CABG) compared to men (Figure 4) post-CCTA and FFR_{CT}. When the FFR_{CT} was positive (≤0.80), women remained more likely to have an MT plan recommended (n = 452 [48.3%] vs. n = 963 [43.6%]; p = 0.014) but no significant difference in recommendations for revascularization (n = 373 [39.9% vs. n = 956 [43.3%]; p = 0.054) (Table 4). A strongly positive FFR_{CT} (≤0.75) showed no difference in treatment recommendations between women and men (MT, n = 213 [35.3%] vs. n = 508 [33.0%]; p = 0.31) and revascularization (n = 339 [56.1%] vs. n = 898 [58.3%]; p = 0.43).

ACTUAL MANAGEMENT, RATE OF NONOBSTRUCTIVE ANGIOGRAPHY, AND REVASCULARIZATION. Actual management at 90 days showed that women were more likely to receive MT (n = 1,288 [80.3%] vs. n = 2,285 [72.9%]) and men more likely to undergo revascularization (n = 315 [19.7%] vs. n = 849 [37.1%]) (Figures 4 and 5). No difference in ICA rate was observed (women, n = 510 [54.5%] vs. men, n = 1,249 [56.5%]; p = 0.31) when FFR_{CT} was positive (≤0.80). At ICA, women had more nonobstructive (<50% DS) CAD (n = 208 [32.1%] vs. n = 354 [24.5%]; p = 0.0003) and lower rates of revascularization (n = 294 [31.4%] vs. n = 800 [36.2%]; p < 0.0001), unadjusted for DS or FFR_{CT} value. When assessed by FFR_{CT} positivity, a highly positive FFR_{CT} (≤0.75) showed no significant sex-based difference in revascularization rates (women, n = 253 [41.9%] vs. men, n = 715 [46.4%]; p = 0.06), (Supplemental Table 1, Figure 4). Several predictors of revascularization were identified on logistic regression, including DS, FFR_{CT}, symptoms, and low V/M. Female sex did not reduce the likelihood of revascularization when all of these factors were modelled (Table 4).

DISCUSSION

In this study of stable CAD patients being investigated with CCTA and FFR_{CT} we found several important sex-related differences. Women have an inherently higher FFR_{CT} independent of anatomical DS and are less likely to have obstructive CAD at ICA and receive revascularization. The relatively lower myocardial mass to coronary volume in women results in a higher V/M and FFR_{CT} compared to men. This difference in sex-specific FFR_{CT} and V/M ratio offers a new insight that may help to determine appropriate treatment for women with CAD on CCTA (Central Illustration).



Women have worse outcomes in the instance of established CAD such as angina or after myocardial infarction (3) and are consistently underdiagnosed and undermanaged compared to men (4,18). This variation has remained challenging to counter due to inherent difficulties in establishing the best diagnostic test, as key trials have often experienced a gender imbalance with no male comparator (19). The ADVANCE registry assesses the utility of a CCTA and FFR_{CT} diagnostic strategy in a real-world, unselected patient population across different countries, ethnicities, and sexes. The patient cohort was representative of a balanced stable CAD population, one-third of who were female. Women were older and had greater cardiovascular risk factors (hypertension and hypercholesterolemia), but they presented more frequently with atypical symptoms and had lower cardiovascular disease (CVD) risk scores. Despite the atypical presentation and underestimation of CVD risk models for women, the guidelines recommend a pre-test CVD likelihood stratification before deciding upon a test strategy and have no sex-specific guidance as to which test is preferable (6). Women are less able to achieve maximal exercise capacity and have reduced diagnostic accuracy for common investigations such as single-photon emission computed tomography (20,21). This has been somewhat offset by newer techniques such as cardiac magnetic resonance stress perfusion imaging, but significantly different disease prevalence between sexes in the study populations limits their generalizability (8,22).

ADVANCE is unique in that it only selected patients with evidence of CAD, enabling a more balanced disease prevalence model between the sexes. Similar to other ischemic heart disease and CCTA studies, women had a lower incidence of obstructive (≥50% DS) or multivessel CAD on CCTA (18,23). FFR_{CT} has been shown to improve diagnostic accuracy and discrimination of ischemia between the sexes versus other noninvasive imaging strategies (10,12,13). As may be expected in instances of lower disease severity, the FFR_{CT} was on average significantly higher in women, but importantly the proportion of FFR_{CT}-positive stenoses in the moderate (50% to 69%) to severe (70% to 90%) range was also lower in women compared to men. These results in noninvasive FFR_{CT} are almost identical to those of the invasive FAME

TABLE 4 Predictors of Revascularization

	Estimate (SE)	Odds Ratio (95% CI)	p Value
Intercept revascularization	4.7014 (0.38)		<0.0001
Overall stenosis ≥50	0.7347 (0.10)	4.3465 (2.91–6.49)	<0.0001
Overall stenosis ≥70	0.5345 (0.06)	2.9127 (2.35–3.62)	<0.0001
FFR _{CT}	-7.0911 (0.47)	0.0008 (0.0003–0.002)	<0.0001
≥2 vessel disease	0.0923 (0.06)	1.2026 (0.96–1.49)	0.0986
Symptoms	0.2316 (0.06)	1.5891 (1.26–2.00)	<0.0001
Volume/myocardial mass ratio	-0.0517 (0.01)	0.9496 (0.93–0.96)	<0.0001
Female	-0.060 (0.05)	0.887 (0.71–1.10)	0.284

Logistic regression. Reference categories are: male; overall stenosis <50; <2 VD; FFR_{CT} was modelled as a continuous variable. Abbreviations as in Tables 2 and 3.



(Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy (24).

Explanations for observed sex differences in the physiology of moderate to severe stenosis include a blunted coronary vasodilator response in postmenopausal women, secondary to reduced estrogen, nitric oxide, and endothelial dysfunction (19). This may explain the lower absolute coronary volume observed in women from our study despite fewer obstructive lesions. Alternatively, it may be a surrogate for overall plaque burden or simply reflect females' typically smaller body surface area.

In contrast to other noninvasive, non-CCTA studies, our results show in the instance of a

positive test (FFR_{CT}) that women have similar rates of referral to ICA. This observation is similar to the recently published SCOTHEART (Scottish Computed Tomography of the Heart Trial) sex associations data (23) as the ability to visualize CAD on CCTA reduces sex-based concerns over false-negative results (small hearts, reduced spatial resolution, and reduced exercise capacity) observed in other noninvasive tests (25,26). SCOTHEART also showed CCTA to have a higher rate of false-positive results compared to physiological (predominantly exercise) testing. Similarly, in our study females were less likely to have anatomical obstructive stenosis at ICA and be revascularized. Unique to this study, we have been able to

are associated with increased likelihood of revascularization independent of patient sex. These findings suggest the relationship between DS and physiological significance differs between men and women and that these differences may influence patient management decisions, treatment strategies, and clinical outcomes.

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ADDRESS FOR CORRESPONDENCE: Dr. Timothy A. Fairbairn, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool, United Kingdom. E-mail: timothy.fairbairn@lhch.nhs.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Women are less likely to have a positive FFR_{CT} (≤ 0.80) compared to men for an anatomically obstructive ($>50\%$ degree) stenosis. Following a positive FFR_{CT} women, are equally likely to be referred for invasive angiography at 54.5% versus 56.5%, but have a lower rate of revascularization at 31.4% versus 36.2% due to a lower incidence of obstructive stenosis and higher V/M ratio. Coronary V/M ratio provides a novel mechanistic explanation for sex-based differences in FFR_{CT} and eventual revascularization. When adjusted for the level of FFR_{CT} positivity (≤ 0.75) and coronary V/M no difference in revascularization rates existed at 41.9% versus 46.4%.

TRANSLATIONAL OUTLOOK: Further studies are required to explore the relationship of coronary V/M to myocardial ischemia and predicting revascularization in different populations. Smoking, diabetes, and hypertension are all risk factors that may impact either coronary volume or myocardial mass and may thus influence the likelihood of a positive FFR_{CT} and eventual management decisions for MT, percutaneous intervention, or CABG.

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KEY WORDS coronary computed tomography angiography, coronary volume/mass, fractional flow reserve derived from computed tomography, sex

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