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ORIGINAL RESEARCH

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

## Lessons From ADVANCE

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## 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 $FFR_{CT} \leq 0.80$ for the same degree stenosis ($p < 0.0001$). A positive $FFR_{CT} \leq 0.80$ 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 $mm^3$/g vs. 24.76 ± 7.22 $mm^3$/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/).

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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.

**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

## 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

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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 Author Center.

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**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 ($mm^3$) 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 redetermine 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 | (n = 1,049) | (n = 2,061) | (N = 3,110)* | |
| $FFR_{CT}$ | 0.75 ± 0.11 | 0.72 ± 0.11 | 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 | |

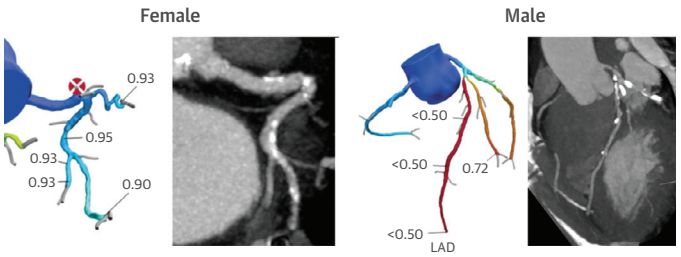
Values are n (%) or mean ± SD. Tests of general association were performed using chi square tests for categorical variables. *The coronary volume and myocardial mass is based on a smaller subpopulation.

$FFR_{CT}$ = 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.

**FIGURE 1 Anatomical Stenosis Severity and $FFR_{CT}$ in Women and Men**




Severe anatomical stenosis (>70%) in a male and female with the male having a positive $FFR_{CT}$ and the female having a negative $FFR_{CT}$ ($FFR_{CT}$ = fractional flow reserve derived from computed tomography).

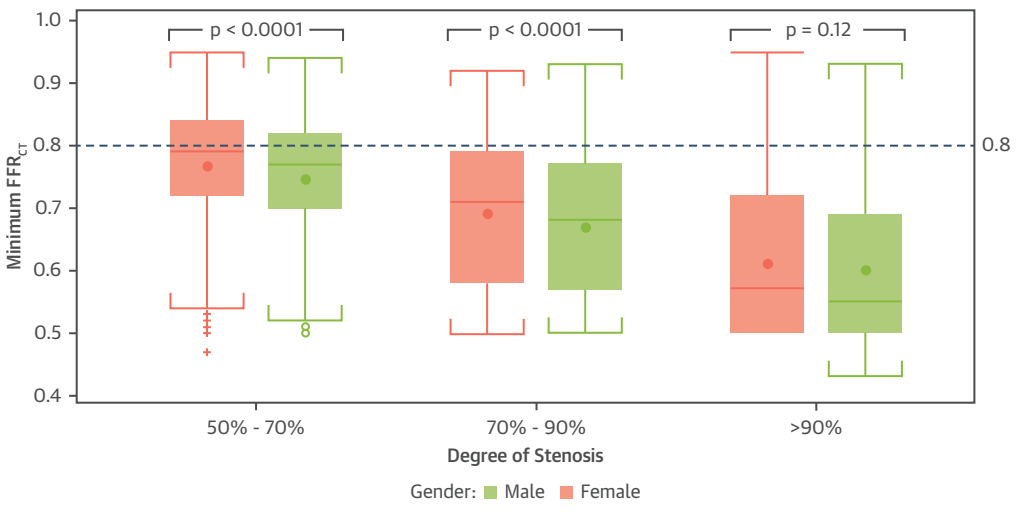
## RESULTS

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.

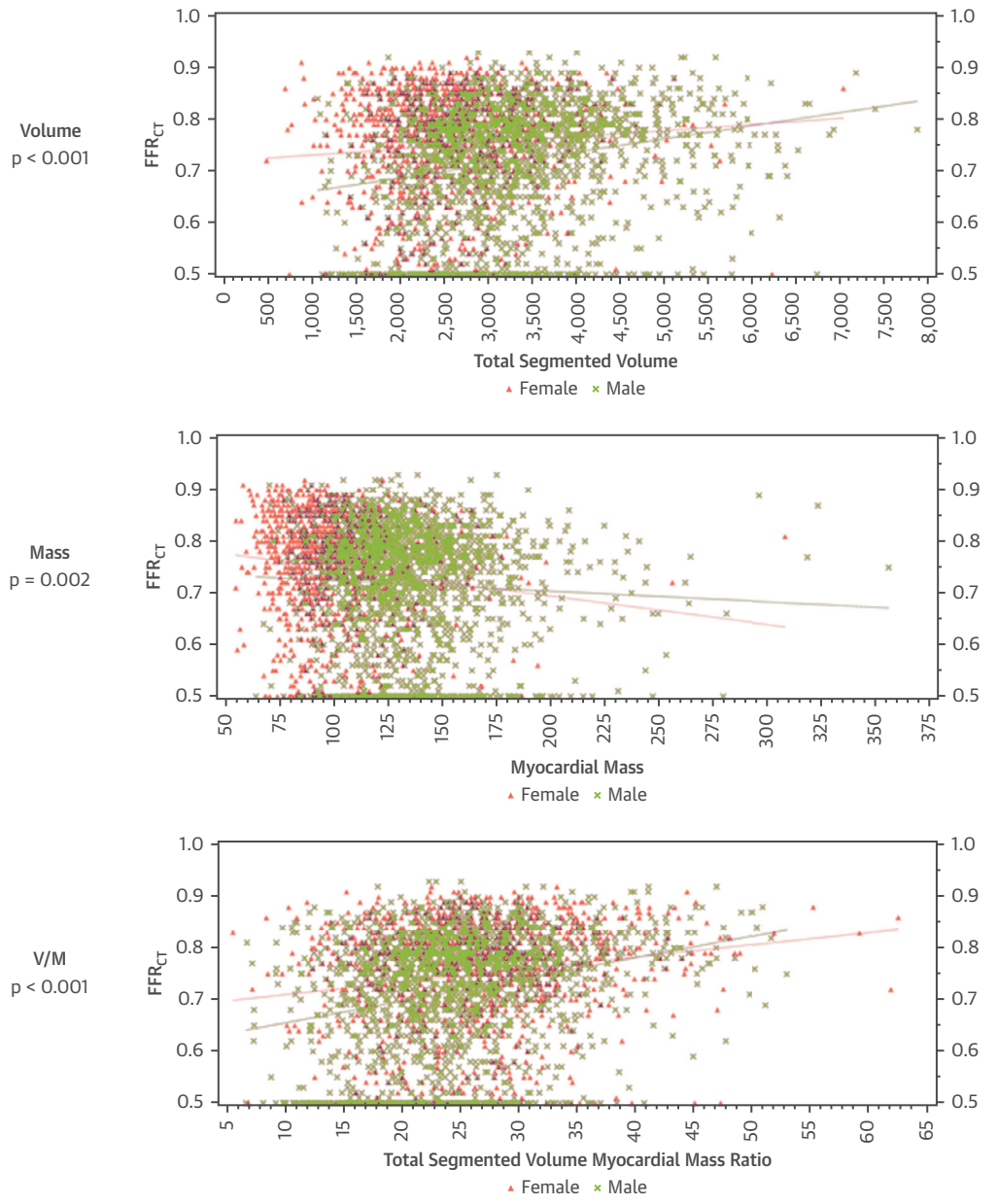
**CAD ON CCTA.** Women had smaller coronary arteries by volume but less anatomically obstructive (≥50% DS) CAD (65.4% vs. 74.7%; p < 0.0001) and severe (≥70% DS) CAD (27.1% vs. 34.9%; p < 0.001) than men. Rates of single-vessel obstructive CAD was similar between the sexes (female, 43% vs. male, 44.6%; 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 2 $FFR_{CT}$ Values According to CCTA Stenosis Severity**




Box-plot relationship of anatomical degree stenosis and $FFR_{CT}$ values for men and women in obstructive CAD categories. Outliers identified as **red** for females and **green** for males. These are displayed only if any observations fall below the lower/upper fence. Median = central line; Mean = central dot. CAD = coronary artery disease; CCTA = coronary computed tomography angiography; $FFR_{CT}$ = fractional flow reserve derived from computed tomography.

**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 ($0.76 \pm 0.12$ vs. $0.73 \pm 0.12$; $p < 0.0001$) and per-vessel basis (LAD, $0.78 \pm 0.11$ vs. $0.75 \pm 0.11$; LCx, $0.87 \pm 0.09$ vs. $0.84 \pm 0.11$; and RCA, $0.85 \pm 0.10$ vs. $0.84 \pm 0.11$; 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 $mm^3$ vs. 3,225.8 ± 977.4 $mm^3$; 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 $mm^3$/g vs. 24.76 ± 7.22 $mm^3$/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).

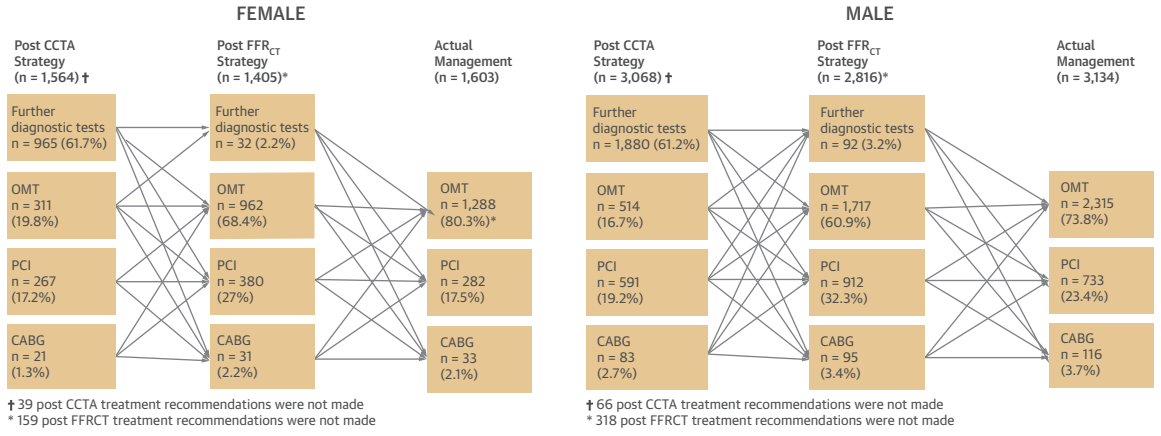
**RECOMMENDED CLINICAL MANAGEMENT STRATEGIES AND RECLASSIFICATION FOLLOWING CCTA AND $FFR_{CT}$.** The reclassification of recommended management did not differ by sex (women = 63.13 [95% CI: 60.51 to 65.69]; men = 63.74 [95% CI: 61.91 to 65.53]; p = 0.70). Women were more frequently recommended for 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).

**FIGURE 4** Reclassification of Patient Management Following CCTA Alone, Post-$FFR_{CT}$ and Actual Management at 90 Days by Sex




Female: 39 post-CCTA treatment recommendations were not made; *159 post-$FFR_{CT}$ treatment recommendations were not made. Male: 66 post-CCTA treatment recommendations were not made; *318 post-$FFR_{CT}$ treatment recommendations were not made. CABG = coronary artery bypass graft; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; other abbreviations as in Figures 1 and 2.

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

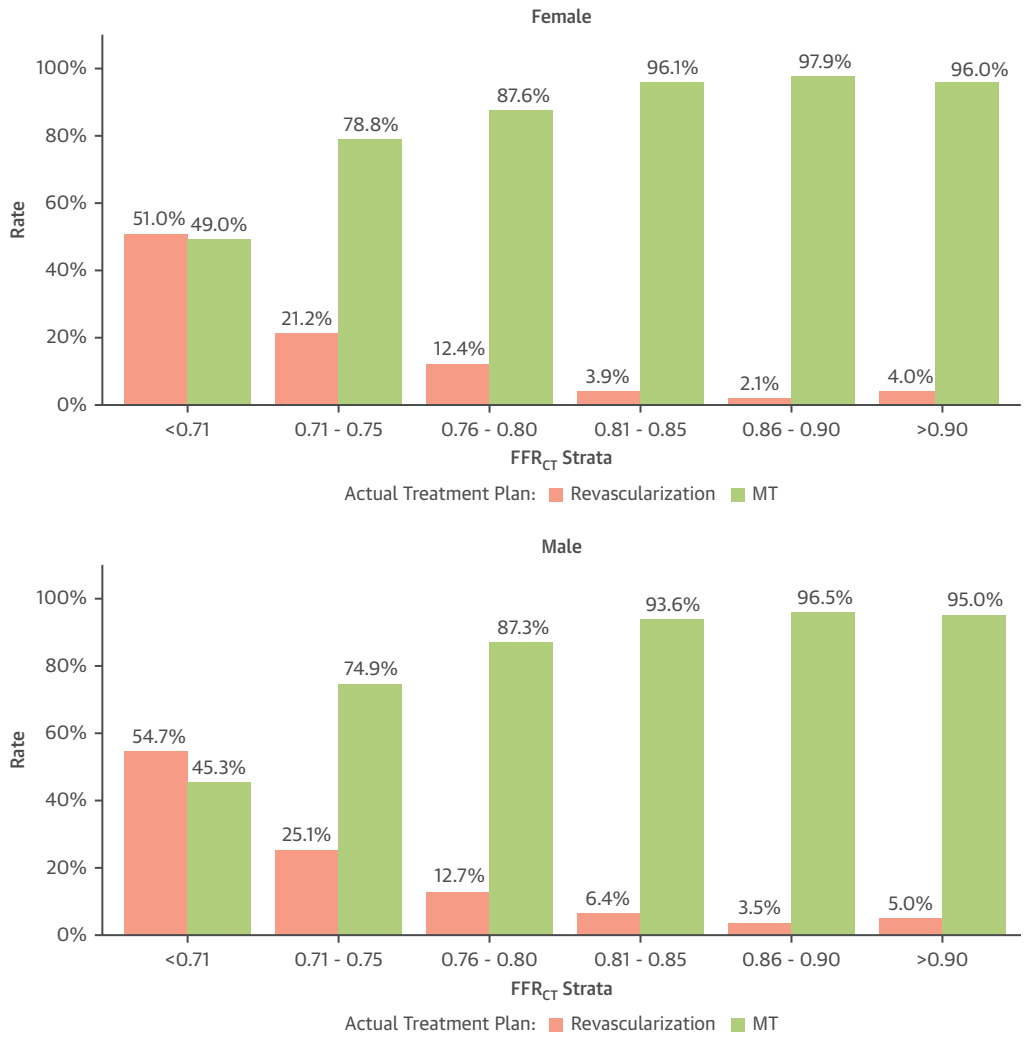
**TABLE 4** Predictors of Revascularization

| | 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.

**FIGURE 5** Actual Management Strategy (MT or Revascularization [CABG and PCI]) per $FFR_{CT}$




Actual management was subcategorized according to 0.05 increments in $FFR_{CT}$ strata. MT = medical treatment; other abbreviations as in Figures 1 and 4.

(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

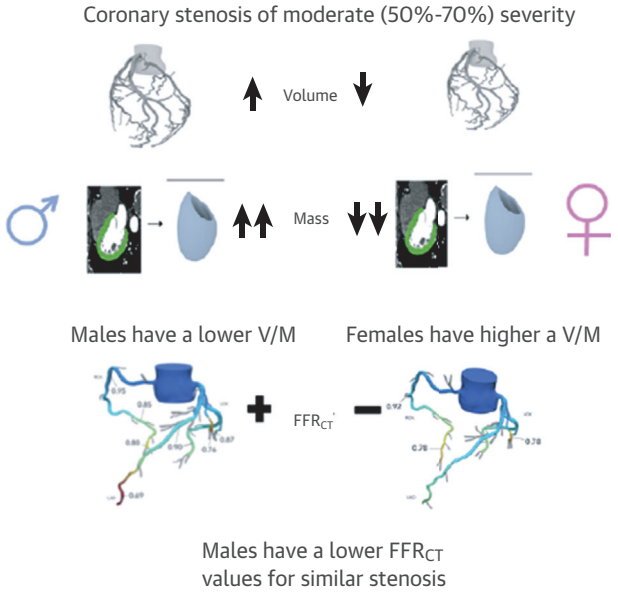
explore sex differences in coronary volume and mass. A strong relationship exists between coronary volume, myocardial mass, and V/M to $FFR_{CT}$ for both sexes. A weak correlation has been shown to exist between V/M and myocardial blood flow in obstructive CAD and a stronger relationship to invasive FFR (27). Our results emphasize that the higher V/M in women predicts reduced likelihood of revascularization independent of the $FFR_{CT}$ value or DS.

The knowledge that women have a higher intrinsic FFR value requiring special consideration and interpretation has been well described in the invasive literature, leading to suggestions that decisions of revascularization need to be nuanced and multifaceted rather than using dichotomous cutoffs for invasive FFR or noninvasive $FFR_{CT}$ (17,25,28). This balanced judgement does appear to have occurred in this study, as an incrementally positive $FFR_{CT}$ increased the likelihood of revascularization in both sexes and when the degree of ischemia was outside of the grey-zone (<0.75) there was no difference in revascularization rates between men and women. A conservative management approach in the grey zone has been shown to be reasonable, as revascularization has not been shown to have better outcomes in this group (29).

Our observation that women have a higher V/M ratio independent of stenosis severity and that this is associated with reduced revascularization at ICA may help the complex decision-making processes of when and who to refer for revascularization. Once all factors such as DS, $FFR_{CT}$, V/M, and symptoms were considered, female sex was no longer a determinant of revascularization. The longer-term consequences of a higher deferral rate to MT in $FFR_{CT}$-positive women will have to be determined in the future, as retrospective observational data from Denmark suggests this subgroup may have a long-term increased risk of nonfatal MI (30).

**STUDY LIMITATIONS.** This study was a real-world registry study; therefore, patient selection bias cannot be fully accounted for. A small percentage of patients' data was either not sent for analysis or was unanalyzable. However, there was no difference between these patients' demographics and those of the final population. As a post hoc analysis of the ADVANCE study, in only 3,110 of 4,737 studies was it possible to calculate the V/M due to software development processes during the study period. Unfortunately, given the pragmatic large-scale nature of this registry, quantified plaque volume measures are not available for evaluation and as such we cannot comment on potential differences between men and women regarding atheroma volume nor any potential impact on $FFR_{CT}$. In addition, coronary calcification scores were not mandated before CCTA thus limiting our ability to compare calcium burden between the sexes and any impact on stenosis assessment, $FFR_{CT}$, and future management. There was no mandate to perform invasive FFR at time of ICA, thus limiting comparisons between noninvasive and invasive management decisions. Net reclassification primarily occurs from more information to medical treatment, which may be expected following the provision of a functional test result. Endpoints other than reclassification are secondary and should be interpreted accordingly.

**CENTRAL ILLUSTRATION Sex Differences in Coronary Lumen Volume, Myocardial Mass, and Fractional Flow Reserve Derived From Computed Tomography**




**Fairbairn, T.A. et al. J Am Coll Cardiol Img. 2020;13(12):2576–87.**

Females have a lower coronary volume and lower myocardial mass, but higher volume to mass (V/M) ratio for the same degree coronary stenosis. This is associated with a higher $FFR_{CT}$ value and reduced likelihood of revascularization. $FFR_{CT}$ = fractional flow reserve derived from computed tomography.

## CONCLUSIONS

$FFR_{CT}$ shows sex variations with a higher $FFR_{CT}$ for the same degree of stenosis in women. In $FFR_{CT}$-positive CAD, women have similar rates of ICA to males but less obstructive CAD and revascularization at catheterization. Lower $FFR_{CT}$ value and V/M ratio

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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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## AUTHOR DISCLOSURES

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## 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.