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ORIGINAL RESEARCH

Sex Differences in Computed Tomography Coronary Stenosis Severity Versus Flow Impairment and Impact on Revascularization, Clinical Events and Health Care Costs: A FORECAST Substudy

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BACKGROUND: The impact of sex-related differences in coronary atheroma and flow impairment severity on clinical events and costs remains unclear.

METHODS AND RESULTS: This is a secondary analysis of patients with stable coronary artery disease who underwent both coronary computed tomography angiography and fractional flow reserve derived from computed tomography as part of the FORECAST (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain) trial, investigating (1) the relationship between coronary stenosis severity on coronary computed tomography angiography and fractional flow reserve derived from computed tomography FFR_{CT} by sex and (2) the association with revascularization, resource usage, and adverse clinical events. A total of 212 patients (64 female participants [32.1%]) and 1245 vessels were included. There was no significant sex difference in the frequencies of significant coronary artery disease (38.2% of women versus 51.3% of men; *P*=0.073), but female participants had significantly less coronary flow impairment, according to the presence of at least 1 fractional flow reserve derived from computed tomography≤0.8 (47.0% versus 71.5%; *P*=0.008). Female subjects underwent fewer revascularization procedures (23.5% versus 42.3%; *P*=0.014), less coronary artery bypass graft surgery (2.9% versus 13.1%; *P*=0.025) and were less likely to be on statin treatment (72.0% versus 84.7%; *P*=0.022) by 9-month follow-up. This resulted in lower overall health care costs for female participants compared with male counterparts (median total cost, £1276 versus £2051; *P*=0.014). In multivariable Cox analysis the presence of significant coronary artery disease (hazard ratio [HR], 2.91; 95% CI, 1.30–6.51) and having a positive fractional flow reserve derived from computed tomography (HR, 4.11; 95% CI, 1.15–14.69) were independent predictors of major adverse cardiovascular events at 9 months, whereas sex was not statistically significant (*p*=0.13).

CONCLUSIONS: There are significant sex differences in the anatomico-functional assessment of coronary artery disease leading to differences in clinical management, costs, and adverse events.

Key Words: coronary artery disease ■ coronary computed tomography angiography ■ fractional flow reserve derived from computed tomography ■ major adverse cardiovascular events ■ revascularization ■ risk stratification ■ sex differences

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CLINICAL PERSPECTIVE

What Is New?

- The discordance between anatomic coronary artery disease severity via computed tomography and estimated flow impairment is more frequent in female compared with male subjects.
- By 9-month follow-up, despite having less revascularization and less optimal medical therapy, the overall rate of adverse events was lower in women with symptomatic coronary artery disease compared with their male counterparts.

What Are the Clinical Implications?

- As both the anatomic and functional severity of coronary artery disease are independent predictors of adverse outcomes, they should be used as complementary guides for deciding clinical management in both sexes.

Nonstandard Abbreviations and Acronyms

ADVANCE	Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care
DS	diameter stenosis
FFR	fractional flow reserve
FFR_{CT}	fractional flow reserve derived from computed tomography
FORECAST	Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain
ICA	invasive coronary angiography
ISCHEMIA	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
MACE	major adverse cardiovascular event
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
SCOT-HEART	Scottish Computed Tomography of the Heart

Cardiovascular disease remains the leading cause of death globally in both women and men and is responsible for the death of 35% of women.[1] Furthermore, the age-standardized prevalence of cardiovascular disease in women has remained static since 2010, with an estimated 272.5 million women having cardiovascular disease worldwide.[1] Ischemic heart disease, the most common type of cardiovascular disease in women,[1] is also the most significant cause of disability-adjusted life-year loss globally in 2019.[2] Moreover, women have a worse prognosis than men following a diagnosis of chronic or acute coronary syndromes.[3–6] These differences are likely to be multifactorial in origin, related to sex-specific differences in presentation, the underlying mechanism causing myocardial ischemia, and risk factor burden[7,8] but also variability in the rate of investigations requested, as well as pharmacological and revascularization therapies offered.[6,8,9]

Coronary computed tomography angiography (CCTA) is an increasingly widely used first-line imaging test for the assessment of patients with new-onset chest pain, and its accuracy appears to be similar in both men and women.[10] Current evidence demonstrates a prognostic benefit for the use of CCTA, derived from optimizing medical therapy in response to the detection of coronary atheroma.[11] Nevertheless, it is also increasingly recognized that ischemia with nonobstructed coronaries is more prevalent in women and is associated with poor prognosis.[1] Complementing the anatomic information derived from CCTA, fractional flow reserve derived from computed tomography (FFR_{CT}; HeartFlow, Mountain View, CA) uses computational fluid dynamics to model flow impairment in coronary arteries. FFR_{CT} has been validated against invasive coronary angiography (ICA) and fractional flow reserve (FFR) and has a large body of evidence showing clinical utility and safety.[12–16] Moreover, the addition of FFR_{CT} is proven to improve the accuracy and discriminatory ability for detecting ischemia compared with CCTA alone.[17,18]

Observational data suggest that both the coronary stenosis severity and distribution on CCTA and the impairment in coronary flow via FFR_{CT} are associated with adverse clinical events.[19–21] However, the relationship between these parameters and their relative prognostic value remains unclear. Recent data suggests there are significant sex-differences, with (1) higher observed FFR_{CT} values for the same degree of coronary stenosis severity in women and (2) lower rates of revascularization in women with positive FFR_{CT}.[22]

The aim of this study was to describe sex-related differences in coronary stenosis severity and FFR_{CT}, and their relationship with (1) use of invasive coronary angiography and revascularization, (2) rate of clinical events, and (3) overall cardiac costs in a cohort of patients with new-onset chest pain who underwent both CCTA and FFR_{CT}.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Population

This analysis is a substudy of the FORECAST (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain; NCT03187639) trial, including only the patients who underwent both CCTA and FFR_{CT}. The FORECAST trial has been reported previously in detail.[15,23] Briefly, FORECAST was a multicenter trial that prospectively enrolled 1400 stable patients with chest pain who were randomized to an initial testing pathway using CCTA and selective FFR_{CT} (experimental group) or to the standard care pathway (standard group). Despite a significant reduction in the usage of ICA, there were no significant differences in clinical events and overall costs between the CCTA/FFR_{CT} pathway and standard care.[15] The trial received full ethical approval (REC Reference 18/SC/0490, IRAS Project ID: 231037), and all patients provided informed consent.

Of the 700 patients randomized to the FORECAST experimental group, 254 (38%) patients met the criteria for FFR_{CT} analysis (≥40% stenosis in at least 1 epicardial coronary artery), with an additional 5 patients also being referred for FFR_{CT} (without meeting protocol criteria). Forty-seven patients were excluded due to missing FFR_{CT}, either because FFR_{CT} could not be computed (39 patients) or failure to retrieve FFR_{CT} data due to technical issues (8 patients). In summary, this analysis includes 212 patients with complete CCTA and FFR_{CT} data and a total of 1245 vessels with matched CCTA data and distal FFR_{CT} (Figure 1).

Data Acquisition

As per the FORECAST trial methodology,[15,23] the coronary stenosis distribution and severity was determined at site level and recorded in the electronic Case Report Form, from which it was then extracted for this analysis. Significant coronary artery disease (CAD) is defined as any luminal diameter stenosis (DS) ≥70% for non–left main stem coronary arteries or ≥50% for lesions involving the left main stem. Obstructive CAD is defined as ≥50% luminal DS in any epicardial coronary. For this analysis, 2 cardiologists (L.G., M.K.), blinded to other patient-specific details and to each other's opinion, reviewed all the FFR_{CT} data. The FFR_{CT} was measured within the distal third of all coronary arteries of a diameter suitable for revascularization (at a similar site where invasive FFR would be measured in clinical practice), as per the trial protocol.[15,23]

Invasive Procedures, Clinical Events, and Costs

Patients in the FORECAST trial were followed up for 9 months. Baseline characteristics (including biological sex: binary male/female), ICA, revascularization, resource usage, and clinical events were collected as per the trial protocol via direct patient contact by research

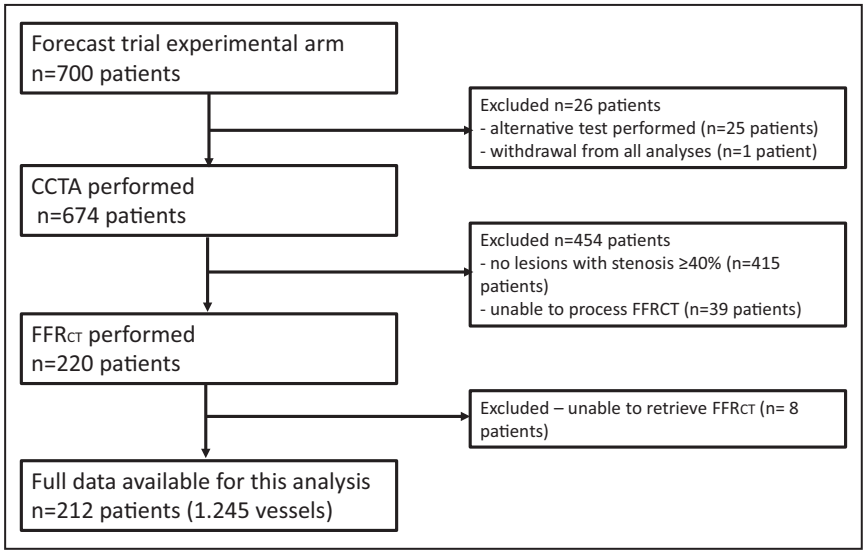

Figure 1. Flow diagram of patients included in FORECAST subanalysis.
CCTA indicates coronary computed tomography angiography; FFR_{CT}, fractional flow reserve derived from computed tomography; and FORECAST, Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain.

staff at each center, as well as from local health care records. Major adverse cardiovascular events (MACEs) were defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, and cardiovascular hospitalization. As per the FORECAST trial protocol, the total per-patient costs represented the sum of each individual prespecified resource used over the follow-up interval (investigation/procedure, hospital visit and/or admission, medication) weighted by UK tariffs.[15]

Statistical Analysis

Continuous data are presented as mean±SD or median (interquartile range [IQR]), as appropriate, depending on data distribution. Categorical data are presented as frequency and percentage. Characteristics were compared using the Student *t* test or Mann–Whitney *U* test as appropriate for continuous variables and Pearson χ^2 test or the Fisher exact test for discrete variables. Cumulative event rates were demonstrated using Kaplan–Meier survival curves and compared using the log-rank test. Univariable and multivariable Cox regression analysis was used to identify independent predictors of MACE by 9-month follow-up. Hazard ratio (HR) was assessed as an estimation of risk with 95% CI. Differences were considered statistically significant when the 2-sided *P* values were ≤0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows version 28 (IBM Corp., Armonk, NY) and RStudio (PBC, Boston, MA).

RESULTS

This analysis includes 212 eligible patients (Figure 1), of whom 144 (67.9%) were men and 68 (32.1%) women. The baseline demographics and risk factors by sex are well balanced, including the pretest CAD probability, with the single exception of age, women being significantly older (mean age, 67.0±8.0 years for female participants versus 64.0±9.0 years for male participants; p=0.007; Table 1).

Per-Patient Anatomico-Functional Assessment by Sex

In the overall cohort, 100 of 212 (47.1%) patients had significant CAD (defined as at least 1 epicardial coronary lesion with DS ≥70% or left main stem lesion with DS ≥50%) and 139 (65.6%) patients had at least 1 positive FFR_{CT} value (≤0.8). The distribution and severity of luminal coronary stenosis was similar in both sexes, except for the presence of nonobstructive CAD (DS <50%), which was more frequent in female subjects (Table 2). However, there was a higher prevalence of coronary flow impairment in men according to the proportion of patients having at least 1 FFR_{CT} ≤0.8 (71.5% of male versus 47.0% of female subjects; p=0.008) and also by the lowest per-patient FFR_{CT} and distal left anterior descendant artery FFR_{CT}, both being lower in male compared with female participants (Table 2).

Per-Vessel Anatomico-Functional Assessment by Sex

The per-vessel analysis included 1245 vessels (384 vessels in women and 861 vessels in men) with matched-vessel maximal luminal stenosis severity and distal FFR_{CT} values. Overall, 395 of 1245 (31.7%) of the vessels analyzed had a positive FFR_{CT}, 89 of 384 vessels (23.1%) in the female subjects compared with 309 of 861 vessels (39.5%) in male subjects (p<0.001). The overall median FFR_{CT} was 0.86 (IQR, 0.77–0.91).

Table 1. Baseline Characteristics Per Sex Group

Characteristic	Female group (n=68 patients)	Male group (n=144 patients)	Total (n=212 patients)
Age, mean±SD*	67.0±8.0	64.0±9.0	64.9±9.3
BMI, mean±SD*	30.3±6.2	28.7±5.2	29.3±5.6
Smoking status, n (%)†			
Current smoker	4 (5.8)	19 (13.1)	23 (10.8)
Former smoker	32 (47.1)	60 (41.6)	92 (43.4)
Never smoked	32 (47.1)	65 (45.1)	97 (45.8)
Diabetes, n (%)†	8 (11.7)	26 (18.0)	34 (16.0)
Treated hypertension, n (%)†	33 (48.5)	76 (52.7)	109 (51.4)
Treated hyperlipidemia, n (%)†	27 (39.7)	65 (45.1)	92 (43.3)
Renal impairment, n (%)†	3 (4.4)	0 (0.0)	3 (1.4)
Family history of CAD, n (%)†	47 (68.7)	79 (54.2)	126 (59.4)
Diamond–Forrester, mean±SD*	39.4±33.2	48.2±31.6	45.5±32.3
Seattle Angina Questionnaire, mean±SD*	59.6±11.7	63.9±17.2	62.5±17.5

BMI indicates body mass index; and CAD, coronary artery disease.
*Mean values and SDs per each group.
†Number of patients and percentages per each group.

Although the median FFR_{CT} was above the conventionally accepted threshold for clinically important flow impairment (≤0.8) in both sexes, the observed values were higher in female (median FFR_{CT}, 0.88 [IQR, 0.81–0.92]) compared with male participants (median FFR_{CT}, 0.85 [IQR, 0.75–0.91]; $p<0.001$; Figure 2 and Table 3).

In the overall cohort, significant flow impairment by FFR_{CT} (cutoff ≤0.8) was discordant to anatomically significant CAD in 237 of 1245 (19.0%) of vessels, with 44 (3.5%) vessels having significant CAD but negative distal FFR_{CT} (>0.8) and 193 of 1245 (15.5%) vessels having positive FFR_{CT} (≤0.8) despite nonsignificant CAD (Figure 3). This anatomico-functional discordance was observed significantly less frequently in female subjects (60/384; 15.6% of vessels) compared with males (177/861; 20.5% vessels; $p=0.04$). Moreover, within the group of anatomically obstructive CAD 42% (50/118) of vessels in female participants and 26% (85/316) of vessels in male participants had negative distal vessel FFR_{CT}.

Invasive Angiography and Revascularization

By 9-month follow-up, 102 (48.1%) patients had at least 1 ICA, and 11 (5.2%) patients had multiple ICAs; 77 (36.3%) patients were revascularized, 56 (26.4%) by percutaneous coronary intervention and 21 (9.9%) by coronary artery bypass graft surgery (CABG). There was no significant difference in the overall rate of ICA by sex, with 28 of 68 (41.1%) female participants and 74 of 144 (51.3%) male participants undergoing at least 1 ICA within the 9-month follow-up. However, there was a significantly lower rate of revascularization in female compared with male subjects (23.5% versus 42.3%; $p=0.008$), with an ICA-to-revascularization ratio of 1.7:1 in female subjects and 1.2:1 in male subjects. This difference was mainly driven by a significantly lower rate of CABG in female patients (2.9% versus 13.1%; $p=0.025$), while the

Table 2. Per-Patient Summary of Anatomic Coronary Luminal Stenosis Severity and Lowest Distal FFR_{CT} by Sex Category

Per-patient characteristics	Female group (n=68)	Male group (n=144)	Total (n=212)	*P* value†
CAD severity (any vessel DS ≥50%), n (%)*				Overall 0.08
3 vessels	5 (7.3)	23 (15.9)	28 (13.2)	
2 vessels	13 (19.1)	32 (22.2)	45 (21.2)	0.08
1 vessel	22 (32.3)	52 (36.1)	74 (34.9)	
No DS >50%	28 (41.1)	37 (25.6)	65 (30.7)	0.02
Significant CAD (DS >70% and/or LMS DS >50%), n (%)*				Overall 0.14
3 vessels	2 (2.9)	14 (9.7)	16 (7.5)	0.08
2 vessels	7 (10.2)	23 (15.9)	30 (14.2)	
1 vessel	17 (25.0)	37 (25.6)	54 (25.5)	
No significant CAD	42 (61.7)	70 (48.6)	112 (52.8)	0.07
LMS DS >50%, n (%)*	1 (1.4)	9 (6.2)	10 (4.7)	0.12
LAD DS >50%, n (%)*	35 (51.4)	87 (60.4)	122 (57.5)	0.19
CX DS >50%, n (%)*	12 (17.6)	35 (24.3)	47 (22.1)	0.25
RCA DS >50%, n (%)*	19 (27.9)	50 (34.7)	69 (32.5)	0.30
Any DS >50%, n (%)*	40 (58.8)	107 (74.3)	147 (69.3)	0.02
Any DS >70% and/or LMS DS >50%, n (%)*	26 (38.2)	74 (51.3)	97 (46.8)	0.07
Positive FFR_{CT} (≤0.8), n (%)*	32 (47.0)	103 (71.5)	119 (57.4)	0.01
Lowest per-patient FFR_{CT}, median (IQR)	0.80 (0.55–0.86)	0.71 (0.50–0.82)	0.74 (0.50–0.83)	0.01
Main coronary vessel distal FFR_{CT}, median (IQR)				
LAD	0.80 (0.75–0.89)	0.78 (0.68–0.84)	0.80 (0.69–0.86)	0.01
CX	0.89 (0.84–0.93)	0.86 (0.79–0.81)	0.87 (0.80–0.92)	0.17
RCA	0.90 (0.87–0.93)	0.90 (0.82–0.93)	0.90 (0.85–0.93)	0.27

CAD indicates coronary artery disease; CX, circumflex artery; DS, luminal diameter stenosis; FFR_{CT}, fractional flow reserve derived from computed tomography; IQR, interquartile range; LAD, left anterior descendent artery; LMS, left main stem; and RCA, right coronary artery.

*Number of patients and percentage within each group.

†Difference between male and female groups for continuous variables were tested using a Student *t* test for normally distributed variables and a Mann–Whitney *U* test as appropriate for nonnormally distributed variables; tests of general association were performed using a χ^2 test or Fisher exact test, as appropriate, for categorical variables.

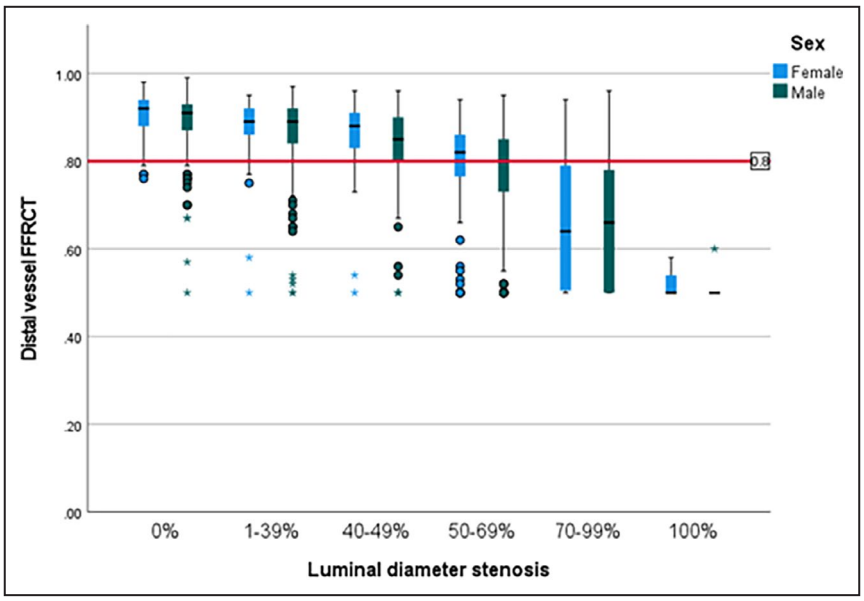

Figure 2. Box plot of vessel FFR_{CT} by stenosis severity category, stratified by sex.
The horizontal red line represents the cut-off point of FFR_{CT} for significant flow impairment (≤0.80). FFR_{CT} indicates fractional flow reserve derived from computed tomography.

rates of percutaneous coronary intervention were similar (20.5% in women versus 29.5% in men; p=0.5; Table S1).

Furthermore, upon dividing the cohort by FFR_{CT} intervals (Table 4 and Figure S1), there were significantly lower rates of revascularization in female participants with severe flow impairment (FFR_{CT}, 0.50–0.55), with only 47% of female subjects in this group undergoing revascularization compared with 78% of men within the same category (p=0.014), despite similar rates of ICA in this subgroup (100% of female group versus 88% of male group; p=0.32). Conversely, none of the patients with FFR_{CT} >0.8 underwent revascularization, despite 1 female (3.1%) and 2 male patients (6.4%) without a positive FFR_{CT} (FFR_{CT} ≤0.8) undergoing ICA.

Medical Therapy

Medical therapy at baseline was similar by sex. However, at 9-month follow-up, fewer female subjects were receiving statin therapy (72% versus 84%; p=0.022) or an angiotensin-converting enzyme inhibitor (20.5% versus 40.2%; p=0.004) compared with their male counterparts (Table 5). Importantly, the sex differences in medication use were observed in patients with anatomically significant CAD (Tables S2 and

Table 3. Proportion of Positive FFR_{CT} and Median FFR_{CT} per Stenosis Severity Category, Stratified by Sex

Stenosis severity strata (DS%)	Per-vessel FFR_{CT} positive (≤0.8), n*/n† (%)			P value‡	Median FFR_{CT} (IQR)§			P value‖
	Female group (384 vessels)	Male group (861 vessels)	Total (1245 vessels)		Female group (384 vessels)	Male group (861 vessels)	Total (1245 vessels)	
0%	5/137 (3.6)	16/190 (8.4)	21/306 (6.4)	NA	0.92 (0.88–0.94)	0.91 (0.87–0.93)	0.91 (0.88–0.94)	NA
1%–39%	8/77 (10.3)	28/224 (12.5)	36/291 (12.0)	NA	0.89 (0.86–0.92)	0.89 (0.84–0.92)	0.89 (0.85–0.92)	NA
40%–49%	8/52 (15.3)	34/131 (25.9)	42/183 (23.0)	NA	0.88 (0.83–0.91)	0.85 (0.80–0.90)	0.86 (0.81–0.90)	NA
50%–69%	26/63 (41.2)	68/122 (55.7)	91/185 (50.8)	NA	0.82 (0.76–0.86)	0.80 (0.73–0.85)	0.80 (0.73–0.85)	NA
70%–99%	38/51 (74.5)	145/176 (82.3)	183/227 (80.6)	NA	0.64 (0.50–0.81)	0.66 (0.50–0.78)	0.65 (0.50–0.78)	NA
100% (occlusion)	4/4 (100)	18/18 (100)	22/22 (100.0)	NA	0.50 (0.50–0.54)	0.50 (0.50–0.50)	0.50 (0.50–0.50)	NA
Overall	89/384 (23.1)	309/861 (39.5)	398/1245 (31.9)	<0.001	0.88 (0.81–0.92)	0.85 (0.75–0.91)	0.86 (0.77–0.91)	<0.001

DS indicates luminal diameter stenosis; FFR_{CT}, fractional flow reserve derived from computed tomography; IQR, interquartile range; and NA, not applicable.
*Number of vessels with positive FFR_{CT} values (≤0.8).
†Number of vessels in each DS category.
‡χ^2 test or Fisher exact test, as appropriate.
§Median distal vessel FFR_{CT} (IQR) in each stenosis severity subgroup.
‖Mann–Whitney U test as appropriate for nonnormally distributed variables.

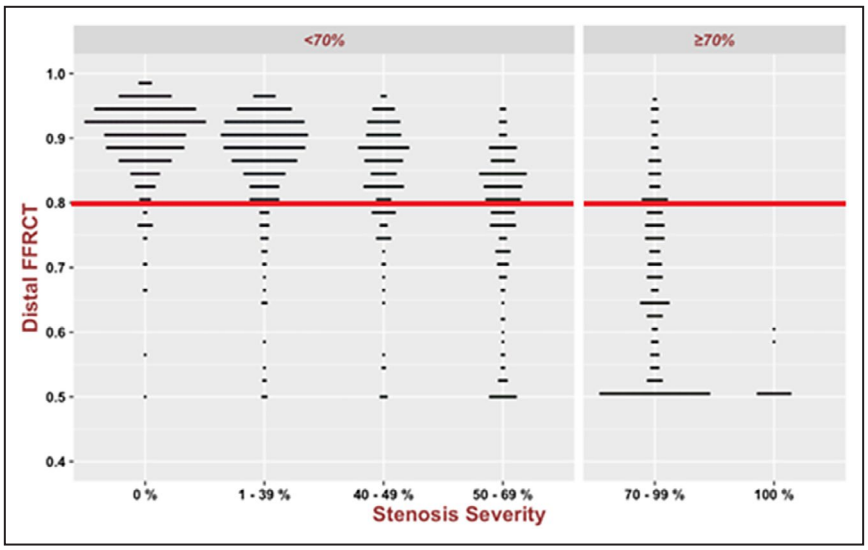

Figure 3. Line plot of distal FFR_{CT} by stenosis severity category (n=1245 vessels). The horizontal red line represents the cut-off point of FFR_{CT} for significant flow impairment (≤0.80). FFR_{CT} indicates fractional flow reserve derived from computed tomography.

S3). There was no significant difference by sex in the use of antiplatelet agents, β blockers, nitrates, or calcium channel blockers (Table 5).

Resource Usage by Total Cardiac Costs at 9-Month Follow-Up

By 9-month follow-up, the overall cardiac costs (calculated using UK tariffs) were significantly lower for female patients (median total cost, £1276 [IQR, £1121–£2724]) compared with male patients (median total costs, £2051 [IQR, £1137–£4386]; p=0.014; Figure S2). The initial cost was the same in both groups, since all patients had CCTA/FFR_{CT} as their first test. Hence, the cost difference resulted from the follow-up costs, with a median per-patient follow-up cost of £991 (IQR, £836–£2439) for female and £1766 (IQR, £852–£4101) for male subjects. This was driven mainly by the increased rates of CABG, as well as medication usage in the male group. Table S1 shows a detailed breakdown of resource usage by sex.

Table 4. Rates of ICA and Revascularization by FFR_{CT} Intervals, Stratified by Sex

FFR_{CT} strata	ICA			Revascularization		
	Female group (n=68 patients) ICA n*/n† (%)	Male group (n=144 patients) ICA n*/n† (%)	*P* value§	Female group (n=68 patients) revascularization n‡/n† (%)	Male group (n=144) revascularization n‡/n† (%)	*P* value§
0.50–0.55	17/17 (100.0)	45/51 (88.2)	0.32	8/17 (47.0)	40/51 (78.4)	0.01
0.56–0.60	1/1 (100.0)	4/4 (100)	NA	1/1 (100.0)	4/4 (100.0)	NA
0.61–0.65	4/4 (100.0)	4/6 (66.6)	NS	4/4 (100.0)	3/6 (50.0)	NS
0.66–0.70	0/1 (0.0)	7/8 (87.5)	NS	0/1 (0.0)	5/8 (62.5)	NS
0.71–0.75	3/4 (75.0)	7/16 (43.7)	NS	2/4 (50.0)	4/16 (25.0)	NS
0.76–0.80	2/9 (22.2)	5/18 (27.7)	NS	1/9 (11.1)	5/18 (27.7)	NS
0.81–0.85	0/15 (0.0)	1/29 (3.4)	NS	0/15 (0.0)	0/29 (0.0)	NA
0.86–0.90	1/15 (6.6)	1/12 (8.3)	NS	0/15 (0.0)	0/12 (0.0)	NA
0.91–0.95	0/2 (0.0)	0/0	NA	0/2 (0.0)	0/0	NA
0.96–1.00	0/0	0/0	NA	0/0	0/0	NA
Overall	28/68 (41.1)	74/144 (51.3)	0.16	16/67 (23.5)	61/144 (42.3)	0.01

FFR_{CT} indicates fractional flow reserve derived from computed tomography; ICA, invasive coronary angiography; NA, not applicable due to 0 patients included; and NS, not significant.

*Number of patients undergoing ICA within each FFR_{CT} strata.

†Number of female patients within each strata.

‡Number of patients undergoing revascularization within each FFRCT strata.

§χ^2 test or Fisher exact test, as appropriate.

Table 5. Medication at Baseline and 9-Month Follow-Up Stratified by Sex

Medication	Baseline			9-month follow-up		
	female group (n=68 patients)	Male group (n=144 patients)	*P* value†	Female group (n=68 patients)	Male group (n=144 patients)	*P* value†
Aspirin, n(%)*	26 (38.2)	52 (36.1)	NS	46 (67.6)	111 (77.0)	NS
P2Y12 inhibitors, n (%)*						
Clopidogrel	4 (5.8)	7 (4.8)	NS	16 (23.5)	41 (28.4)	NS
Prasugrel	0 (0.0)	0 (0.0)		0 (0.0)	1 (0.6)	
Ticagrelor	1 (1.4)	1 (0.6)		0 (0.0)	3 (2.0)	
β blocker, n (%)*	10 (14.7)	15 (9.7)	NS	28 (41.1)	73 (50.6)	NS
Calcium channel blocker, n (%)*	14 (20.5)	45 (31.2)	NS	20 (29.4)	52 (36.1)	NS
Statin, n(%)*	28 (41.1)	65 (45.1)	NS	49 (72.0)	122 (84.7)	0.02
Other cholesterol-lowering medication, n (%)*	2 (2.9)	0 (0.0)	NA	2 (2.9)	1 (0.6)	NS
ACE inhibitor, n (%)*	12 (17.6)	35 (24.3)	NS	14 (20.5)	58 (40.2)	0.01
ARB, n (%)*	9 (13.2)	15 (10.4)	NS	7 (10.2)	14 (9.7)	NS
GTN spray, n (%)*	29 (42.6)	45 (31.2)	NS	26 (38.2)	51 (35.4)	NS
Oral nitrate, n (%)*	2 (2.9)	3 (2.0)	NS	17 (25.0)	25 (17.3)	NS
Diuretic therapy, n (%)*	10 (14.7)	12 (8.3)	NS	10 (14.7)	17 (11.8)	NS

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GTN, glycerine trinitrate; NA, not applicable due to 0 patients included in at least 1 category; and NS, not significant.

*Number of patients and percentage of patients in each group who are in receipt of each medication category.

†χ^2 test or Fisher exact test, as appropriate.

Major Adverse Cardiac Events at 9 Months

By 9-month follow-up, 46 patients (21.6%) experienced at least 1 MACE, with 2 patients (0.9%) having a nonfatal myocardial infarction and 46 patients (21.6%) being hospitalized for a cardiac event. There were no deaths or ischemic strokes in this cohort. Female participants had a significantly lower rate of MACEs (8/68 [11.7%]) compared with male participants (38/144 [26.3%]; p=0.016; Figure 4, Table 6).

The rate of MACEs increased from 8.0% of patients without any obstructive CAD to 31.5% of patients with 1-vessel CAD, 36.7% of patients with 2-vessel CAD, and 56.3% of patients with 3-vessel CAD, respectively (p<0.001). Upon dividing the cohort by luminal DS severity strata (Table 6), there was a higher rate of MACEs in the male group with significant CAD compared with the female group with similar anatomy (38.3% versus 9.5%; p=0.014).

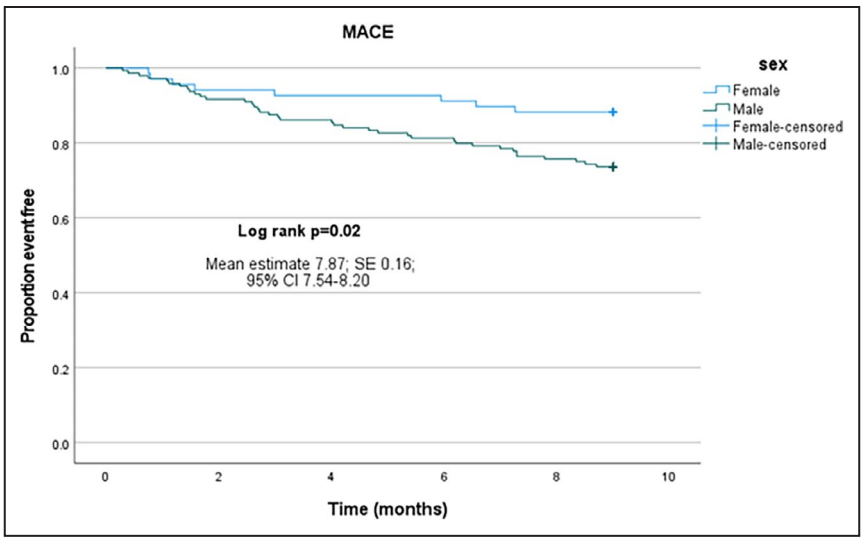

Figure 4. Kaplan–Meier plot for time to first MACE by sex.
MACE indicates major adverse cardiovascular event.

Table 6. MACE by Stenosis Severity and FFR_{CT} Intervals, Stratified by Sex

Luminal stenosis severity category (DS%)	MACE by 9-month follow-up			
	Total (212 patients) n*/n† (%‡)	Female group (68 patients) n*/n† (%‡)	Male group (144 patients) n*/n† (%‡)	*P* value§
0%	0/3 (0.0)	0/1 (0.0)	0/2 (0.0)	NA
1%–39%	1/2 (50.0)	1/1 (100)	0/1 (0.0)	NS
40%–49%	8/57 (14.0)	3/25 (12.0)	5/32 (15.6)	NS
50%–69%	8/47 (17.0)	2/12 (16.6)	6/35 (17.1)	NS
70%–99%	25/81 (30.8)	2/21 (9.5)	23/60 (38.3)	0.01
100%	4/17 (23.5)	0/7 (0.0)	4/10 (40.0)	NS
FFR_{CT}	Total (212 patients) n*/n† (%‡)	Female group (68 patients) n*/n† (%‡)	Male group (n=144 patients) n*/n† (%‡)	
0.50–0.55	26/68 (38.2)	3/17 (17.6)	23/51 (45.0)	0.05
0.56–0.60	2/5 (40.0)	1/1 (100.0)	1/4 (25.0)	NS
0.61–0.65	4/10 (40.0)	2/4 (50.0)	2/6 (33.3)	NS
0.66–0.70	3/9 (33.3)	0/1 (0.0)	3/8 (37.5)	NS
0.71–0.75	6/20 (30.0)	1/4 (25.0)	5/16 (31.5)	NS
0.76–0.80	2/27 (7.4)	0/9 (0.0)	2/18 (11.1)	NS
0.81–0.85	1/44 (2.2)	0/15 (0.0)	1/29 (3.4)	NS
0.86–0.90	2/23 (8.6)	1/15 (6.6)	1/12 (8.3)	NS
0.91–0.95	0/2 (0.0)	0/2 (0.0)	0/0	NA
0.96–1.00	0/0	0/0	0/0	NA
Overall	46/212 (21.6)	8/68 (11.7)	38/144 (26.3)	0.01

DS indicates diameter stenosis; FFR_{CT}, fractional flow reserve derived from computed tomography; MACE, major adverse cardiovascular event; NA, not applicable due to 0 patients included in at least one category; and NS, not significant.

*Number of patients experiencing a MACE in each strata.

†Total number of patients in each strata.

‡Percentage of patients experiencing a MACE in each strata.

§χ^2 test or Fisher exact test, as appropriate, comparing the female and male groups.

The FFR_{CT} strata was significantly and inversely associated with adverse clinical events. Specifically, 38.2% of patients in the 0.50 to 0.55 FFR_{CT} strata and 40% of patients with FFR_{CT} values between 0.56 to 0.65 had a MACE compared with 7.4% of patients with FFR_{CT} values between 0.86 and 0.90 and 0% of patients with FFR_{CT} >0.90 ($p<0.001$). Overall, MACEs occurred in 30.9% of patients who had a positive FFR_{CT} compared with 4.1% of patients with FFR_{CT} values >0.8 (relative risk, 1.38 [95% CI, 1.23–1.56]; $P<0.001$). There were no significant sex differences in the rates of MACEs between FFR_{CT} strata, except in the subgroup of severe flow impairment (FFR_{CT}, 0.50–0.55) in which there was a significantly higher rate of MACEs in male compared with female participants (45% versus 17%; $p=0.05$; Table 6). In the subgroup of patients with obstructive CAD (100 patients [26 women and 74 men]), there were 37 MACEs, all occurring in patients with at least 1 positive FFR_{CT}.

Male sex, Diamond–Forrester score, significant CAD, and positive FFR_{CT} (≤0.8) were all significant predictors of MACEs in univariable Cox regression analysis. In multivariable Cox regression, including all the above significant predictors from the univariable analysis, the presence of significant CAD (HR, 2.91 [95% CI, 1.30–6.51]; $p=0.009$) and a positive FFR_{CT} (HR, 4.11 [95% CI, 1.15–14.69]; $P=0.029$) were significant predictors of MACEs by 9-month follow-up, whereas sex was no longer significant ($p=0.13$; see Table 7). Additional Cox regression models including clinical outpatient visits and medication use by 9-month follow-up yielded similar findings, as depicted in Table S4.

DISCUSSION

This study has 3 main findings. First, in this clinical trial cohort, there were significant sex-specific differences in the distribution of coronary stenosis severity and the extent of significant flow impairment as determined by FFR_{CT} in patients with stable chest pain. Second, the management of patients was different by sex, particularly the completeness of optimal medical therapy and the use of CABG surgery. Third, the total cardiac costs expended on female patients were less than their male counterparts in this population.

Table 7. Cox Regression Analysis Predictors of MACE by 9-Month Follow-Up

Variable	HR	95% CI	*P* value
Univariable Cox regression			
Sex			
Female	1.00		Reference
Male	2.41	1.12–5.16	0.02
Diamond–Forester	1.01	1.00–1.01	0.04
Significant CAD*	5.44	2.62–11.29	<0.01
Any positive FFR_{CT} (≤0.8)	8.76	2.71–28.24	<0.01
Multivariable Cox regression			
Sex			
Female	1.00		Reference
Male	1.79	0.83–3.86	0.13
Diamond–Forester	1.00	0.99–1.01	0.57
Significant CAD*	2.91	1.30–6.51	0.01
Any positive FFR_{CT} (≤0.8)	4.11	1.15–14.69	0.03

CAD indicates coronary artery disease; FFR_{CT}, indicates fractional flow reserve derived from computed tomography; HR, hazard ratio; and MACE, major adverse cardiovascular event.

*Significant CAD: CAD with luminal stenosis ≥70% in any vessel or ≥50% left main stem stenosis.

Previous data have consistently demonstrated that women have a worse prognosis in the context of established CAD[24] or after an acute coronary event,[25] yet they are underdiagnosed and undermanaged compared with their male counterparts.[7,26] Beyond the pretest likelihood of CAD, current guidelines do not offer sex-tailored investigatory pathways and management for patients presenting with chest pain.[27,28]

The population in this FORECAST substudy represents patients with stable chest pain and established CAD on CCTA. The sex subgroups are well matched apart from women being, on average, 3 years older than their male counterparts (Table 1). Nonobstructive CAD (DS <50%) was more frequent in female participants (Table 2). Previously published data in unselected symptomatic patients undergoing CCTA, such as the SCOT-HEART (Scottish Computed Tomography of the Heart) cohort (obstructive CAD was found in 11.5% of women versus 29.8% of men)[29] or the ADVANCE (Assessing Diagnostic Value of Noninvasive FFR_{CT} in Coronary Care) registry cohort (luminal DS ≥70% found in 27.1% of women versus 37.9% of men; $p<0.001$)[22] found that men were more frequently diagnosed with significant CAD. In this FORECAST subcohort, although numerically more male subjects had significant CAD, this did not reach statistical significance (38.2% of female participants versus 51.3% of male participants; $p=0.07$).

Similar to previous invasive[30] and noninvasive studies,[22] our per-patient analysis demonstrated that female patients have significantly less coronary flow impairment compared with male patients, as reflected by both the per-patient median FFR_{CT} and the proportion of individuals having at least 1 positive FFR_{CT}. The per-vessel analysis further corroborated these findings, showing overall lower median FFR_{CT} values and higher proportion of positive FFR_{CT} in the male group compared with the female group, without any significant sex differences within each stenosis severity strata. These data are consistent with previous evidence, thought to be, at least in part, due to women having a higher coronary volume to myocardial mass ratio compared with men.[22]

A discordance between anatomic severity (significant CAD) and functional severity (FFR_{CT} ≤0.8) occurred overall in 19% of the analyzed vessels. This finding is consistent with previous invasive angiography and pressure wire studies, which have shown between 13% and 57% anatomico-functional mismatch, depending on study population but also the coronary vessel investigated.[31,32] Adding functional assessment to anatomic stenosis severity is important, as it leads to management changes in 21% to 48% of patients in a wide variety of populations.[31,33,34] The novel finding in the current analysis is that anatomico-functional discordance is significantly more frequent in male subjects compared with female subjects (20% versus 15% of vessels; $p=0.04$).

Similar to previous studies of CCTA in stable CAD,[22] the referral rate for invasive angiography did not differ between sexes. However, in contrast to the ADVANCE registry,[22] in the current analysis, female participants with severe flow impairment (FFR_{CT} ≤0.55) were less likely to receive revascularization compared with their male counterparts. Importantly, the overall differences in revascularization were mainly due to significantly lower CABG rates in the female group compared with the male group. This is an important observation that highlights previously reported sex disparities in clinical management, including lower overall CABG usage,[35] lower odds of undergoing guideline-recommended CABG revascularization,[36] and higher post-CABG mortality rate in women compared with men.[35] The underpinning reasons for this observation are multiple, likely related to procedural considerations; however, implicit sex bias among some clinicians may also play a role, as demonstrated by previous publications.[37]

We found that female participants in this study were less likely than male participants to be receiving prognostically important medication at 9 months, in the form of statins and angiotensin-converting enzyme inhibitors, although the baseline medication usage was equally balanced between the sexes. This observation, which replicates previous findings from the larger and multimodality PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial,[38] could be partially explained by accumulating data showing that women are more likely to experience side

effects from statin therapy and discontinue this medication compared with men.[10]

In this population, the overall cardiac costs expended on female patients was significantly lower than for male patients, mostly related to the overall lower rates of revascularization and optimal medical therapy usage in the female group. Interestingly, this does not appear to come at the expense of higher adverse outcomes within the 9-month follow-up. In actual fact, the rate of MACEs, mostly driven by cardiovascular hospitalization, was significantly lower in female compared with male participants.

Despite their proven individual prognostic value, the relative role of the presence and extent of coronary atheroma and ischemia in predicting adverse events remains unclear. Substudies of both the PROMISE[39] and ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches)[40] trials suggest than incremental atheroma burden is better at predicting adverse clinical events compared with ischemia burden. Our data suggest that, when combined in a Cox proportional model, both the presence of significant CAD and the detection of any positive FFR_{CT} are independent predictors of MACEs at 9-month follow-up, whereas sex was no longer statistically significant (p=0.13).

This study has a number of important limitations. First, as this is a secondary analysis of prospectively collected data, all findings are exploratory and need to be interpreted in light of the FORECAST study inclusion/exclusion criteria.[15,23] Importantly, no data were collected regarding the gender of participants; hence, the variations observed in relation to sex should not be extrapolated to gender. Second, although the rate of clinical events in this cohort was relatively high, this consisted mostly of hospitalization for cardiac events, rather than by "harder" events. Importantly, the number of adverse events in the female group was particularly low, with only 8 of 68 women experiencing a MACE by 9-month follow-up. Third, our analysis does not include advanced CCTA analyses describing adverse plaque characteristics,[41,42] atheroma patterns,[43] and adverse hemodynamic characteristics,[42] which are proven to have additional prognostic value; nor did we perform different measurements of FFR_{CT} such as lesion-specific FFR_{CT}[44] and delta FFR_{CT},[45] which are emerging as important discriminators of significant CAD. Nevertheless, these should be strongly considered for future research, as they are likely to enrich our understanding of sex-related differences in the patterns of CAD.

In conclusion, there are significant sex differences in the anatomico-functional assessment of CAD associated with significant differences in clinical management, costs, and adverse events. Sex-clustered analyses in larger, adequately powered cohorts are required to inform future clinical practice.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S2

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