**Sex differences in computed tomography coronary stenosis severity versus flow impairment and impact on revascularization, clinical events and healthcare costs: a FORECAST substudy**

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# Abstract

## 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 (CAD) who underwent both coronary computed tomography angiography (CCTA) and fractional flow reserve derived from computed tomography (FFRCT) as part of the FORECAST trial, investigating: (a) the relationship between coronary stenosis severity on CCTA and FFRCT by sex and (b) the association with revascularization, resource utilization and adverse clinical events.

212 patients (64 female participants, 32.1%) and 1245 vessels were included. There was no significant sex difference in the frequencies of significant CAD (38.2% of females vs 51.3% of males, p=0.073) but female participants had significantly less coronary flow impairment, according to the presence of at least one FFRCT≤0.8 (47.0% vs 71.5%, p=0.008). Female subjects underwent fewer revascularization procedures (23.5% vs 42.3%, p=0.014), less CABG (2.9% vs 13.1%, p=0.025) and were less likely to be on statin treatment (72.0% vs 84.7%, p=0.022) by 9-month follow-up. This resulted in lower overall healthcare costs for female participants compared with male counterparts (median total cost £1276 vs £2051, p=0.014). In multivariable Cox analysis the presence of significant CAD (HR 2.91; 95% confidence interval [CI] 1.30-6.51) and having a positive FFRCT (HR 4.11; 95% CI 1.15-14.69) were independent predictors of MACE 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, risk stratification, sex differences, coronary computed tomography angiography, fractional flow reserve derived from computed tomography, revascularization, major adverse cardiovascular events.

# Clinical perspective

**1) What Is New?**

• The discordance between anatomical 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 females with symptomatic coronary artery disease compared to their male counterparts.

**2) What Are the Clinical Implications?**

• As both the anatomical 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.

**Non-standard Abbreviations and Acronyms**

CAD……..coronary artery disease

CCTA……coronary computed tomography angiography

CI…………confidence interval

CVD…….cardiovascular disease

DS……….diameter stenosis

FFR……..fractional flow reserve

FFRCT….fractional flow reserve derived from computed tomography

HR……….hazard ratio

ICA………invasive coronary angiography

IQR………interquartile range

MACE….major adverse cardiovascular events

MI……….myocardial infarction

SD……….standard deviation

UK……….United Kingdom

# Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality globally in both women and men, and is responsible for the death of 35% of women [1]. Furthermore, the age-standardized prevalence of CVD in women has remained static since 2010, with an estimated 272.5 million women suffering from cardiovascular disease worldwide [1]. Ischemic heart disease, the commonest type of CVD 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 ischaemia, risk factor burden[7,8], but also variability in the rate of investigations requested, as well as pharmacological and revascularisation 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 ischaemia with non-obstructed coronaries is more prevalent in women and is associated with poor prognosis [1]. Complementing the anatomical information derived from CCTA, fractional flow reserve derived from computed tomography (FFRCT, HeartFlow, Mountain View, California, United States) utilises computational fluid dynamics to model flow impairment in coronary arteries. FFRCT 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 FFRCT is proven to improve the accuracy and discriminatory ability for detecting ischaemia 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 FFRCT 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 (a) higher observed FFRCT values for the same degree of coronary stenosis severity in women and (b) lower rates of revascularization in women with positive FFRCT [22].

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

# 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 trial, including only the patients who underwent both CCTA and FFRCT. The FORECAST trial (NCT03187639) has been reported previously in detail [15,23].Briefly, FORECAST was a multicentre trial that prospectively enrolled 1400 stable patients with chest pain who were randomized to an initial testing pathway using CCTA and selective FFRCT (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/FFRCT 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.

Out of the 700 patients randomized to the FORECAST experimental group, 254 (38%) patients met the criteria for FFRCT analysis (≥40% stenosis in at least one epicardial coronary artery), with an additional 5 patients also being referred for FFRCT (without meeting protocol criteria). 47 patients were excluded due to missing FFRCT, either because FFRCT could not be computed (39 patients) or failure to retrieve FFRCT data due to technical issues (8 patients). In summary, this analysis includes 212 patients with complete CCTA and FFRCT data and a total of 1245 vessels with matched CCTA data and distal FFRCT  [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 (LMS) coronary arteries and/or ≥50% for lesions involving the LMS. Obstructive CAD is defined as ≥50% luminal diameter stenosis in any epicardial coronary. For this analysis 2 cardiologists (LG, MK), blinded to other patient-specific details and to each other’s opinion, reviewed all the FFRCT data. The FFRCT was measured within the distal third of all coronary arteries of a diameter suitable for revascularisation (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 utilization and clinical events were collected as per the trial protocol via direct patient contact by research staff at each centre, as well as from local healthcare records. Major adverse cardiovascular events (MACE) were defined as a composite of all-cause death, non-fatal myocardial infarction (MI), stroke and cardiovascular hospitalization. As per the FORECAST trial protocol the total per-patient costs represented the sum of each individual pre-specified resource used over the follow-up interval (investigation/procedure, hospital visit and/or admission, medication) weighted by United Kingdom (UK) tariffs [15].

## Statistical analysis

Continuous data are presented as mean (± standard deviation, 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 chi-square 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% confidence interval (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, N.Y., USA) and RStudio, PBC (Boston, Massachusetts, USA).

# 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 pre-test 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), see Table 1.

## Per-patient anatomico-functional assessment by sex

In the overall cohort, 100/212 (47.1%) patients had significant CAD (defined as at least any epicardial coronary lesion with DS≥70% or LMS lesion with DS≥50%) and 139 (65.6%) patients had at least one positive FFRCT value (≤0.8). The distribution and severity of luminal coronary stenosis was similar in both sexes, except for the presence of non-obstructive 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 one FFRCT≤0.8 (71.5% of male versus 47.0% of female subjects, p=0.008) and also by the lowest per-patient FFRCT and distal left anterior descendant (LAD) FFRCT, both being lower in male compared to female participants [Table 2].

## Per vessel anatomico-functional assessment by sex

The per vessel analysis included 1245 vessels (384 vessels in female and 861 vessels in males) with matched vessel maximal luminal stenosis severity and distal FFRCT values. Overall, 395/1245 (31.7%) of the vessels analysed had a positive FFRCT, 89/384 vessels (23.1%) in the female subjects compared with 309/861 vessels (39.5%) in male subjects, p<0.001. The overall median FFRCT was 0.86 (IQR 0.77-0.91). Although the median FFRCT was above the conventionally accepted threshold for clinically important flow impairment (≤0.8) in both sexes, the observed values were higher in female (median FFRCT 0.88, IQR 0.81-0.92) compared with male participants (median FFRCT 0.85, IQR 0.75-0.91), p<0.001 [Figure 2 and Table 3].

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

## Invasive angiography and revascularization

By 9-month follow-up 102 (48.1%) patients had at least one ICA and 11 (5.2%) patients had multiple ICAs; 77 (36.3%) patients were revascularized, 56 (26.4%) by percutaneous coronary intervention (PCI) 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 28/68 (41.1%) of female participants and 74/144 (51.3%) of male participants undergoing at least one 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 rate of 1.7:1 in female subjects and 1.2:1 in males. This difference was mainly driven by a significantly lower rate of CABG in female patients (2.9% vs 13.1%, p=0.025), whilst the rates of percutaneous coronary intervention were similar (20.5% in females vs 29.5% in males, p=0.5), see Table S1.

Furthermore, upon dividing the cohort by FFRCT intervals [Table 4 and Figure S1] there were significantly lower rates of revascularization in female participants with severe flow impairment (FFRCT 0.50-0.55), with only 47% of female subjects in this group undergoing revascularization compared to 78% of males 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 FFRCT above 0.8 underwent revascularization, despite one female (3.1%) and two male patients (6.4%) without a positive FFRCT (FFRCT≤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% vs 84%, p=0.022) or an ACE inhibitor (20.5% vs 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 S3]. There was no significant difference by sex in the use of anti-platelet agents, beta-blockers, nitrates or calcium channel blockers [Table 5].

## Resource utilisation 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 males (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/FFRCT 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 utilisation by sex.

## Major adverse cardiac events at 9 months

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

The rate of MACE 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 MACE in the male group with significant CAD compared to the female group with similar anatomy (38.3% versus 9.5%, p=0.014).

The FFRCT strata was significantly and inversely associated with adverse clinical events. Specifically, 38.2 % of patients in the 0.50-0.55 FFRCT strata and 40% of patients with FFRCT values between 0.56-0.65 had a MACE compared with 7.4% of patients with FFRCT values between 0.86-0.90 and 0% of patients with FFRCT above 0.90 (p<0.001). Overall, MACE occurred in 30.9% of patients who had a positive FFRCT compared with 4.1% of patients with FFRCT values above 0.8 (RR 1.38; 95% CI 1.23-1.56, p<0.001). There were no significant sex differences in the rates of MACE between FFRCT strata, except in the subgroup of severe flow impairment (FFRCT 0.50-0.55) in which there was a significantly higher rate of MACE in male compared with female participants (45% versus 17%, p=0.05), see Table 6. In the subgroup of patients with obstructive CAD (100 patients, 26 females and 74 males) there were 37 MACE, all occurring in patients with at least one positive FFRCT.

Male sex, Diamond-Forrester score, significant CAD and positive FFRCT (≤0.8) were all significant predictors of MACE 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 FFRCT (HR 4.11, 95% CI: 1.15-14.69, p=0.029) were significant predictors of MACE 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-months follow-up yielded similar findings, as depicted in Table S4.

# Discussion

This study has 3 main findings. Firstly, 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 FFRCT in patients with stable chest pain. Secondly, the management of patients was different by sex, particularly the completeness of optimal medical therapy and the use of CABG surgery. Thirdly, the total cardiac costs expended on female patients were less than their male counterparts in this population.

Previous data have consistently demonstrated that women have a worse prognosis in the context of established CAD [24]24 or after an acute coronary event [25], yet they are underdiagnosed and undermanaged compared with their male counterparts [7,26]. Beyond the pre-test likelihood of coronary artery disease, 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 represent patients with stable chest pain and established CAD on CCTA. The sex subgroups are well matched apart from females being on average 3 years older than their male counterparts [Table 1]. Non-obstructive CAD (DS<50%) was more frequent in female participants [Table 2]. Previously published data in unselected symptomatic patients undergoing CCTA, such as the SCOTHEART cohort (obstructive CAD was found in 11.5% of women vs. 29.8% of men) [29] or the ADVANCE registry cohort (luminal DS≥70% found in 27.1% of women vs 37.9% of men , p<0.001) [30], found men were more frequently diagnosed with significant CAD. In this FORECAST sub-cohort, although numerically more male subjects had significant CAD, this did not reach statistical significance (38.2% of female vs 51.3% of male participants, p=0.07).

Similar to previous invasive[31] and non-invasive studies[30], 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 FFRCT and also the proportion of individuals having at least one positive FFRCT. The per-vessel analysis further corroborated these findings, showing overall lower median FFRCT values and higher proportion of positive FFRCT in the male group compared to the female group, without any significant sex differences within each stenosis severity strata. These data are consistent with previous evidence, mooted to be, at least in part, due to women having a higher coronary volume to myocardial mass ratio compared with men [30].

A discordance between anatomical severity (significant CAD) and functional severity (FFRCT≤0.8) occurred overall in 19% of the analysed vessels. This finding is consistent with previous invasive angiography and pressure wire studies which have shown between 13% and 57% anatomical-functional mismatch, depending on study population but also the coronary vessel investigated [32,33]. Adding functional assessment to anatomical stenosis severity is important as it leads to management changes in 21-48% of patients in a wide variety of populations [32, 34, 35]. The novel finding in the current analysis is that anatomico-functional discordance is significantly more frequent in male subjects compared to females (20% versus 15% of vessels, p=0.04).

Similar to previous studies of CCTA in stable CAD [30], the referral rate for invasive angiography did not differ between sexes. However, in contrast to the ADVANCE registry [30], in the current analysis female participants with severe flow impairment (FFRCT≤0.55) were less likely to receive revascularization compared to their male counterparts. Importantly, the overall differences in revascularization were mainly due to significantly lower CABG rates in the female group compared to the male group. This is an important observation that highlights previously reported sex disparities in clinical management, including lower overall CABG usage [36], lower odds of undergoing guideline recommended CABG revascularization [37], and higher post-CABG mortality in women compared to men [36]. 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 [38].

We found that female participants in this study were less likely than males to be receiving prognostically important medication at 9 months, in the form of statin and ACE inhibitors, although the baseline medication usage was equally balanced between sexes. This observation, which replicates previous findings from the larger and muti-modality PROMISE trial [39], could be partially explained by accumulating data showing women are more likely to experience side effects from statin therapy and discontinue this medication compared to men [10].

In this population the overall cardiac costs expended on female patients was significantly lower than for males, 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 MACE, mostly driven by cardiovascular hospitalization, was significantly lower in females compared to male participants.

Despite their proven individual prognostic value, the relative role of the presence and extent of coronary atheroma and ischaemia in predicting adverse events remains unclear. Substudies of the PROMISE [40] and ISCHEMIA [41] trials both suggest than incremental atheroma burden is better at predicting adverse clinical events compared to ischaemia burden. Our data suggest that, when combined in a Cox proportional model, both the presence of significant CAD and the detection of any positive FFRCT are independent predictors of MACE at 9-month follow-up, whereas sex was no longer statistically significant (p 0.13).

This study has a number of important limitations. Firstly, 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 was collected regarding the gender of participants hence, the variations observed in relation to sex should not be extrapolated to gender. Secondly, 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 within with only 8 out of 68 females experiencing a MACE by 9-month follow-up. Thirdly, our analysis does not include advanced CCTA analyses describing adverse plaque characteristics [42,43], atheroma patterns [44], and adverse haemodynamic characteristics [43], which are proven to have additional prognostic value; nor did we perform different measurements of FFRCT such as lesion-specific FFRCT [45] and delta FFRCT [46] 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 coronary artery disease 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.

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**Supplemental Material** – Tables S1-4, Figures S1-2.

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# Tables and Figures

## Table 1. Baseline characteristics per sex.

|  |  |  |  |
| --- | --- | --- | --- |
| **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 Former smoker Never smoked  | 4 (5.8%)32 (47.1%)32 (47.1%) | 19 (13.1%)60 (41.6%)65 (45.1%) | 23 (10.8%)92 (43.4%)97 (45.8%) |
| Diabetes mellitus -n(%)† | 8 (11.7%) | 26 (18.0%) | 34 (16.0%) |
| Treated hypertension -n(%)† | 33 (48.5%) | 76 (52.7%) | 109 (51.4%) |
| Treated hyperlipidaemia -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) | * 1. (±17.5)
 |

\*Mean values and standard deviation per each group. †Number of patients and percentages per each group. SD= standard deviation; BMI=body mass index; CAD=coronary artery disease

## Table 2. Per patient summary of anatomical coronary luminal stenosis severity and lowest distal FFRCT 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 (%)\** 3 vessels
* 2 vessels
* 1 vessel
* No DS>50%
 | 5 (7.3%)13 (19.1%)22 (32.3%)28 (41.1%) | 23 (15.9%)32 (22.2%)52 (36.1%)37 (25.6%) | 28 (13.2%)45 (21.2%)74 (34.9%)65 (30.7%) | Overall 0.080.08**0.02** |
| Significant CAD (DS>70% and/or LMS DS>50%) -n(%)\** 3 vessels
* 2 vessels
* 1 vessel
* No significant CAD
 | 2 (2.9%)7 (10.2%)17 (25.0%)42 (61.7%) | 14 (9.7%)23 (15.9%)37 (25.6%)70 (48.6%) | 16 (7.5%)30 (14.2%)54 (25.5%)112 (52.8%) | Overall 0.140.080.07 |
| LMS DS>50%- n(%)\*LAD DS>50% - n(%)\*CX DS >50% - n(%)\*RCA DS>50% -n(%)\*Any DS>50% - n(%)\*Any DS > 70% and/or LMS DS>50% - n(%)\* | 1 (1.4%)35 (51.4%)12 (17.6%)19 (27.9%)40 (58.8%) 26 (38.2%) | 9 (6.2%)87 (60.4%)35 (24.3%)50 (34.7%)107 (74.3%) 74 (51.3%) | 10 (4.7%)122 (57.5%)47 (22.1%)69 (32.5%)147 (69.3%)97 (46.8%) | 0.120.190.250.30**0.02**0.07 |
| Positive FFRCT (≤0.8) -n(%)\* | 32 (47.0%) | 103 (71.5%) | 119 (57.4%) | **0.01** |
| Lowest per patient FFRCT-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 FFRCT – median (IQR)* LAD
* CX
* RCA
 | 0.80 (0.75-0.89)0.89 (0.84-0.93)0.90 (0.87-0.93) | 0.78 (0.68-0.84)0.86 (0.79-0.81)0.90 (0.82-0.93) | 0.80 (0.69-0.86)0.87 (0.80-0.92)0.90 (0.85-0.93) | **0.01**0.170.27 |

\*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 non-normally distributed variables; tests of general association were performed using a chi square test or Fisher exact test, as appropriate, for categorical variables. CAD=coronary artery disease; LMS=left main stem; LAD=left anterior descendent artery; CX=circumflex artery; DS=luminal diameter stenosis; FFRCT=fractional flow reserve derived from computed tomography; IQR= Interquartile range.

## Table 3. Proportion of positive FFRCT and median FFRCT per stenosis severity category, stratified by sex.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Stenosis severity strata (DS%)** | **Per-vessel FFRCT positive (≤0.8) – n\*/n**†**(%)** | **p value**‡ | **Median FFRCT (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** |

\*Number of vessels with positive FFRCT values (≤0.8). †Number of vessels in each DS category. ‡Chi square test or Fisher exact test, as appropriate. §Median distal vessel FFRCT (Interquartile range) in each stenosis severity sub-group. || Mann-Whitney U test as appropriate for non-normally distributed variables. DS=luminal diameter stenosis; FFRCT= fractional flow reserve derived from computed tomography.

## Table 4. Rates of ICA and revascularization by FFRCT intervals, stratified by sex.

|  |  |  |
| --- | --- | --- |
| **FFRCT strata** | **Invasive coronary angiography (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** |

\*Number of patients undergoing ICA within each FFRCT strata. †Number of female patients within each strata. ‡Number of patients underboing revascularization within each FFRCT strata. § Chi square test or Fisher exact test, as appropriate. FFRCT=fractional flow reserve derived from computed tomography; ICA=invasive coronary angiography; NS=not significant, p value above 0.05; NA=not applicable due to zero patients included.

## Table 5. Medication at baseline and 9-month follow-up stratified by sex.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Medication | Baseline | p value† | 9-month follow-up | p value† |
| Female Group(n=68 patients) | Male Group(n=144 patients) | Female Group(n=68 patients) | Male Group(n=144 patients) |
| Aspirin – n(%)\* | 26 (38.2%) | 52 (36.1%) | NS | 46 (67.6%) | 111 (77.0%) | NS |
| P2Y12 inhibitors – n(%)\** Clopidogrel
* Prasugrel
* Ticagrelor
 | 4 (5.8%)0 (0.0%)1 (1.4%) | 7 (4.8%)0 (0.0%)1 (0.6%) | NS | 16 (23.5%)0 (0.0%)0 (0.0%) | 41 (28.4%)1 (0.6%)3 (2.0%) | NS |
| Beta-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 |

\* Number of patients and percentage of patients in each group wo are in receipt of each medication category. †Chi square test or Fisher exact test, as appropriate. ACE= angiotensin-converting enzyme; ARB= angiotensin receptor blocker; GTN=glycerine trinitrate; NS= not significant, p above 0.05; NA=not applicable due to zero patients included in at least one category.

## Table 6. MACE by stenosis severity and FFRCT intervals, stratified by sex.

|  |  |  |
| --- | --- | --- |
|  | **MACE by 9 month follow-up**  | **p value**§ |
| **Luminal stenosis severity category (DS%)** | **Total** **(212 patients)****n\*/n† (%‡)** | **Female Group****(68 patients)****n\*/n† (%‡)** | **Male Group****(144 patients)****n\*/n† (%‡)** |
| 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 |
| **FFRCT**  | **Total** **(212 patients)****n\*/n† (%‡)** | **Female Group****(68 patients)****n\*/n† (%‡)** | **Male Group****(n144 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** |

\*Number of patients experiencing a MACE in each strata. † Total number of patients in each strata. ‡Percentage of patients experiencing a MACE in each Fstrata. § Chi square test or Fisher exact test, as appropriate, comparing the female and male groups. DS=diameter stenosis; FFRCT= fractional flow reserve derived from computed tomography; MACE= major adverse cardiovascular events; NS= not significant, p above 0.05; NA=not applicable due to zero patients included in at least one category.

## Table 7. Cox regression analysis - predictors of MACE by 9-month follow-up.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **HR** | **95% CI** | **p value** |
| **Univariable Cox regression** |
| Sex* Female
* Male
 | 1.002.41 | 1.12-5.16 | Reference0.02 |
| Diamond-Forester | 1.01 | 1.00-1.01 | 0.04 |
| Significant CAD\* | 5.44 | 2.62-11.29 | <0.01 |
| Any positive FFRCT (≤0.8) | 8.76 | 2.71-28.24 | <0.01 |
| **Multivariable Cox regression** |
| Sex* Female
* Male
 | 1.001.79 | 0.83-3.86 | Reference0.13 |
| Diamond-Forester | 1.00 | 0.99-1.01 | 0.57 |
| Significant CAD\* | 2.91 | 1.30-6.51 | 0.01 |
| Any positive FFRCT (≤0.8) | 4.11 | 1.15-14.69 | 0.03 |

\*Significant CAD=coronary artery disease with luminal stenosis ≥70% in any vessel and/or ≥50% left main stem stenosis; FFRCT= fractional flow reserve derived from computed tomography; HR=hazard ratio; CI=confidence interval.

## Figure 1. Flow diagram of patients included in FORECAST subanalysis.

CCTA= coronary computed tomography angiography; FFRCT=fractional flow reserve derived from computed tomography.



## Figure 2. Boxplot of vessel FFRCT by stenosis severity category, startified by sex.

 FFRCT= fractional flow reserve derived from computed tomography. The horizontal red-line represents the cut-off point of FFRCT for significant flow impairment (≤0.80).



## Figure 3. Line plot of distal FFRCT by stenosis severity category (n=1245 vessels).

FFRCT= fractional flow reserve derived from computed tomography. The horizontal red-line represents the cut-off point of FFRCT for significant flow impairment (≤0.80).

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## Figure 4. Kaplan Meier Plot for time to first MACE by sex

MACE= major adverse cardiovascular event; SE= Standard error; CI=confidence interval.

