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Influence of sex on the functional assessment of myocardial ischemia

Short title: Impact of sex on the FFR and iFR/RFR in CAD

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WHAT'S NEW?

This study explores the impact of sex on invasive assessment of intermediate coronary stenoses using hyperemic (fractional flow reserve) and non-hyperemic (instantaneous wave-free ratio/resting full-cycle ratio) pressure ratios. As both non-hyperemic methods are considered equal, their results were combined. Results reveal men have more significant ischemia than women, but sex is not a predictor of discordant results between hyperemic and non-hyperemic methods. Furthermore, we were able to discern specific predictors for positive fractional flow reserve | negative instantaneous wave-free ratio/resting full-cycle ratio discordance and negative fractional flow reserve | positive instantaneous wave-free ratio/resting full-cycle ratio discordance in men, while no such associated factors were found in women.

ABSTRACT

Background: Fractional flow reserve (FFR) and non-hyperemic resting pressure ratios, such as instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR), are recommended for evaluating the significance of angiographically intermediate coronary stenoses. Despite their usefulness, approximately 20% of assessed lesions exhibit discordance between FFR and iFR/RFR.

Aims: The role of sex in this discrepancy remains uncertain; thus, we aimed to investigate its impact on the discordance between FFR and iFR/RFR.

Methods: We reviewed 417 consecutive intermediate stenotic lesions from 381 patients, stratified by sex and assessed with both FFR and iFR/RFR. FFR ≤0.80 and iFR/RFR ≤0.89 were considered positive for ischemia.

Results: Among the 381 patients, 92 (24.1%) were women. Women were older, had lower estimated glomerular filtration rate (eGFR), a higher ejection fraction, and were more likely to have peripheral artery disease than men. Median FFR and iFR/RFR values were lower in men than in women (FFR 0.86 vs. 0.80; P <0.001; iFR 0.92 vs. 0.90; P = 0.049). However, overall discordance prevalence was similar for both sexes (20.6% vs. 15.1%; P = 0.22). In men, eGFR, insulin-treated diabetes mellitus, and arterial hypertension were predictors of positive FFR | negative iFR/RFR discordance, while eGFR, insulin-treated diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease were predictors of negative FFR | positive iFR/RFR discordance. No factors associated with either discordance were identified in women.

Conclusions: FFR and iFR/RFR results indicating significant ischemia were more common in men than women when assessing intermediate coronary stenoses. Nevertheless, sex did not predict discordant results.

Key words: borderline lesions; coronary artery disease; discordance; gender; physiological assessment

INTRODUCTION

Current guidelines recommend assessing the significance of intermediate coronary stenoses, defined as luminal narrowing with a diameter stenosis of 50% to 90% in angiography, using invasive physiological methods (class I recommendation, level of evidence A) [1, 2]. Fractional flow reserve (FFR) remains the gold standard for detecting ischemia-inducing stenoses during maximum hyperemia, achieved through adenosine administration. Instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR) are alternative invasive measurements for evaluating coronary stenosis significance without requiring vasodilators [3, 4]. FFR and non-hyperemic methods (iFR/RFR) results are closely correlated [4–9]. However, a notable 20% discordance exists in identifying significant ischemia between FFR and iFR/RFR [4, 10–15]. Several clinical and anatomical factors have been suggested to contribute to this discordance, including diabetes mellitus, chronic kidney disease, valvular heart diseases, diastolic dysfunction, heart rate, and coronary artery stenosis severity and location [4, 16-18]. However, the role of sex in this discrepancy remains uncertain [4, 17]. Thus, we sought to investigate the impact of sex on the discordance between FFR and non-hyperemic methods (iFR/RFR) in patients undergoing invasive assessment of angiographically intermediate lesions.

METHODS

The main results of our study have been previously published [19]. Data were retrospectively collected for all consecutive patients hospitalized at the Clinical Department of Cardiology and Cardiovascular Interventions of the University Hospital in Kraków between January 2020 and December 2021, in whom invasive physiological assessment of the coronary angiographically intermediate lesions was performed, regardless of the method used. For this analysis, patients were stratified by sex.

All procedures were performed according to standard clinical methods via the radial or femoral approach, based on individual operator preferences. FFR and another non-hyperemic method were conducted using either diagnostic or guiding catheters. The FFR was measured during maximal hyperemia, achieved through an intracoronary bolus of adenosine ranging from 100-400 μg. The iFR or RFR was used for the non-hyperaemic assessment depending on the operator's preferences and device availability. The mean value of three measurements was analyzed. As both methods are considered equal, iFR and RFR results were combined. Values of ≤0.89 for iFR/RFR and ≤0.80 for FFR were deemed positive for ischemia. In total, 599 vessels underwent FFR and/or iFR/RFR assessments, with both FFR and iFR/RFR measurements available for 417 vessels. Vessels assessed by FFR or iFR/RFR only, amounting

to 182, were excluded from the analysis (Figure 1). Lesions were classified into four groups based on iFR/RFR and FFR concordance ([FFR+|iFR/RFR+] and [FFR-|iFR/RFR-]) or discordance ([FFR-|iFR/RFR+/] and [FFR+|iFR/RFR-]). Additional analyses were conducted separately for lesions within the left anterior descending artery (LAD) and non-LAD arteries (diagonal branch, circumflex artery, marginal branch, right coronary artery). Lesions within the left main coronary artery were not evaluated in this study.

Ethics approval (approval no. 1072.6120.257.2022, November 16, 2022) was granted from the institutional ethical board of the Jagiellonian University Medical College for this retrospective registry.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean, standard deviation (SD), or median with interquartile range (IQR). Differences between groups were compared using Student's t-test for normally distributed variables and the Wilcoxon test for non-normally distributed continuous variables. Categorical variables were compared by Pearson's chi-squared test. Receiver operating characteristic (ROC) curves were created to assess the optimal cut-off values of FFR for predicting iFR/RFR ≤0.89 and iFR/RFR for predicting FFR ≤0.80. The optimal cut-off values were established by maximizing the Youden index. Univariable analyses based on logistic regression for FFR|iFR/RFR discordance predictors were presented. Two-sided *P*-values <0.05 were considered statistically significant. All calculations were performed with JMP®, Version 16.1.0 (SAS Institute Inc.).

RESULTS

Data were collected for 381 patients hospitalized at the Clinical Department of Cardiology and Cardiovascular Interventions of the University Hospital in Krakow between 2020 and 2021. A total of 599 vessels were assessed by FFR and/or iFR/RFR in these patients with 92 (24.1%) of them being women (Figure 1). Women were older, had lower estimated glomerular filtration rate (eGFR), a higher ejection fraction, and were more likely to have peripheral artery disease than men (Table 1).

For further analysis, 417 vessels assessed with FFR and non-hyperemic methods (iFR or RFR) were selected. Among these, 106 vessels (25.4%) were assessed in women and 311 (74.6%) in men. The distribution of FFR and iFR/FFR values stratified by sex is shown in Figure 2. Overall, the median FFR and iFR/RFR were higher in women than men (FFR 0.86 vs. 0.80; *P*

<0.001; iFR/RFR 0.92 vs. 0.90; *P* = 0.049), and men more frequently achieved positive results for both FFR and iFR/RFR (Table 2). In the analysis limited to lesions within LAD, women had higher FFR and iFR/RFR results than men, and results indicating significant ischemia were less common (Table 2). The prevalence of overall discordant results of FFR and iFR/RFR was similar between women and men (15.1% vs. 20.6%; *P* = 0.22). However, FFR-|iFR/RFR- concordant results were more common in women, while FFR+|IFR/RFR+ concordant results were more common in men (Figure 3). Among men, eGFR, insulin-treated diabetes mellitus, and arterial hypertension were predictors of FFR+|iFR/RFR- discordance, and eGFR, insulin-treated diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease were predictors of FFR-|iFR/RFR+ discordance. No factors associated with either discordance were identified in women (Table 3).

ROC analysis confirmed the optimal cut-off point for FFR to identify patients with iFR/RFR ≤0.89 of 0.83 for women and 0.80 for men. Additionally, the optimal cut-off point for distinguishing groups with FFR ≤0.80 for iFR/RFR was 0.90 for women and 0.91 for men (Table 4).

DISCUSSION

We found that among assessed intermediate coronary stenoses, median FFR and iFR/RFR values were lower in men than in women. As a result, FFR and iFR/RFR values indicating significant ischemia were more common among men. However, sex was not identified as an independent predictor of FFR and iFR/RFR discordance.

Numerous randomized studies have shown that coronary revascularization guided by invasive measurements has better outcomes than revascularization guided by angiography alone [1, 3, 20]. Consequently, physiological testing of borderline coronary lesions with either hyperemic or non-hyperemic methods is recommended for identifying stenoses responsible for ischemia [1]. The iFR-SWEDEHEART [21] and DEFINE-FLAIR [22] studies confirmed the non-inferiority of iFR compared to FFR in assessing borderline coronary lesions, but the relative performance of these methods may be affected by sex [23, 24]. For instance, in the DEFINE-FLAIR [25], the FFR-guided strategy was associated with a lower revascularization rate than the iFR-guided strategy in women, while this difference was not observed in men. Consistent with our study, FFR values were lower in men than women, and women had fewer functionally significant lesions [25]. However, iFR values were similar for both groups. Similarly, a study by Verdoia et al. evaluated 371 intermediate coronary stenoses in 325 patients undergoing coronary angiography and found that iFR values did not differ by sex [26]. In our study,

iFR/RFR values were higher in women than men, but these differences were only marginally significant, possibly due to the inclusion of RFR-assessed patients.

Various factors might explain the higher FFR values in women than men, such as differences in myocardial masses, myocardial perfusion territories, vessel size, plaque structure, diastolic function, and higher resting coronary blood flow in women [23, 24]. Additionally, women have higher resting coronary blood flow compared with men [27]. Thus, it may affect FFR measurement, which depends on net changes [3]. Microcirculatory disorders, more common in women, can also influence FFR values. A blunted coronary hyperemic response in patients with microvascular dysfunction could result in a smaller pressure gradient across a stenotic lesion and higher FFR values [16]. Women typically experience their first presentation of coronary artery disease about ten years later than men, often after menopause [24]. Older age is linked to a decrease in coronary flow reserve and an increase in microvascular resistance under hyperemia, which may lead to an underestimation of stenosis severity by FFR [28, 29]. Also, the absence of estrogens in postmenopausal women is thought to be related to the development and progression of microvascular dysfunction [30]. Female sex and older age are associated with the development of various comorbidities. In our study, women were more likely to have chronic kidney disease, resulting in lower eGFR observed in this group. Chronic kidney disease is associated with microcirculation damage and vessel calcifications; thus, the response to drugs inducing hyperemia may be falsified [16]. For instance, the FREAK study found a higher percentage of negative FFR values in patients with chronic kidney disease, suggesting a link between FFR results and creatinine levels [31]. Similarly, diabetes mellitus is often associated with diffuse vascular dysfunction in both large and micro-vessels [7, 18, 32–35]. Women have a longer life expectancy than men, so they are more likely to experience other age-related diseases, such as severe aortic stenosis [36]. Notably, in patients with severe aortic stenosis, FFR and iFR/RFR values may be affected by a falsely low aortic pressure due to the restricted orifice of the aortic valve [7, 16]. Furthermore, a reduced vasodilation ability in patients with severe aortic stenosis may result from myocardial hypertrophy, microvascular dysfunction, and elevated left ventricular end-diastolic pressure [16].

In previous research, we found discrepancies between FFR and iFR/RFR in 19.2% of assessed angiographically intermediate stenoses [19]. The present analysis revealed that sex was not associated with an increased risk of discordant results. However, studies by Lee et al. [12], Arashi et al. [37], and Aoi et al. [38] identified female sex as an independent predictor of FFR+|iFR- discordance. Several clinical, angiographic, and hemodynamic factors can contribute to differences between FFR and iFR/RFR, including age, diabetes mellitus, chronic

kidney disease, coronary artery stenosis location, atrial fibrillation, elevated left ventricular end-diastolic pressure, diastolic dysfunction, and microcirculation dysfunction [4, 10–14]. Microcirculation dysfunction is particularly prominent in women and is the strongest predictor [16]. For instance, Legutko et al. [39] found that microcirculation disorders were more prevalent in discrepant FFR/RFR vessels, independent of sex. In our study, both insulin-treated diabetes mellitus and eGFR were identified as predictors of FFR-|iFR/RFR+ discordance in men. As mentioned, diabetes mellitus and chronic kidney disease are associated with microcirculation dysfunction and more complex and diffused coronary disease and thus influence hyperemic response during FFR measurements. Our research suggests that not only diabetes mellitus presence but also its treatment and control may contribute to discrepancies. In addition, atrial fibrillation was a predictor of overall FFR vs. iFR/RFR discrepancy in men. A recent study highlighted increased beat-to-beat variability of individual iFR measurements in patients with atrial fibrillation, resulting in reduced reproducibility and increased lesion reclassification [40]. In contrast, FFR variability, reproducibility, and lesion reclassification were comparable between patients with atrial fibrillation and sinus rhythm. No predictors of discordance between FFR and iFR/RFR were identified in women, possibly due to a small sample size. In addition, microcirculatory dysfunction may be of particular importance in this subgroup.

The reliability of cutoff values of ≤0.80 for FFR and ≤0.89 for iFR/RFR indicating significant ischemia has been confirmed in numerous clinical studies [1, 3]. However, women tend to have higher FFR values at maximum hyperemia than men [23]. This discrepancy may be attributed to women's higher resting flow and more prevalent microcirculatory dysfunction. Previous studies on sex-related differences in FFR report an average difference of about 0.02 (0.01 to 0.04) between men and women [23, 25, 41]. Based on our study, an FFR cutoff of ≤0.83 seems reasonable for detecting ischemia-inducing lesions in women. On the other hand, in the DEFINE-FLAIR study [25], FFR-guided and iFR-guided strategies using standard cutoffs yielded similar clinical outcomes for both sexes. Clinicians should always take into account the influence of microcirculation dysfunction when interpreting FFR and iFR/RFR results [4, 16]. Notably, for women with borderline FFR values (0.80–0.83) and symptoms suggestive of ischemia, additional assessment of microvascular dysfunction using the index of myocardial resistance measurement should be strongly considered to guide treatment [23]. Microvascular disease is particularly concerning because it can contribute to adverse long-term cardiovascular outcomes even in the absence of significant coronary disease [42]. The suitability of applying a fixed FFR cutoff value for all patients is debatable and warrants further investigation.

Limitations

Our analysis is primarily limited by its small sample size and the imbalance between the number of women and men included. This may restrict the assessment of the impact of comorbidities on FFR and iFR/RFR results in women. Additionally, the study did not incorporate a noninvasive assessment of myocardial ischemia, which could have served as an additional reference technique. Furthermore, there was a lack of data on microcirculatory dysfunction, coronary flow reserve, concomitant valvular heart disease, and central venous pressure. We did not collect data on active and prior COVID-19 infections for this study, so their impact on FFR and iFR/RFR results was not evaluated. Lastly, the study did not provide quantitative coronary angiography analysis.

CONCLUSIONS

FFR and iFR/RFR results indicating significant ischemia were more common in men than women when assessing intermediate coronary stenoses. Nevertheless, sex did not predict discordant results.

Article information

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Table 1. Baseline clinical characteristic of study population

Variable	**Sex**		***P*-value**
	Female 92 (24.1%)	**Male 289 (75.9%)**	
Age, years, mean (SD)	71.6 (9.6)	66.4 (10.1)	<0.001
Height, cm, median (IQR)	162.0 (158.0–165.0)	174.0 (170.0-178.0)	<0.001
Weight, kg, median (IQR)	78.0 (67.0–89.0)	85.0 (78.0-95.0)	<0.001
BMI, kg/m^2, median (IQR)	30.2 (24.9–33.4)	28.4 (25.7-31.2)	0.13
Diabetes mellitus, n (%)	39 (42.4)	115 (39.8)	0.66
Arterial hypertension, n (%)	83 (90.2)	248 (86.1)	0.31
Atrial fibrillation, n (%)	21 (23.1)	54 (18.7)	0.36
Previous MI, n (%)	36 (39.1)	142 (49.1)	0.09
Previous PCI, n (%)	42 (45.7)	154 (53.3)	0.20
Previous CABG, n (%)	7 (7.6)	46 (16.0)	0.38
PAD, n (%)	25 (16.3)	28 (12.3)	0.04
Current smoker, n (%)	34 (37.0)	156 (54.0)	0.005
COPD, n (%)	7 (7.6)	20 (6.9)	0.83
Previous stroke/TIA, n (%)	11 (12.0)	24 (8.3)	0.30
Dyslipidemia, n (%)	75 (81.5)	218 (75.4)	0.23
eGFR, ml/min/1.73 m^2, mean (SD)	70.9 (27.0)	78.2 (25.6)	0.02
HbA_{1c}, %, median (IQR)	6.7 (5.7–7.95)	6.8 (6.05-9.2)	0.24

LVEF, %, median (IQR)	55.0 (45.0–60.0)	50.0 (39.75-60.0)	0.02
Radial access, n (%)	79 (85.9)	234 (81.0)	0.29

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricle ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack

Table 2. The results of vessel assessment in the study groups (per vessel)

Variable	**Sex**		***P*-value**
	Female **106 (25.4%)**	**Male** **311 (74.6%)**	
Vessel assessed			
LAD, n (%)	65 (61.3)	184 (59.2)	0.70
non-LAD, n (%)	41 (38.7)	127 (40.8)	
All vessels			
FFR ≤0.80, n (%)	36 (34.0)	164 (52.7)	<0.001
FFR, median (IQR)	0.86 (0.77–0.90)	0.80 (0.75-0.86)	<0.001
iFR/RFR ≤0.89, n (%)	40 (37.7)	154 (49.5)	0.04
iFR/RFR, median (IQR)	0.92 (0.87–0.95)	0.90 (0.85-0.94)	0.049
LAD			
FFR ≤0.80, n (%)	26 (40.0)	123 (66.9)	0.001
FFR, median (IQR)	0.83 (0.77–0.88)	0.78 (0.73-0.83)	<0.001
iFR/RFR ≤0.89, n (%)	30 (46.2)	115 (62.5)	0.02
iFR/RFR, median (IQR)	0.90 (0.86–0.93)	0.88 (0.83-0.91)	0.02
Non-LAD			
FFR ≤0.80, n (%)	10 (24.4)	41 (32.3)	0.34
FFR, median (IQR)	0.89 (0.82–0.93)	0.84 (0.78-0.90)	0.03
iFR/RFR ≤0.89, n (%)	10 (24.4)	39 (30.7)	0.44
iFR/RFR, median (IQR)	0.94 (0.90–0.97)	0.93 (0.88-0.97)	0.69

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IQR, interquartile range; LAD, left anterior descending artery; RFR, resting full-cycle ratio

Table 3. Univariable analysis for predictors of discordance between fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio stratified by sex

Variables	**Male crude OR (95% CI)**	***P*-value**	**Female crude OR (95% CI)**	***P*-value**
Predictors of FFR+ | iFR/RFR- discordance				
eGFR per 1 ml/min/1.73 m^2	1.02 (1.01–1.03)	0.04	1.03 (0.99–1.06)	0.05
DM treatment (insulin vs. others)	0.20 (0.06–0.74)	0.02	–	–
Arterial hypertension (no vs. yes)	3.12 (1.37–7.08)	0.007	–	–
Predictors of FFR- | iFR/RFR+ discordance				
DM treatment (insulin vs. others)	5.14 (1.02–25.82)	0.047	5.83 (0.84–40.32)	0.07
AF (no vs. yes)	0.35 (0.15–0.80)	0.01	1.59 (0.32–7.96)	0.57
eGFR per 1 ml/min/1.73 m^2	0.98 (0.96–0.99)	0.02	1.00 (0.98–1.02)	0.95
COPD (no vs. yes)	0.20 (0.07–0.56)	0.002	1.05 (0.12–9.14)	0.97
Predictors of overall concordance				
AF (no vs. yes)	2.03 (1.07–3.85)	0.03	0.56 (0.15–2.13)	0.40

Abbreviations: AF, atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IQR, interquartile range; OR, odds ratio; RFR, resting full-cycle ratio

Table 4. Receiver operating characteristic curves: classification accuracy of fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio stratified by sex

	Optimal cut-off point	**AUC (95% CI)**	***P*-value**
iFR/RFR to predict FFR ≤0.80			
Female	0.90	0.94 (0.88-0.98)	<0.001
Male	0.91	0.88 (0.84-0.91)	<0.001
FFR to predict iFR/RFR ≤0.89			
Female	0.83	0.90 (0.83-0.96)	<0.001
Male	0.80	0.88 (0.84-0.91)	<0.001

Abbreviations: AUC, the area under the curve; CI, confidence interval; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, resting full-cycle ratio

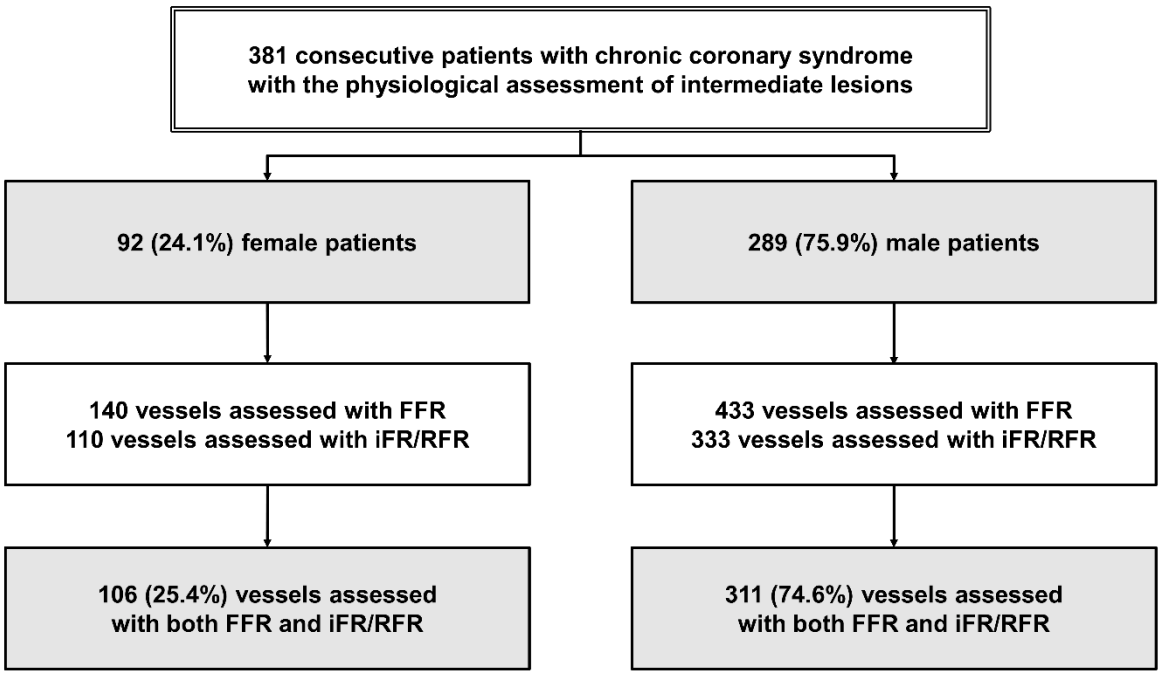

Figure 1. Patients and vessels allocation. Study groups marked with light grey color
Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, resting full-cycle ratio

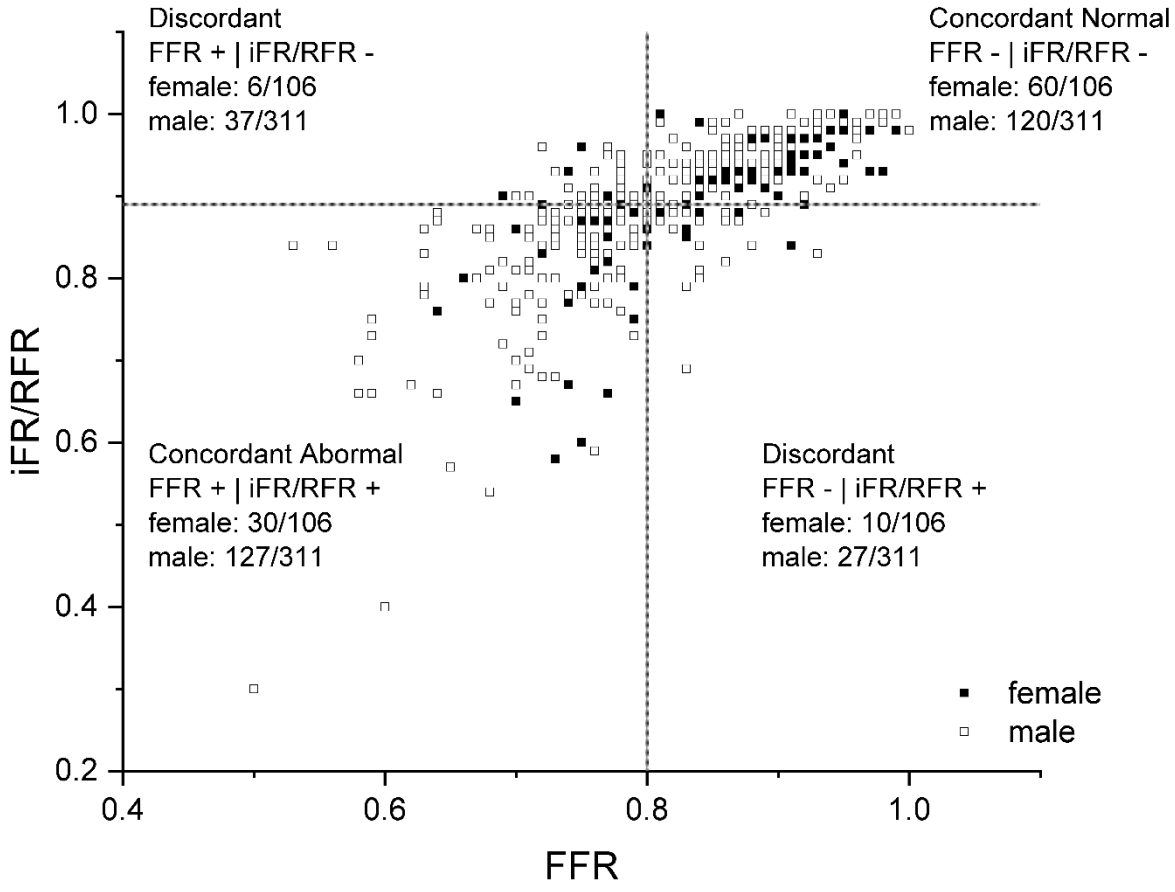

Figure 2. Fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio results depending on sex

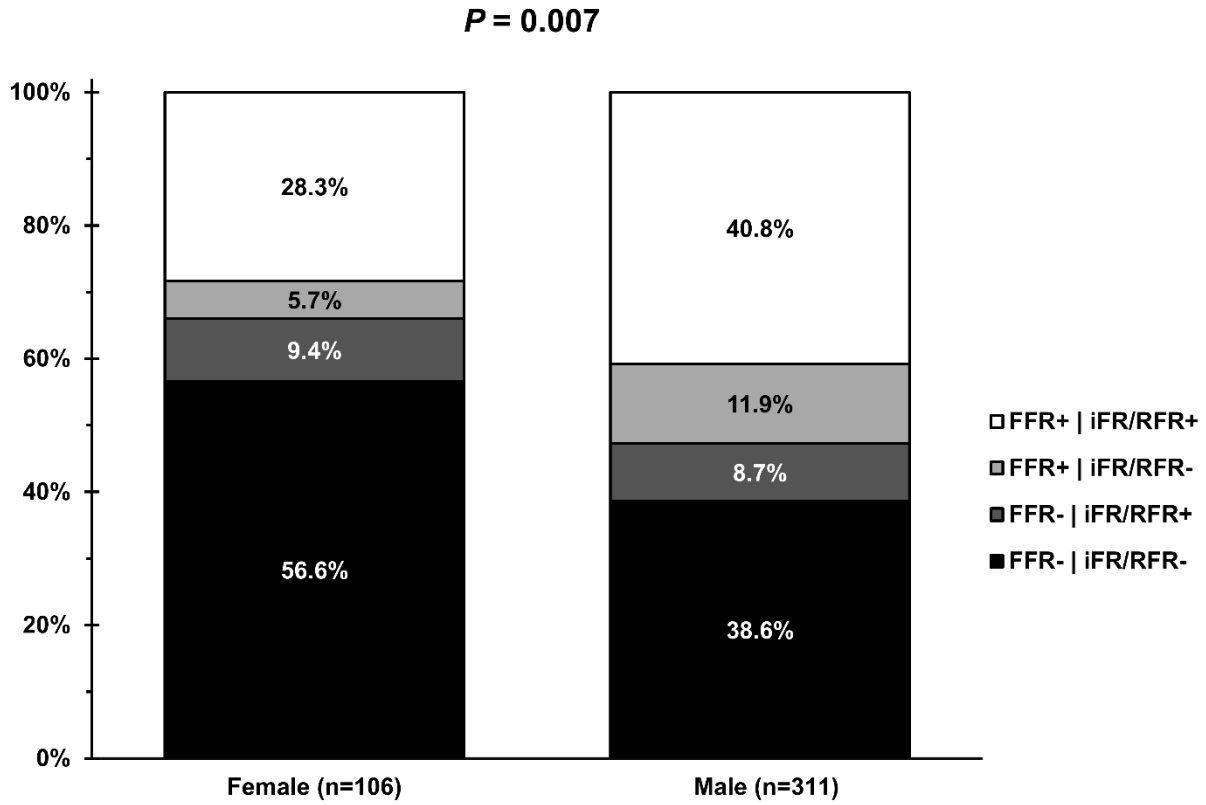

Figure 3. Frequency of different types of the discrepancy between fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio stratified by sex

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, resting full-cycle ratio