Sex Differences in Procedural Characteristics and Clinical Outcomes of Instantaneous Wave-free Ratio or Fractional Flow Reserve-Guided Revascularization Strategy

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Abstract

Objectives: This study sought to evaluate sex differences in procedural characteristics and clinical outcomes of instantaneous wave-free ratio (iFR)- and fractional flow reserve (FFR)-guided revascularization strategies.

Background: While iFR-guided strategy has shown a lower revascularization rate than FFR-guided strategy without the difference in clinical outcomes between the 2 strategies, the influence of male versus female sex has not yet been fully investigated.

Methods: This is a post-hoc analysis of DEFINE-FLAIR (Functional Lesion Assessment of Intermediate stenosis to guide Revascularization) study, in which 601 women and 1,891 men were randomized to iFR- or FFR-guided strategy. iFR≤0.89 and FFR≤0.80 were used as criteria for revascularization. The primary endpoint was 1-year major adverse cardiac events (MACE), a composite of all-cause death, nonfatal myocardial infarction, or unplanned revascularization.

Results: Among the entire population, women had lower number of functionally significant lesions per patient (0.31 ± 0.51 vs. 0.43 ±0.59, p < 0.001) and less frequently underwent revascularization than men (42.1% vs. 53.1%, p < 0.001). There was no sex difference in iFR value (0.91 ± 0.09 vs. 0.91 ± 0. 10, p = 0.442). However, FFR value was lower in men than in women (0.83 ± 0.09 vs. 0.85 ± 0.10, p = 0.001). In men, FFR-guided strategy was associated with a higher rate of revascularization than iFR-guided strategy (57.1% vs. 49.3%, p = 0.001). There was no difference in revascularization rate between iFR- and FFR-guided strategies in women (41.4% vs. 42.6%, p = 0.757). At 1 year, MACE rate was not different according to sex (women vs. men, 5.49% vs. 6.77%, adjusted HR 0.82, 95% CI 0.53-1.28, p = 0.380). There was no difference in MACE rates between iFR- and FFR-guided strategies in both women (5.36% vs. 5.61%, adjusted HR 1.10, 95% CI 0.50-2.43, p = 0.805) and men (6.55% vs. 7.00%, adjusted HR 0.98, 95% CI 0.66-1.46, p = 0.919).

Conclusions: FFR-guided strategy was associated with a higher rate of revascularization than iFR-guided strategy in men, but not in women. However, iFR- and FFR-guided treatment strategies showed comparable clinical outcome, regardless of sex.

Trial Registration: DEFINE-FLAIR ClinicalTrials.gov number, NCT02053038.

Key Words: instantaneous wave-free ratio; fractional flow reserve; sex; clinical outcome.

Abbreviations

iFR = instantaneous wave-free ratio

FFR = fractional flow reserve

MACE = major adverse cardiac events

MI = myocardial infarction

PCI = percutaneous coronary intervention

HR = hazard ratio

CI = confidence interval

Condensed Abstract

The current study is a post-hoc analysis of DEFINE-FLAIR study focusing on sex differences in iFR- and FFR-guided strategies. iFR value was not different according to sex, but FFR value was lower in men. In men, FFR-guided strategy resulted in higher revascularization rate than iFR-guided strategy. There was no difference in revascularization rate between iFR- and FFR-guided strategies in women. Despite these differences, iFR- and FFR-guided strategies showed comparable risk of clinical outcome at 1 year in women and men.

Introduction

Ischemia-guided coronary revascularization is a standard approach for patients with coronary artery disease.[1, 2] Fractional flow reserve (FFR) is a hyperemic physiologic index to define the ischemia-causing stenosis in a cardiac catheterization laboratory.[3-5] Instantaneous wave-free ratio (iFR) is a resting physiologic index that does not require hyperemia and was introduced as an alternative to FFR. Two large randomized clinical trials, DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) and iFR-SWEDEHEART (Instantaneous Wave-Free Ratio Versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) compared iFR- and FFR-guided revascularization and demonstrated non-inferiority of iFR-guided strategy.[6, 7]

Previous study showed that FFR was higher in women than men for the same stenosis severity.[8] In addition, the resting coronary flow and response to hyperemic agents can differ according to sex, and sex is reported as an independent factor for discordance between iFR and FFR.[9, 10, 11] Therefore, iFR- and FFR-guided strategies might result in different revascularization rate and clinical outcomes according to sex. However, sex influence on iFR- and FFR-guided strategies have not been investigated yet. The current study sought to evaluate sex differences in procedural characteristics and prognostic implications of iFR- or FFR-guided strategy.

Methods

Study Population and Procedure

The current study was a post-hoc analysis of the DEFINE-FLAIR trial which was designed to investigate non-inferiority of iFR-guided strategy compared with FFR-guided strategy.[6] The trial was a multicenter, international, randomized, blinded trial performed at 49 interventional sites in 19 countries. Detailed study protocol and clinical outcome at 1 year have been previously published.[6] Patients at least 18 years of age who had intermediate coronary artery disease (40-70% stenosis of the diameter on visual assessment) with at least one native artery were eligible for inclusion in the trial. Patients with previous coronary artery bypass surgery, significant left main stenosis, tandem stenoses, total coronary occlusions, restenotic lesions, hemodynamic instability at the time of intervention, contraindication to adenosine administration, heavily calcified or tortuous vessels, significant hepatic or lung disease, pregnancy, ST-segment elevation myocardial infarction (STEMI) within 48 hours, severe valvular heart disease, acute coronary syndrome with more than one target vessel were excluded. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating center and all patients provided written informed consent.

Eligible patients were randomly assigned 1:1 to either iFR- or FFR-guided revascularization. iFR and FFR measurements were obtained in the routine manner with the use of a coronary-pressure guidewire (Philips Volcano, San Diego, USA) in all vessels with intermediate stenosis. Revascularization was performed according to prespecified treatment thresholds of iFR≤0.89 or FFR≤0.80.

Endpoints

The primary endpoint was 1-year major adverse cardiac events (MACE), a composite of death, nonfatal myocardial infarction (MI), or unplanned revascularization. Death was considered to be from cardiovascular causes unless a definite noncardiovascular cause could be established. Revascularization was considered to be unplanned when it was not the index procedure and was not identified at the time of the index procedure as a staged procedure to occur within 60 days. Endpoint events were adjudicated by an independent committee of experts who were unaware of patient identities and their treatment group.

Statistical Analysis

Continuous variables were presented as mean with standard deviation or median with interquartile range (Q1-Q3) as appropriate, and were compared using Student t-test. Categorical variables were presented as numbers with percentages and compared with the chi-square test. The time-to-event analysis was conducted with the use of the Kaplan–Meier method. A Cox proportional hazards regression model was used to calculate hazard ratio (HR) and two-sided 95% confidence interval (CI). The validity of the proportional hazards assumption was tested with Schoenfeld and there were no signs of violation of the proportional hazards assumption. Patients who withdrew from the study before 1-year of clinical follow-up and event-free until the last visit were excluded from the risk-difference analysis for the primary endpoint. Data from these patients were censored at the last follow-up for the time-to-event analysis.[6] For a multivariable adjusted analysis, adjustment for age, clinical presentation, Canadian Cardiovascular Society (CCS) class for grading of angina pectoris, hypertension, diabetes mellitus, hyperlipidemia, previous MI, and previous percutaneous coronary intervention (PCI) was performed.

Results

Patients Characteristics

Of the total 2,492 participants included in the analysis, 601 (24%) were women. The baseline patient characteristics are shown in Table 1. Women were older, presented more frequently with stable coronary disease, and showed a higher prevalence of hypertension than men. Current smoker, history of previous MI or PCI were less frequent in women. Compared with men, women had higher systolic blood pressure, lower diastolic blood pressure, and higher heart rate. In both women and men, clinical characteristics were well balanced between iFR and FFR strategies.

Procedural Characteristics

Table 2 shows procedural characteristics according to sex. Women had significantly lower number of functionally significant lesions per patient, lower prevalence of patients with at least ≥1 functionally significant lesion, and less frequently underwent revascularization. Table 3 shows procedural characteristics between iFR- and FFR-guided strategies in each sex. The type or number of evaluated vessels per patients was not different between iFR and FFR strategies in both sexes. Regarding physiologic assessment, iFR value was not different between women and men (0.91 ± 0.09 vs. 0.91 ± 0.10, $p = 0.442$). However, FFR value was lower in men than in women (0.83 ± 0.09 vs. 0.85 ± 0.10, $p = 0.001$). In women, there were no differences in number of functionally significant lesions per patient, proportion of patients with at least ≥1 functionally significant lesion, or rate of revascularization in both iFR- and FFR-guided strategies. In men, FFR-guided strategy was associated with a higher number of functionally significant lesions per patient, higher prevalence of patients with at least ≥1 functionally significant lesion, and more frequent revascularization (57.1% vs. 49.3%, p = 0.001) in comparison with iFR-guided strategy.

Clinical Outcomes

At 1 year, MACE rate was not different according to sex (women vs. men, 5.49% vs. 6.77%, adjusted HR 0.82 95% CI 0.53-1.28, p = 0.380) (Figure 2 and Supplementary Table 1). The individual rates of death from any cause, nonfatal MI and unplanned revascularization were not significantly different between sexes (Supplementary Table 1).

When patients were stratified according to sex, iFR- and FFR-guided strategies showed comparable risk of MACE in both women (5.36% vs. 5.61%, adjusted HR 1.10, 95% CI 0.50-2.43, p = 0.805) and men (6.55% vs. 7.00%, adjusted HR 0.98, 95% CI 0.66-1.46, p = 0.919) (Table 4, Supplementary Table 2 and Figure 3). There was no significant interaction between treatment strategy and sex in death from any cause, cardiovascular death, nonfatal MI, and unplanned revascularization (Table 4). These findings were consistent among patients in which revascularization was deferred based on iFR or FFR (Table 5, Supplementary Table 3, and Figure 4).

Discussion

The current study evaluated the sex differences in iFR- and FFR-guided treatment strategies. The main findings are as follows: 1) Among the entire population, women had lower number of functionally significant lesions per patient and less frequently underwent revascularization than men; 2) iFR value was not different according to sex, but FFR value was lower in men; 3) There was no difference in revascularization rate between 2 physiologic indices in women. However, FFR-guided strategy was associated with a higher revascularization rate in men compared with iFR-guided strategy; and 4) Despite the difference in baseline and procedural characteristics, iFR- and FFR-guided strategies showed comparable risk of MACE in women and men.

Difference in Baseline Characteristics between Women and Men

In the majority of studies dealing with coronary artery disease, women are older and have more cardiovascular comorbidities than men. Older age and higher prevalence of hypertension in women can result in increased arterial stiffness and endothelial dysfunction, accompanied by higher systolic blood pressure, pulse pressure and left ventricular end-diastolic pressure.[12] In our study, these characteristics in women were similarly observed, and baseline heart rate was also higher in women. Therefore, it can be assumed that there can be differences in baseline coronary flow and response to hyperemic stimuli in women and men. Those differences in baseline characteristics can cause the discordance of these 2 pressure-derived physiologic indices, as FFR and iFR are determined by the hyperemic and resting flows, respectively.

Difference in FFR and iFR between Women and Men

Higher FFR in women than in men was consistently reported in previous studies,[8, 13] and the differences in microvascular function,[14] myocardial mass,[15] coronary height,[16] vessel size,[17] plaque characteristics,[18, 19] and diastolic function[20] were suggested as its mechanism. However, the influence of sex on resting pressure index has not been investigated well. In our study, there was no difference in iFR value according to sex in contrast to FFR. In a previous study, microvascular dysfunction assessed by low coronary flow reserve (CFR) was reported to be frequent in women.[14] Therefore, blunted hyperemic response was regarded as an important reason for higher FFR in women.[10] However, a recent study on sex differences in invasive measurements of microvascular function showed that the hyperemic coronary flow and index of microcirculatory resistance were not different according to sex.[9] Rather, resting coronary flow was higher in women, accounting for low CFR in women.[9] Our study results can also be explained by the lower CFR in women compared to men. However, further studies on how sex difference in microvascular function affects iFR and FFR values are needed, as this study does not have data on coronary flow and microvascular dysfunction.

Difference in Procedural Characteristics and its Influence on Outcomes

In DEFINE-FLAIR and iFR-SWEDEHEART studies, FFR-guided strategy was associated with higher revascularization rate than iFR-guided strategy.[6, 7] Lee et al. reported that FFR was more sensitive to anatomical and hemodynamic stenosis severity than iFR.[21] In our study, revascularization was performed in 49.3% and 57.1% in the iFR and FFR-guided strategies, respectively, in men. However, this difference in revascularization rate was not translated into difference in clinical outcomes. In women, revascularization rate was not different between the 2 strategies. Like in previous studies, both the stent size and the number of stents implanted were smaller in women than in men in our study. Despite all these differences in procedural characteristics, clinical outcomes of iFR- and FFR-guided strategies were not different in both women and men. This result implies that both iFR and FFR can be effectively used to guide revascularization, regardless of sex, despite the physiologic backgrounds for the difference between women and men.

Limitations

Several limitations of this study need to be addressed. First, this was a post hoc analysis of the DEFINE-FLAIR trial. Second, invasive measurement of microvascular dysfunction was not performed. Third, as the DEFINE-FLAIR trial followed exclusive allocation into iFR- or FFR-guided strategy, incidence and prognostic implications of iFR-FFR discordance according to sex was unavailable.

Conclusions

FFR-guided strategy was associated with a higher rate of revascularization than iFR-guided strategy in men, but not in women. However, iFR- and FFR-guided treatment strategies showed comparable clinical outcome, regardless of sex.

Clinical Perspectives

What's known? iFR-guided strategy has shown relatively lower revascularization than FFR-guided strategy without the difference in clinical outcomes between the 2 strategies.

What's new? iFR value was not different according to sex, but FFR value was lower in men. In men, FFR-guided strategy resulted in higher revascularization rate than iFR-guided strategy. However, no difference in revascularization rate according to physiologic indices was observed in women. Despite these differences, iFR- and FFR-guided strategies showed comparable risk of clinical outcomes at 1 year in both women and men.

What's next? Further studies on how sex difference in microvascular function affects iFR and FFR values, and clinical implications of iFR-FFR discordance according to sex are needed.

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Figure Legends

Figure 1. Study Flow

In the current post-hoc analysis of the DEFINE-FLAIR study, 601 women and 1,891 men who were randomized to iFR- or FFR-guided strategy were analyzed.

Abbreviations: iFR, instantaneous wave-free ratio; FFR, fractional flow reserve.

Figure 2. Comparison of MACE between Women and Men

Kaplan-Meier curves show the comparison of 1-year rates of MACE according to sex.

Abbreviations: HR, hazard ratio; HRadj, multivariable adjusted hazard ratio; CI, confidence intervals.

Figure 3. Comparison of MACE between iFR- and FFR-Guided Strategies According to Sex

Kaplan-Meier curves show the comparison of 1-year rates of MACE between iFR- and FFR-guided strategies in women and men.

Abbreviations: iFR, instantaneous wave-free ratio; FFR, fractional flow reserve; HR, hazard ratio; HR_{adj}, multivariable adjusted hazard ratio; CI, confidence intervals.

Figure 4. Comparison of MACE between iFR- and FFR-Guided Strategies in Deferred

Patients

Kaplan-Meier curves show the comparison of 1-year rates of MACE of deferred patients according to iFR- and FFR-guided strategies in women and men.

Abbreviations: iFR, instantaneous wave-free ratio; FFR, fractional flow reserve; HR, hazard ratio; HR_{adj}, multivariable adjusted hazard ratio; CI, confidence intervals.