Sex Differences in Instantaneous Wave-free Ratio or Fractional Flow

Reserve-Guided Revascularization Strategy

Chee Hae Kim, MD,1 Bon-Kwon Koo, MD, PhD,2 Hakim-Moulay Dehbi, PhD,3 Joo Myung Lee, MD, MPH, PhD,4 Joon-Hyung Doh, MD, PhD,5 Chang-Wook Nam, MD, PhD,6 Eun-Seok Shin, MD, PhD,7 Christopher M. Cook, MBBS PhD,8 Rasha Al-Lamee, MBBS PhD,8 Ricardo Petraco, MD, PhD,8 Sayan Sen, MBBS, PhD,8 Iqbal S. Malik, PhD,8 Sukhjinder S. Nijjer, MB ChB, PhD,8 Hernán Mejía-Rentería, MD,9 Eduardo Alegria-Barrero, MD, PhD10, Ali Alghamdi, MD11, John Altman, MD12, Sérgio B Baptista, MD, PhD13, Ravinay Bhinda, MB, BS, PhD14, Waldemar Bojara, MD15, Salvatore Brugaletta, MD, PhD16, Pedro Canas Silva, MD17, Carlo Di Mario, MD, PhD18, Andrejs Erglis, MD, PhD19, Robert T Gerber, PhD20, Olaf Going, MD21, Tobias Härle, MD22, Farrel Hellig, MB, BS23, Ciro Indolfi, MD24, Luc Janssens, MD25, Allen Jeremias, MD26, Rajesh K Kharbanda, MD, PhD27, Ahmed Khashaba, MD28, Yuetsu Kikuta, MD29, Florian Krackhardt, MD30, Mika Laine, MD, PhD31, Sam J Lehman, MB, BS, PhD32, Hitoshi Matsuo, MD, PhD33, Martijn Meuwissen, MD, PhD34, Giampaolo Niccoli, MD, PhD35, Jan J Pick, MD, PhD36, Flavo Ribichini, MD37, Habib Samady, MD38, James Sapontis, MB, BS39, Arnold H Seto, MD, MPA40, Murat Sezer, MD41, Andrew SP Sharp, MD42, Jasvindar Singh, MD43, Hiroaki Takashima, MD, PhD44, Suneel Talwar, MB, BS, MD45, Nobuhiro Tanaka, MD, PhD46, Kare Tang, MD47, Eric Van Belle, MD, PhD48, Niels van Royen, MD, PhD49, Hugo Vinhas, MD50, Christaan J Vrints, MD, PhD51, Darren Walters, MB, BS52, Hiroyoshi Yokoi, MD53, Bruce Samuels, MD54, Chris Buller, MD55, Manesh R Patel, MD56, Patrick Serruys, MD, PhD5, Javier Escaned, MD, PhD5, Justin E Davies, MD, PhD5

Affiliations:

1VHS Medical Center, Seoul, South Korea; 2Seoul National University Hospital and Institute on Aging, Seoul National University, Seoul, South Korea; 3CRUK & UCL Cancer Trials Centre, University College London, London, United Kingdom; 4Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 5Inje University Ilsan Paik Hospital, Daehwa-Dong, South Korea; 6Keimyung University Dongsan Medical Center, Daegu, South Korea; 7Ulsan Hospital, Ulsan, South Korea and Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea; 8Hammersmith Hospital, Imperial College London, United Kingdom; 9Hospital Clínico San Carlos, IDIiSSC and Universidad Complutense de Madrid, Madrid, Spain; 10Hospital Universitario de Torrejón y Universidad Francisco de Vitoria, Spain; 11King Abdulaziz Medical City Cardiac Center, Riyadh, Saudi Arabia; 12Colorado Heart and Vascular, Lakewood, United States of America; 13Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; 14Royal North Shore Hospital, Sydney, Australia; 15Gemeinschaftsklinikum Mittelhein, Kemphof Koblenz, Koblenz, Germany; 16Cardiovascular Institute, Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; 17Hospital Santa Maria, Lisbon, Portugal; 18Royal Brompton Hospital, Imperial College London, United Kingdom and University of Florence,
Florence, Italy; 19 Pauls Stradins Clinical University Hospital, Riga, Latvia; 20 Conquest Hospital, St Leonards-on-Sea, United Kingdom; 21 Sana Klinikum Lichtenberg, Lichtenberg, Germany; 22 Klinikum Oldenburg, European Medical School, Carl von Ossietzky University, Oldenburg, Germany; 23 Sunninghill Hospital, Johannesburg, South Africa; 24 University Magna Graecia, Catanzaro, Italy; 25 Imelda Hospital, Bonheiden, Belgium; 26 Stony Brook University Medical Center, New York, United States of America; 27 John Radcliffe Hospital, Oxford University Hospitals Foundation Trust, Oxford, United Kingdom; 28 Ain Shams University, Cairo, Egypt; 29 Fukuyama Cardiovascular Hospital, Fukuyama, Japan; 30 Charite Campus Virchow Klinikum, Universitaetsmedizin, Berlin, Germany; 31 Helsinki University Hospital, Helsinki, Finland; 32 Flinders University, Adelaide, SA, Australia; 33 Gifu Heart Center, Gifu, Japan; 34 Amphia Hospital, Breda, The Netherlands; 35 Catholic University of the Sacred Heart, Rome, Italy; 36 AMC Heart Center, Academic Medical Center, The Netherlands; 37 University Hospital Verona, Verona, Italy; 38 Emory University, Atlanta, United States of America; 39 MonashHeart and Monash University, Melbourne, VIC, Australia; 40 Veterans Affairs Long Beach Healthcare System, Long Beach, CA, United States of America; 41 Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey; 42 Royal Devon and Exeter Hospital and University of Exeter, Exeter, United Kingdom; 43 Washington University School of Medicine, St Louis, United States of America; 44 Aichi Medical University Hospital, Aichi, Japan; 45 Royal Bournemouth General Hospital, Bournemouth, United Kingdom; 46 Tokyo Medical University, Tokyo, Japan; 47 Essex Cardiothoracic Centre, Basildon and Anglia Ruskin University, Chelmsford, United Kingdom; 48 Institut Coeur Poumon, Lille University Hospital, and INSERM Unité 1011, Lille, France; 49 VU University Medical Center, Amsterdam, The Netherlands; 50 Hospital Garcia de Horta, Lisbon, Portugal; 51 Antwerp University Hospital, Antwerp, Belgium; 52 Prince Charles Hospital, Brisbane, QLD, Australia; 53 Fukuoka Sannou Hospital, Fukuoka, Japan; 54 Cedars-Sinai Heart Institute, Los Angeles, California, United States of America; 55 St Michaels Hospital, Toronto, Canada; 56 Duke University, Durham, NC (MRP), United States of America.

Address for correspondence:

Bon-Kwon Koo, MD, PhD
Division of Cardiology, Department of Internal Medicine,
Seoul National University Hospital,
101 Daehang-ro, Chongno-gu, Seoul, 03080, Korea
Telephone: 82-2-2072-2062; Fax: 82-2-3675-0805
E-mail: bkkoo@snu.ac.kr

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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: An iFR-guided strategy has shown a lower revascularization rate than FFR-guided strategy, without differences in clinical outcomes.

Methods: This is a post-hoc analysis of the 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. 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 a 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 difference in mean iFR value according to sex (0.91 ± 0.09 vs. 0.91 ± 0.10, p = 0.442). However, the mean FFR value was lower in men than in women (0.83 ± 0.09 vs. 0.85 ± 0.10, p = 0.001). In men, an FFR-guided strategy was associated with a higher rate of revascularization than an iFR-guided strategy (57.1% vs. 49.3%, p = 0.001), but this difference was not observed in women (41.4% vs. 42.6%, p = 0.757). There was no difference in MACE rates between iFR- and FFR-guided strategies in both women (5.4% vs. 5.6%, adjusted HR 1.10, 95% CI 0.50-2.43, p = 0.805) and men (6.6% vs. 7.0%, adjusted HR 0.98, 95% CI 0.66-1.46, p = 0.919).

Conclusions: An 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 strategies showed comparable clinical outcomes, 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. Mean iFR value was not different according to sex, but mean 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 clinical outcomes at 1 year in women and men.
Introduction

Ischemia-guided coronary revascularization is a standard approach for patients with coronary artery disease.\textsuperscript{1,2} Fractional flow reserve (FFR) is a hyperemic physiologic index used to identify ischemia-causing stenoses in the cardiac catheterization laboratory.\textsuperscript{3-5} As an alternative to FFR, the instantaneous wave-free ratio (iFR) is a resting physiologic index that does not require hyperemia.\textsuperscript{6} 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) have recently compared iFR- and FFR-guided revascularization strategies and demonstrated that the iFR-guided approach is non-inferior to the FFR-approach.\textsuperscript{7,8}

A previous study showed that mean FFR value was higher in women than men for the same stenosis severity.\textsuperscript{9} 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.\textsuperscript{10,11,12} Therefore, iFR- and FFR-guided strategies might result in different revascularization rates and clinical outcomes according to sex, but these differences have not yet been investigated. 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 is a post-hoc analysis of the DEFINE-FLAIR trial which was designed to investigate non-inferiority of iFR-guided strategy compared to FFR-guided strategy. The trial was a multicenter, international, randomized, blinded trial performed at 49 interventional sites in 19 countries. Detailed study protocol and clinical outcomes at 1 year have been previously published. In brief, patients who had intermediate coronary artery disease (40 to 70% stenosis of the diameter on visual assessment) with in at least one native artery were eligible for inclusion. A full list of inclusion and exclusion criteria is provided in Supplementary Table 1. 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 an iFR- or FFR-guided revascularization strategy. 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 angiographic stenoses. Revascularization was performed according to prespecified treatment thresholds of iFR \( \leq 0.89 \) or FFR \( \leq 0.80 \).

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 scheduled 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. 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. 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. Conversely, current smoking, 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 a significantly lower number of functionally significant lesions per patient, a 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, mean iFR value was not different between women and men (0.91 ± 0.09 vs. 0.91 ± 0.10, p = 0.442). However, mean FFR value was lower in men than in women (0.83 ± 0.09 vs. 0.85 ± 0.10, p = 0.001). Amongst 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 between 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 \( \geq 1 \) functionally significant lesion, and more frequent revascularization (57.1\% vs. 49.3\%, \( p = 0.001 \)) in comparison with iFR-guided strategy.

Clinical Outcomes

Patients were followed for a median of 365 days (Q1-Q3, 365-365). 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 2). The individual rates of death from any cause, nonfatal MI and unplanned revascularization were not significantly different between sexes (Supplementary Table 2).

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 3 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 4, 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 a lower number of functionally significant lesions per patient and less frequently underwent revascularization than men; 2) the mean iFR value was not different according to sex, but the mean FFR value was lower in men; 3) in men, an FFR-guided strategy was associated with a higher revascularization rate than iFR-guided strategy, but there was no difference in revascularization rates between the two physiologic indices in women; 4) MACE rate was not different according to sex in the entire population, and 5) despite the difference in baseline and procedural characteristics according to sex, both iFR- and FFR-guided strategies showed comparable risk of MACE in women and men.

Difference in FFR and iFR between Women and Men

Higher FFR values in women than in men are consistently reported in previous studies,9, 13 and the differences in microvascular function,14 myocardial mass,15 coronary height,16 vessel size,17 plaque characteristics,18, 19 and diastolic function20 have been suggested as potential mechanisms for this effect. Those factors can cause higher hyperemic coronary flow and lower FFR in men than in women for the same epicardial stenosis. However, the influence of sex on resting pressure indices has not been well-defined. In a CONTRAST substudy, although the number of functionally significant lesions defined by FFR was higher in men than in women, mean FFR and iFR values were not different.21 In our study, mean FFR was higher in women than in men and no difference was observed in the mean iFR value
according to sex. This lack of difference in iFR values between women and men, in contrast to FFR, can be due to relatively higher resting flow in women. In our study, women were older and showed higher prevalence of hypertension, higher systolic blood pressure and heart rate than men, and these factors can cause higher resting coronary flow in women than in men.

Microvascular dysfunction assessed by coronary flow reserve (CFR) was reported to be more frequent in women. Accordingly, a blunted hyperemic response is considered to be an important reason for the higher FFR values often observed in women. 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. Rather, resting coronary flow was noted to be higher in women, thereby potentially accounting for a low CFR. Therefore, further studies on how sex difference in microvascular function and physiologic response to epicardial stenosis affects iFR and FFR values are needed, as this study does not have data on coronary flow, microvascular dysfunction, and quantitative assessment for epicardial disease severity.

**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. In our study, revascularization was performed in 49.3% and 57.1% in the iFR and FFR-guided strategies, respectively, in men like as shown in previous studies. However, this difference in revascularization rate did not translate into a difference in clinical outcomes. This might be due to recent advances in revascularization techniques, stent technology and medical therapies and...
the relatively low-risk population of this study. In women, the revascularization rate was not noted to be different between the two physiologic strategies. As shown 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 similar 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 which may introduce bias. Second, invasive measurement of microvascular dysfunction was not performed which means we cannot definitely understand the differences in FFR values between men and women. Third, as the DEFINE-FLAIR trial followed exclusive allocation into iFR- or FFR-guided strategy, paired data of iFR and FFR in the same patient were not available. As a results, comparisons of physiologic indices between groups were performed based on group data, assuming similar stenosis severity between groups. Forth, data on angiographic disease severity were not available in this study. Therefore, the association between angiographic stenosis severity and iFR/FFR according to sex could not be presented. Fifth, neither the physicians nor the patients were not blinded to the iFR/FFR results and whether or not revascularization was performed. However, patients and physicians who were responsible for the follow-up care were blinded to the group assignments. Sixth, as DEFINE-FLAIR study included a relatively low-risk population, event rates were also
relatively low and may be insufficient to determine the difference in clinical outcomes according to sex.

Conclusions

From this post hoc analysis of the DEFINE-FLAIR trial, an FFR-guided strategy was associated with a higher rate of revascularization than iFR-guided strategy in men, but not in women. Despite this, both iFR- and FFR-guided treatment strategies showed comparable clinical outcome, regardless of sex.
Clinical Perspectives

What’s known? An iFR-guided strategy has shown relatively lower rates of revascularization than an FFR-guided strategy, without differences in clinical outcomes between the two strategies.

What’s new? Mean iFR value was not different according to sex. In contrast, mean 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.
References


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; HRadj, 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.

Central Illustration. Sex Differences in Procedural Characteristics and Clinical Outcomes of iFR- or FFR-Guided Strategy

The current study is a post-hoc analysis of DEFINE-FLAIR study focusing on sex differences in iFR- and FFR-guided strategies. Mean iFR value was not different according to sex, but mean FFR value was lower in men. Amongst women, there were no differences in number of functionally significant lesions per patient or rate of revascularization between iFR- and FFR-guided strategies. In men, FFR-guided strategy was associated with a higher number of functionally significant lesions per patient and more frequent revascularization in comparison with iFR-guided strategy. Despite these differences, iFR- and FFR-guided strategies showed comparable clinical outcomes at 1 year in women and men. Height of the bars indicates the mean value or percentage, and error bars indicate the standard deviation.