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Sex Differences in 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 An iFR-guided strategy has shown a lower revascularization rate than an 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 $\pm$ 0.51 vs. 0.43 $\pm$ 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 $\pm$ 0.09 vs. 0.91 $\pm$ 0.10; $p = 0.442$). However, the mean FFR value was lower in men than in women (0.83 $\pm$ 0.09 vs. 0.85 $\pm$ 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 hazard ratio: 1.10; 95% confidence interval: 0.50 to 2.43; $p = 0.805$) and men (6.6% vs. 7.0%, adjusted hazard ratio: 0.98; 95% confidence interval: 0.66 to 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. (Functional Lesion Assessment of Intermediate Stenosis to guide Revascularization [DEFINE-FLAIR]; NCT02053038) (J Am Coll Cardiol Intv 2019;12:2035–46) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

FFR = fractional flow reserve

HR = hazard ratio

iFR = instantaneous wave-free ratio

MACE = major adverse cardiac events

MI = myocardial infarction

PCI = percutaneous coronary intervention

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 used to identify ischemia-causing stenoses in the cardiac catheterization laboratory (3–5). As an alternative to FFR, the instantaneous wave-free ratio (iFR) is a resting physiologic index that does not require hyperemia (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 noninferior to the FFR-approach (7,8).

SEE PAGE 2047

A previous study showed that mean FFR value was higher in women than men for the same stenosis severity (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 (10–12). Therefore, iFR- and FFR-guided strategies might result in different revascularization rates and clinical

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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 noninferiority of an iFR-guided strategy compared with an FFR-guided strategy (**Figure 1**) (7). 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 (7). In brief, patients who had intermediate coronary artery disease (40% to 70% stenosis of the diameter on visual assessment) with in at least 1 native artery were eligible for inclusion. A full list of inclusion and exclusion criteria is provided in Online 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, California) 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 $\pm$ SD or median (interquartile range), as appropriate, and were compared using Student's *t*-test. Categorical variables were presented as numbers with proportions 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 2-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 (7). For a multivariable adjusted analysis, adjustment for age, clinical presentation, Canadian Cardiovascular Society class for grading of angina pectoris, hypertension, diabetes mellitus, hyperlipidemia, previous MI, and previous percutaneous coronary intervention (PCI) was performed.

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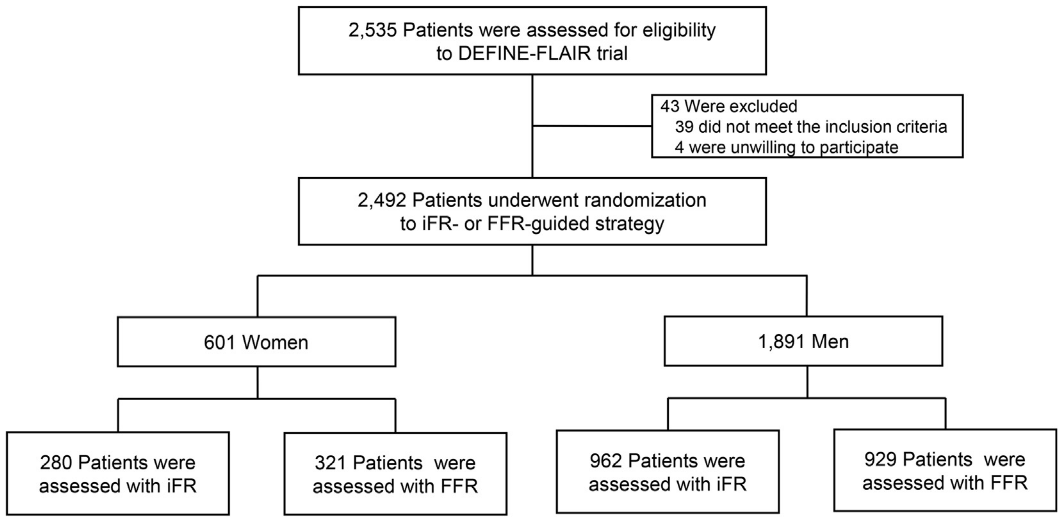
FIGURE 1 Study Flow



In the current post hoc analysis of the DEFINE-FLAIR (Functional Lesion Assessment of Intermediate stenosis to guide Revascularization) trial, 601 women and 1,891 men who were randomized to an instantaneous wave-free ratio (iFR)- or fractional flow reserve (FFR)-guided strategy were analyzed.

TABLE 1 Baseline Clinical Characteristics

	Total Population			Women			Men		
	Women (n = 601)	Men (n = 1,891)	p Value	iFR (n = 280)	FFR (n = 321)	p Value	iFR (n = 962)	FFR (n = 929)	p Value
Age, yrs	69.4 (62.3–75.3)	64.6 (56.9–72.1)	<0.001	70.5 (62.2–76.3)	68.8 (62.3–74.8)	0.199	65.0 (57.0–72.2)	64.1 (56.9–71.9)	0.470
Clinical diagnosis			0.043			0.358			0.724
STEMI	17 (2.8)	74 (3.9)		10 (3.6)	7 (2.2)		39 (4.1)	35 (3.8)	
ACS	71 (11.8)	299 (15.8)		35 (12.5)	36 (11.2)		151 (15.7)	148 (15.9)	
Stable disease	506 (84.2)	1,492 (78.9)		230 (82.1)	276 (86.0)		756 (78.6)	736 (79.2)	
Diabetes mellitus	185 (30.8)	573 (30.3)	0.519	80 (28.6)	105 (32.7)	0.547	302 (31.4)	271 (29.2)	0.334
Hypertension	469 (78.0)	1,288 (68.1)	<0.001	223 (79.6)	246 (76.6)	0.661	650 (67.6)	638 (68.7)	0.636
Hypercholesterolemia	395 (65.7)	1,191 (63.0)	0.477	185 (66.1)	210 (65.4)	0.389	609 (63.3)	582 (62.6)	0.213
Current smoker	94 (15.6)	411 (21.7)	<0.001	43 (15.4)	51 (15.9)	0.188	395 (41.1)	376 (40.5)	0.699
Previous MI	121 (20.1)	613 (32.4)	<0.001	49 (17.5)	72 (22.4)	0.302	309 (32.1)	304 (32.7)	0.118
Previous PCI	204 (33.9)	812 (42.9)	<0.001	88 (31.4)	116 (36.1)	0.186	401 (41.7)	411 (44.2)	0.147
CCS angina class			0.196			0.637			0.093
I	141 (23.5)	511 (27.0)		73 (26.1)	68 (21.2)		274 (28.5)	237 (25.5)	
II	202 (33.6)	542 (28.7)		92 (32.9)	110 (34.3)		282 (29.3)	260 (28.0)	
III	72 (12.0)	209 (11.1)		34 (12.1)	38 (11.8)		93 (9.7)	116 (12.5)	
IV	37 (6.2)	116 (6.1)		15 (5.4)	22 (6.9)		66 (6.9)	50 (5.4)	
Systolic blood pressure, mm Hg	137.0 (121.0–150.0)	130.0 (120.0–144.0)	<0.001	137.0 (122.0–150.0)	136.0 (121.0–150.0)	0.949	130.0 (120.0–144.0)	131.0 (120.0–143.0)	0.693
Diastolic blood pressure, mm Hg	72.0 (65.0–80.0)	75.0 (68.0–82.0)	0.001	72.0 (65.0–80.0)	73.0 (65.0–81.0)	0.309	75.0 (68.0–82.0)	75.0 (68.0–82.0)	0.800
Heart rate, beats/min	70.0 (61.0–78.0)	67.0 (60.0–76.0)	<0.001	70.0 (60.0–78.0)	70.0 (62.0–78.0)	0.455	67.0 (60.0–76.0)	66.0 (60.0–75.0)	0.605

Values are median (interquartile range) or n (%).

ACS = acute coronary syndrome; CCS = Canadian Cardiovascular Society; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RESULTS

PATIENT 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 the 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 and the Central Illustration show 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). Among 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, an 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 an iFR-guided strategy.

TABLE 2 Procedural Characteristics According to Sex

	Women	Men	p Value
Type of vessel evaluated			
Left anterior descending artery	398 (53.6)	1,291 (52.9)	0.764
Left circumflex artery	142 (19.1)	514 (21.1)	0.249
Right coronary artery	189 (25.4)	578 (23.7)	0.329
Other	14 (1.9)	57 (2.3)	0.380
Vessels evaluated or treated per patient	1.44 ± 0.74	1.56 ± 0.79	<0.001
Functionally significant lesions per patient	0.31 ± 0.51	0.43 ± 0.59	<0.001
≥1 functionally significant lesions per patient	175 (29.1)	737 (39.0)	<0.001
Revascularization performed	253 (42.1)	1,004 (53.1)	<0.001
Stents placed per patient	0.56 ± 0.85	0.74 ± 0.97	<0.001
Stent length per patient, mm	28.0 (18.0–40.0)	28.0 (18.0–44.0)	0.148
Stent diameter, mm	2.96 (2.58–3.08)	3.00 (2.75–3.25)	0.027

Values are n (%), mean ± SD, or median (interquartile range).
Abbreviations as in Table 1.

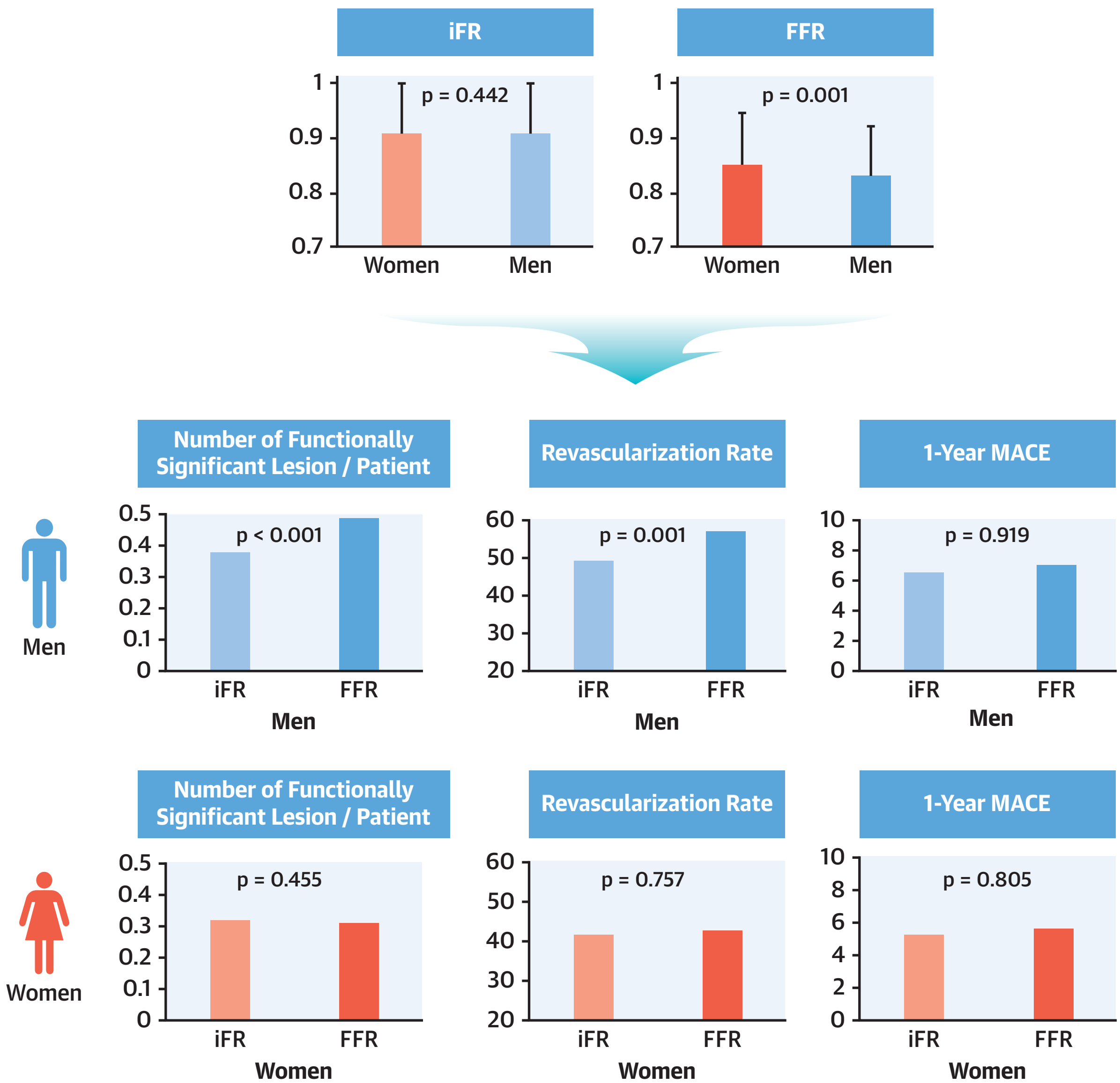
CLINICAL OUTCOMES. Patients were followed for a median of 365 (interquartile range: 365 to 365) days. At 1 year, MACE rate was not different according to sex (women vs. men, 5.49% vs. 6.77%; adjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.53 to 1.28; p = 0.380) (Figure 2, Online Table 2).

TABLE 3 Procedural Characteristics According to iFR- or FFR-Guided Strategy

	Women			Men		
	iFR	FFR	p Value	iFR	FFR	p Value
Type of vessel evaluated						
Left anterior descending artery	189 (55.3)	209 (52.1)	0.392	655 (53.1)	636 (52.7)	0.832
Left circumflex artery	58 (17.0)	84 (20.9)	0.168	265 (21.5)	249 (20.6)	0.601
Right coronary artery	90 (26.3)	99 (24.7)	0.612	284 (23.0)	294 (24.4)	0.442
Other	5 (1.5)	9 (2.2)	0.760	29 (2.4)	28 (2.3)	0.629
Vessels evaluated or treated per patient	1.41 ± 0.73	1.47 ± 0.74	0.211	1.54 ± 0.76	1.58 ± 0.82	0.672
iFR or FFR value	0.91 ± 0.09	0.85 ± 0.10		0.91 ± 0.10	0.83 ± 0.09	
Functionally significant lesions per patient	0.32 ± 0.48	0.31 ± 0.53	0.455	0.38 ± 0.53	0.49 ± 0.63	<0.001
≥1 functionally significant lesions per patient	87 (31.1)	88 (27.4)	0.325	339 (35.2)	398 (42.8)	0.001
Revascularization performed	116 (41.4)	137 (42.6)	0.757	474 (49.3)	530 (57.1)	0.001
Stents placed per patient	0.57 ± 0.87	0.54 ± 0.83	0.719	0.69 ± 0.94	0.79 ± 1.00	0.021
Stent length per patient, mm	30.0 (18.0–41.0)	25.0 (16.0–38.0)	0.416	28.0 (18.0–42.5)	28.0 (18.0–46.0)	0.409
Stent diameter, mm	2.92 (2.50–3.00)	2.96 (2.75–3.13)	0.409	3.00 (2.75–3.25)	3.00 (2.75–3.25)	0.588

Values are n (%), mean ± SD, or median (interquartile range).
Abbreviations as in Table 1.

CENTRAL ILLUSTRATION Sex Differences in Procedural Characteristics and Clinical Outcomes of iFR- or FFR-Guided Strategy



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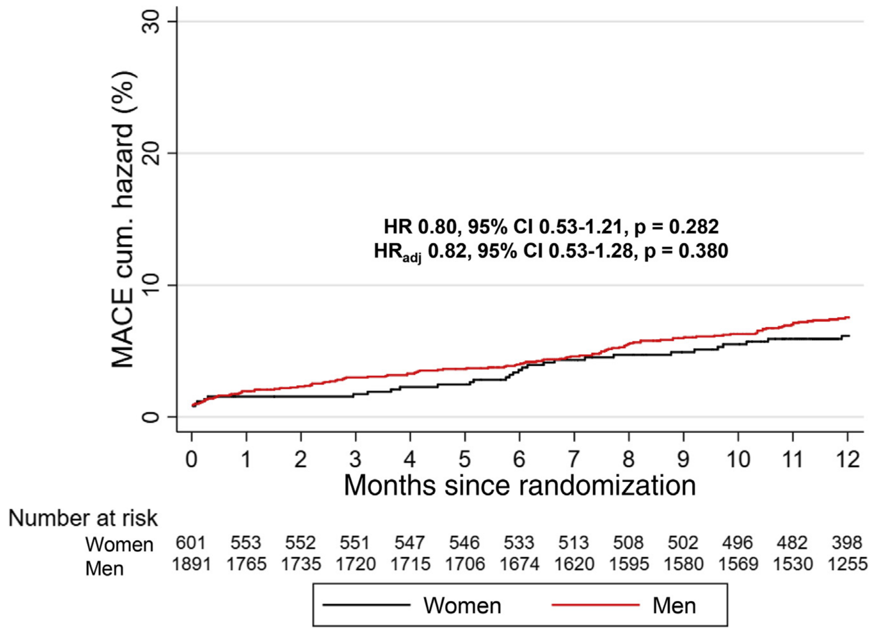
The current study is a post hoc analysis of DEFINE-FLAIR (Functional Lesion Assessment of Intermediate stenosis to guide Revascularization) trial focusing on sex differences in instantaneous wave-free ratio (iFR)- and fractional flow reserve (FFR)-guided strategies. Mean iFR value was not different according to sex, but mean FFR value was lower in men. Among 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 proportion, and error bars indicate the standard deviation.

The individual rates of death from any cause, nonfatal MI, and unplanned revascularization were not significantly different between sexes (Online 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 to 2.43; p = 0.805)

FIGURE 2 **Comparison of MACE Between Women and Men**



Kaplan-Meier curves show the comparison of 1-year rates of major adverse cardiac events (MACE) according to sex. CI = confidence interval; HR = hazard ratio; HR_{adj} = multivariable adjusted hazard ratio.

and men (6.55% vs. 7.00%; adjusted HR: 0.98; 95% CI: 0.66 to 1.46; p = 0.919) (**Table 4**, Online Table 3, **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**, Online Table 4, **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

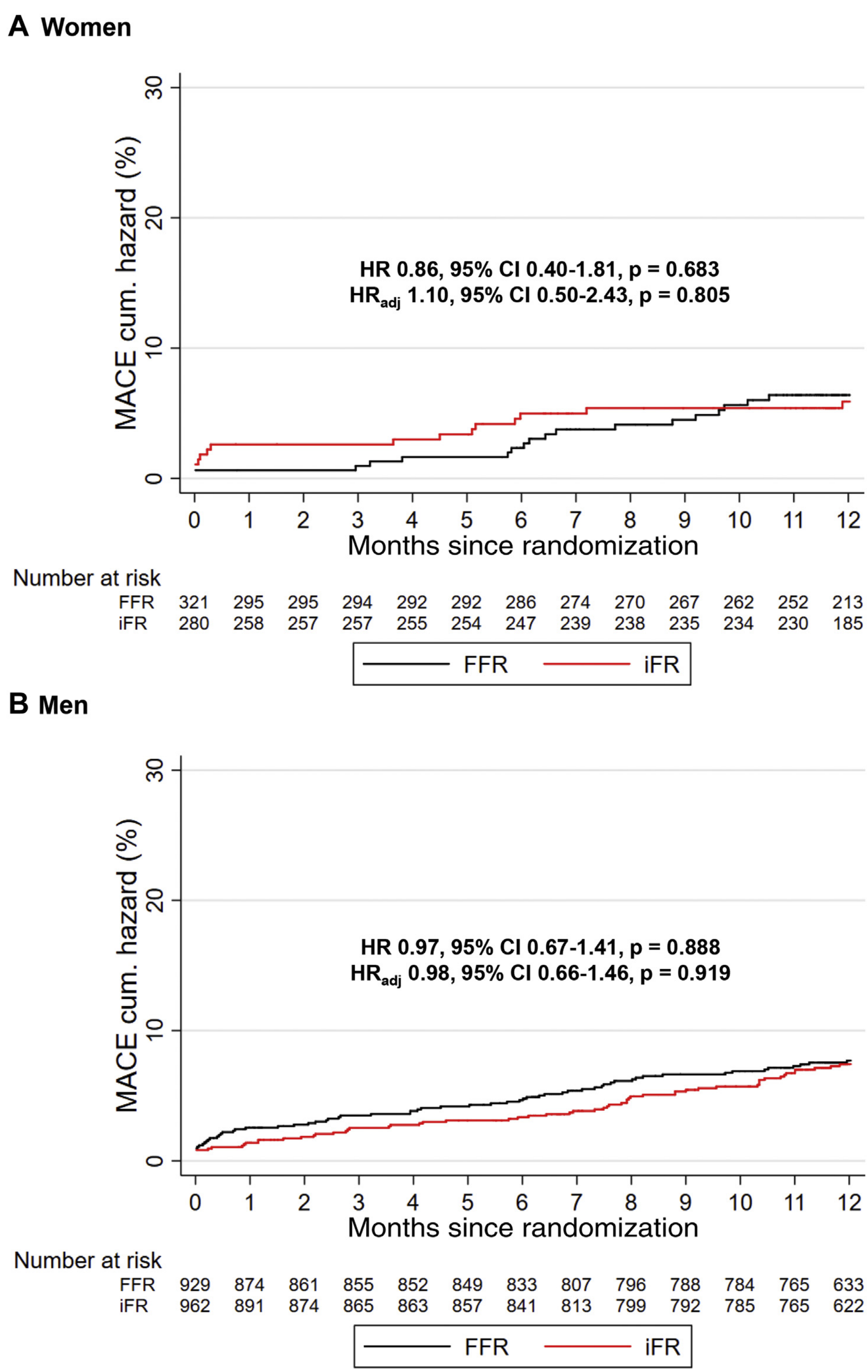
TABLE 4 **Multivariable-Adjusted Clinical Outcomes at 1 Year Between iFR- and FFR-Guided Strategies According to Sex**

	Women				Men				
	iFR (n = 280)	FFR (n = 321)	HR_{adj} (95% CI)	p Value	iFR (n = 962)	FFR (n = 929)	HR_{adj} (95% CI)	p Value	Interaction p Value
Primary endpoint: MACE*	15 (5.36)	18 (5.61)	1.10 (0.50–2.43)	0.805	63 (6.55)	65 (7.00)	0.98 (0.66–1.46)	0.919	0.820
Cardiac death, MI, or unplanned revascularization	13 (4.64)	17 (5.30)	0.97 (0.42–2.23)	0.937	52 (5.41)	57 (6.14)	0.92 (0.60–1.43)	0.719	0.898
Death from any cause, MI	11 (3.93)	5 (1.56)	2.32 (0.65–8.25)	0.192	39 (4.05)	36 (3.88)	1.04 (0.58–1.88)	0.885	0.285
Death from any cause	5 (1.79)	2 (0.62)	2.96 (0.55–16.07)	0.208	17 (1.77)	11 (1.18)	1.22 (0.51–2.91)	0.657	0.361
Death from cardiovascular causes	1 (0.36)	1 (0.31)	1.39 (0.01–169.4)	0.892	6 (0.62)	3 (0.32)	1.25 (0.28–5.63)	0.774	0.936
Death from noncardiovascular causes	4 (1.43)	1 (0.31)	10.97 (0.70–172.2)	0.088	11 (1.14)	8 (0.86)	1.20 (0.41–3.51)	0.735	0.295
Nonfatal myocardial infarction	8 (2.86)	3 (0.93)	4.14 (0.69–24.84)	0.120	23 (2.39)	25 (2.69)	0.97 (0.47–2.00)	0.944	0.173
Unplanned revascularization	9 (3.21)	16 (4.98)	0.99 (0.41–2.41)	0.988	37 (3.85)	47 (5.06)	0.89 (0.56–1.41)	0.609	0.855

Values are n (%), unless otherwise indicated. The included covariates into multivariable adjusted model were age, clinical presentation, CCS class for grading of angina pectoris, hypertension, diabetes, hyperlipidemia, previous MI, and previous PCI. *Composite of death from any cause, nonfatal MI, or unplanned revascularization.

CI = confidence interval; HR_{adj} = adjusted hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction; other abbreviations as in **Table 1**.

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 **(A)** women and **(B)** men. Abbreviations as in Figures 1 and 2.

TABLE 5 Multivariable-Adjusted Clinical Outcomes at 1 Year Between iFR- and FFR-Guided Strategies in Deferred Patients

	Women				Men				
	iFR (n = 164)	FFR (n = 184)	HR_{adj} (95% CI)	p Value	iFR (n = 489)	FFR (n = 400)	HR_{adj} (95% CI)	p Value	Interaction p Value
Primary endpoint: MACE*	5 (3.05)	7 (3.80)	0.68 (0.20–2.38)	0.551	21 (4.29)	20 (5.00)	0.83 (0.41-1.66)	0.593	0.878
Cardiac death, MI, or unplanned revascularization	4 (2.44)	6 (3.26)	0.65 (0.16–2.56)	0.535	17 (3.48)	17 (4.25)	0.81 (0.38–1.72)	0.582	0.943
Death from any cause, MI	2 (1.22)	1 (0.54)	0.93 (0.00–418)	0.981	9 (1.84)	12 (3.00)	0.58 (0.18–1.84)	0.354	0.285
Death from any cause	2 (1.22)	1 (0.54)	2.23 (0.01–843.6)	0.791	5 (1.02)	3 (0.75)	0.62 (0.08–4.75)	0.645	0.564
Death from cardiovascular causes	1 (0.61)	0 (0.00)	–	–	1 (0.20)	0 (0.00)	–	–	–
Death from noncardiovascular causes	1 (0.61)	1 (0.54)	–	–	4 (0.82)	3 (0.75)	0.62 (0.08–4.75)	0.645	–
Nonfatal myocardial infarction	0 (0.00)	0 (0.00)	–	–	4 (0.82)	9 (2.25)	0.51 (0.14–1.86)	0.310	–
Unplanned revascularization	3 (1.83)	6 (3.26)	0.53 (0.12–2.37)	0.409	16 (3.27)	16 (4.00)	0.82 (0.38–1.73)	0.595	0.804

Values are n (%), unless otherwise indicated. The included covariates into multivariable adjusted model were age, clinical presentation, CCS class for grading of angina pectoris, hypertension, diabetes, hyperlipidemia, previous MI, and previous PCI. *Composite of death from any cause, nonfatal MI, or unplanned revascularization.
Abbreviations as in Tables 1 and 4.

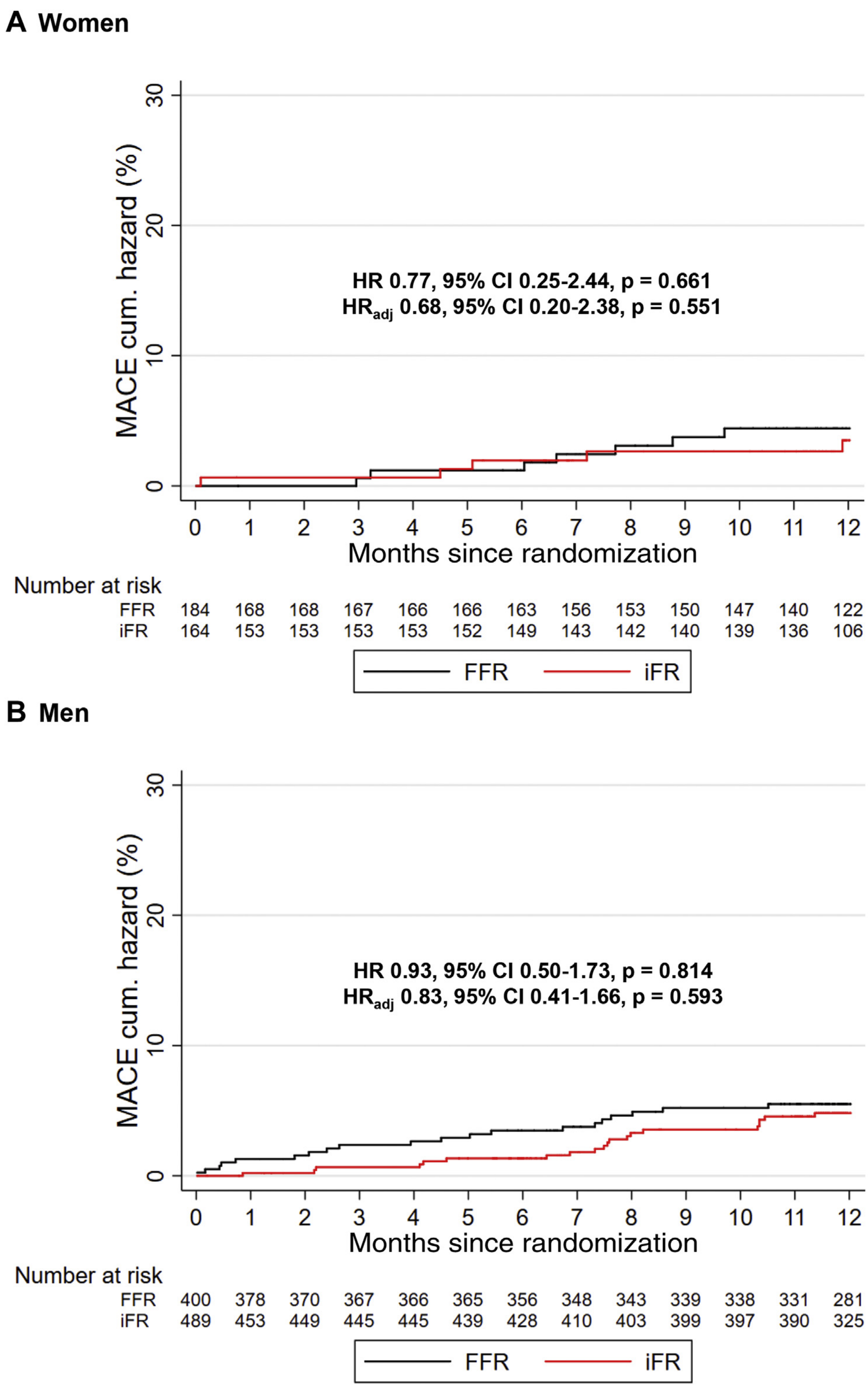
population, women had a lower number of functionally significant lesions per patient and less frequently underwent revascularization than men; 2) the mean iFR value was not different according to sex, but the mean FFR value was lower in men; 3) in men, an FFR-guided strategy was associated with a higher revascularization rate than iFR-guided strategy, but there was no difference in revascularization rates between the 2 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 function (20) 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 (Can Contrast Injection Better Approximate FFR Compared to Pure Resting Physiology?) 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 higher 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 (14). Accordingly, a blunted hyperemic response is considered to be an important reason for the higher FFR values often observed in women (11). 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 (10). Rather, resting coronary flow was noted to be higher in women, thereby potentially accounting for a low CFR (10). 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 the DEFINE-FLAIR and iFR-SWEDEHEART studies, an FFR-guided strategy was associated with higher revascularization rate than an iFR-guided strategy (7,8). In our study, revascularization was performed in 49.3% and 57.1% in the iFR and FFR-guided strategies, respectively, in men, similar to that shown in previous studies (7,8,22,23). However, this difference in revascularization rate did not translate into a difference in

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 **(A)** women and **(B)** men. Abbreviations as in Figures 1 and 2.

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 2 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.

STUDY LIMITATIONS. 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. Fourth, data on angiographic disease severity were not available in this study. Therefore, the association between angiographic stenosis severity and iFR or FFR according to sex could not be presented. Fifth, neither the physicians nor the patients were not blinded to the iFR and 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. Last, as the DEFINE-FLAIR trial 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.

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PERSPECTIVES

WHAT IS KNOWN? An iFR-guided strategy has shown relatively lower rates of revascularization than an FFR-guided strategy, without differences in clinical outcomes between the 2 strategies.

WHAT IS 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 IS 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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KEY WORDS clinical outcome, fractional flow reserve, instantaneous wave-free ratio, sex

APPENDIX For supplemental tables, please see the online version of this paper.