JACC: ASIA VOL. 4, NO. 3, 2024

ORIGINAL RESEARCH

Sex Differences in Clinical Outcomes Associated With Quantitative Flow Ratio-Guided Percutaneous Coronary Intervention

Yundai Chen, MD,[a,*] Lei Gao, MD,[b,*] Birgit Vogel, MD,[c] Feng Tian, MD,[b] Qinhua Jin, MD,[b] Jun Guo, MD,[b] Zhijun Sun, MD,[b] Weixian Yang, MD,[d] Zening Jin, MD,[e] Bo Yu, MD,[f] Guosheng Fu, MD,[g] Jun Pu, MD,[h] Xinkai Qu, MD,[i] Qi Zhang, MD,[j] Yanyan Zhao, MSc,[k] Lilei Yu, MD,[l] Changdong Guan, MSc,[d] Shengxian Tu, PhD,[m] Shubin Qiao, MD,[d] Bo Xu, MBBS,[d,n] Roxana Mehran, MD,[c] Lei Song, MD,[d] on behalf of the FAVOR III China Study Group

ABSTRACT

BACKGROUND FAVOR III China (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease) reported improved clinical outcomes in quantitative flow ratio (QFR) relative to angiography-guided percutaneous coronary intervention (PCI), but the clinical impact of QFR-guided PCI according to sex remains unknown.

OBJECTIVES The authors sought to compare sex differences in the 2-year clinical benefits of a QFR-guided PCI strategy and to evaluate the differences in outcomes between men and women undergoing contemporary PCI.

METHODS This study involved a prespecified subgroup analysis of the FAVOR III China trial, in which women and men were randomized to a QFR-guided strategy or a standard angiography-guided strategy. Sex differences in clinical benefit of the QFR guidance were analyzed for major adverse cardiac events (MACE), a composite of all-cause death, myocardial infarction, or ischemia-driven revascularization within 2 years.

RESULTS A total of 1,126 women and 2,699 men were eligible and the occurrence of 2-year MACE was similar between women and men (10.3% vs 10.5%; $P = 0.96$). Compared with an angiography-guided strategy, a QFR-guided strategy resulted in a 7.9% and 9.7% reduction in PCI rates in men and women, respectively. A QFR-guided strategy resulted in similar relative risk reductions for 2-year MACE in women (8.0% vs 12.7%; HR: 0.62; 95% CI: 0.42-0.90) and men (8.7% vs 12.4%; HR: 0.69; 95% CI: 0.54-0.87) ($P_{interaction} = 0.61$). Furthermore, QFR values were not significantly different between men and women with various angiographic stenosis categories.

CONCLUSIONS A QFR-guided PCI strategy resulted in improved MACE in both men and women at 2 years compared with an angiography-guided PCI strategy. The FAVOR III China Study [FAVOR III China]; (NCT03656848) (JACC: Asia 2024;4:201-212) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, the First Medical Center of Chinese PLA General Hospital, Beijing, China; [b]Senior Department of Cardiology, the Sixth Medical Center of Chinese PLA General Hospital, Beijing, China; [c]Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [d]Department of Cardiology, National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [e]Department of Cardiology, Beijing Tiantan Hospital, Capital Medical University, Beijing China; [f]Department of Cardiology, the Second Affiliated Hospital of Harbin Medical University, Harbin, China; [g]Department of Cardiology, Sir Run Run Shaw Hospital, Zhejiang University

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.09.012

JACC: ASIA, VOL. 4, NO. 3, 2024
MARCH 2024:201–212

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

FFR = fractional flow reserve

IDR = ischemia-driven revascularization

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

QFR = quantitative flow ratio

SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

Ischemia-guided coronary revascularization is a standard approach for patients with coronary artery disease (CAD).[1,2] Fractional flow reserve (FFR) is the most widely used invasive method to identify ischemia-causing stenoses in cardiac catheterization laboratories.[3,4] In recent years, the quantitative flow ratio (QFR) has gradually emerged and shows unique advantages. Previous studies indicated that QFR has good consistency compared with FFR.[5]

The FAVOR III China trial (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease; NCT03656848) found that a QFR-guided strategy of lesion selection improved 1- and 2-year clinical outcomes compared with standard angiography guidance among patients undergoing percutaneous coronary intervention (PCI).[6,7] However, no study has investigated whether the QFR-guided PCI strategy is similarly beneficial in men and women.

Differences in coronary physiology and in the pathogenesis of CAD exist between men and women, resulting in a sex gap in the clinical benefits of PCI.[8] Moreover, randomized controlled studies of FFR and instantaneous wave-free ratio-guided PCI consistently showed similar benefits in both men and women, although FFR-guidance may be associated with increased rates of revascularization in men.[9,10] Our objectives were to: 1) compare sex differences in the clinical benefits of a QFR- with angiography-guided PCI within 2 years; and 2) evaluate the differences in outcomes between men and women undergoing contemporary PCI.

METHODS

STUDY DESIGN AND POPULATION. The current study is a prespecified subgroup analysis of the FAVOR III China trial, which was an investigator-initiated, prospective, multicenter, patient- and clinical assessor-blinded randomized clinical trial performed at 26 hospitals in China. Details of the trial protocol and clinical outcomes have been reported previously.[6,11] In this study, we investigated the sex differences in clinical outcomes of a QFR-guided strategy compared with an angiography-guided strategy (Supplemental Figure 1). Adults (aged ≥18 years) for whom PCI was planned based on angiographic assessment, stable or unstable angina pectoris, myocardial infarction (MI) ≥72 hours before the screening, with ≥1 lesion with a percentage diameter of stenosis of 50% to 90% in a coronary artery with a ≥2.5-mm reference vessel diameter by visual assessment were eligible for inclusion. Major exclusion criteria were moderate or severe chronic kidney disease (creatinine >150 μmol/L or estimated glomerular filtration rate <45 mL/kg/1.73 m^2 [calculated with the Cockcroft-Gault formula]), severe vessel tortuosity, severe overlap in the stenosed segment, and suboptimal angiography likely to preclude QFR determination. A full list of inclusion and exclusion criteria is provided in the appendix of a previous report.[6] The study was approved by the ethics committee at each participating site, and each patient provided written informed consent.

PROCEDURES. After being allocated to treatment with standard angiography guidance by the operator, patients were randomly assigned 1:1 to either the QFR- or the angiography-guided group. QFR values were measured following standard operating procedures with the AngioPlus system (Pulse Medical). Two angiographic imaging assessments were made with a minimum projection angle of 25°, and the images were uploaded to the local network; the received vessel anatomical parameters were calculated and displayed as pullback curves. PCI was performed only if QFR was ≤0.80 and deferred otherwise. The

School of Medicine, Hangzhou, China; [h]Department of Cardiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [i]Department of Cardiology, Huadong Hospital Affiliated to Fudan University, Shanghai, China; [j]Department of Cardiology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; [k]Medical Research and Biometrics Center, National Center for Cardiovascular Diseases, Beijing, China; [l]Department of Cardiology, Renmin Hospital of Wuhan University, Cardiac Autonomic Nervous System Research Center of Wuhan University, Cardiovascular Research Institute, Wuhan University; Hubei Key Laboratory of Cardiology, Wuhan, China; [m]Biomedical Instrument Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China; and the [n]National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen, China. *Drs Chen and Gao contributed equally to this work.

Andy Yong, MBBS, PhD, served as Guest Associate Editor for this paper. William F. Fearon, MD, served as Guest Editor-in-Chief for this paper.

Manuscript received April 18, 2023; revised manuscript received September 18, 2023, accepted September 29, 2023.

deferred patients received medical therapy alone.[6] In the angiography-guided group, PCI was performed based on visual assessment as per local standard practice. The patients and clinical assessors were masked to the group allocation. To ensure participant masking, both groups wore music-playing headphones during the procedure, and a pre-PCI delay of 10 minutes was preset for true or sham QFR calculations. Masked questionnaires were administered to each patient at discharge, 6 months, and 1 year after randomization, to assess the success in concealing the group allocation and the perceptions of treatment assignment. Complete details of the masking methods are provided in the appendix of FAVOR III China study.[6] After the procedures, offline QFR measurements and standard quantitative coronary angiographic analyses were performed for all eligible lesions in all randomized participants by an independent angiographic core laboratory.

OUTCOMES. In this study, we analyzed the 2-year rate of major adverse cardiac events (MACE), defined as the composite of all-cause death, MI, or ischemia-driven revascularization (IDR). And, to decrease the impact of invasive procedure and stenting on clinical outcomes, we also analyzed the 2-year rate of MACE excluding periprocedural MI arising from index or planned staged procedures. Other endpoints included the individual components of the composite endpoints, cardiovascular death, noncardiovascular death, periprocedural MI, nonperiprocedural MI, target vessel revascularization, any revascularization, and stent thrombosis at 2 years, procedural characteristics such as number of stents implanted and change in PCI strategy according to QFR. Details of the definitions were reported before.[6] Landmark analyses were performed within 1 year and between 1 and 2 years to evaluate the benefit trends over time according to sex. Endpoint events were adjudicated by the Clinical Events Committee, consisting of experts in this field who did not participate in this trial.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean $\pm$ SD or median (IQR) and were compared using Student's *t*-test or Mann-Whitney *U* test. The Shapiro-Wilk test was used for normality testing. Categorical variables are presented as numbers and percentages, compared with the chi-square test or Fisher exact test depending on the expected frequencies in the contingency table are >5 or not. Statistical comparisons based on sex were stratified by treatment methods. We used a box-and-whisker plot to assess the QFR value of each lesion and angiographic lesion severity. Survival curves were estimated using Kaplan-Meier methods and were compared with the log-rank test. Between-group risks were estimated by HRs with 95% CIs using a Cox proportional hazards model. The interaction tests between the randomized allocation (QFR-guided strategy vs angiography-guided strategy) and gender, on the primary and secondary endpoints, were performed using Cox regression. Two-tailed *P* values and an interaction *P* of <0.05 were considered statistically significant. All analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS. Of the total of 3,825 participants included in the analysis, 2,699 (70.6%) were men and 1,126 (29.4%) were women (Supplemental Table 1). Compared with men, women were older and showed a higher prevalence of hypertension and diabetes. Conversely, men had a higher body mass index and higher rates of hypercholesterolemia, cigarette smoking, previous MI, and previous PCI. Regarding clinical presentation, men were more likely to present with asymptomatic ischemia and after MI, whereas women were more likely to present with more stable angina and unstable angina. Women compared with men had lower estimated glomerular filtration rates but higher left ventricular ejection fractions. As presented in **Table 1**, all baseline characteristics were well-balanced between the QFR- and angiography-guided groups among women and men.

PROCEDURAL CHARACTERISTICS AND MEDICATION USE. Angiographic findings and procedural results were similar in women and men, except for smaller stent diameter, lower residual anatomic SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) scores and lower residual functional SYNTAX scores in women than men (Supplemental Table 2).

As shown in **Table 2**, compared with the angiography-guided strategy, QFR-guided strategy resulted in an 8.1% and 9.7% decrease in the rate of PCI with fewer drug-eluting stents implanted and fewer drug-coated balloons and non-drug-coated balloons used in men and women, respectively; there was no difference between men and women ($P_{\text{interaction}} = 0.75$). The QFR-guided and angiography-guided groups had similar numbers of stents implanted per patient, but the former was associated with larger stent diameters in women (2.92 ± 0.56 vs 2.80 ± 0.66; $P = 0.002$) and comparable stent diameters in men (2.91 ± 0.75 vs 2.91 ± 0.76; $P = 0.96$).

TABLE 1 Baseline Characteristics

	Men			Women		
	QFR Guided (n = 1,349)	Angiography Guided (n = 1,350)	*P* Value	QFR Guided (n = 564)	Angiography Guided (n = 562)	*P* Value
Age, y	61.0 ± 10.1	61.2 ± 10.3	0.63	66.8 ± 8.8	66.1 ± 8.8	0.17
Body mass index, kg/m^2	25.3 (23.3-27.3)	25.0 (22.9-27.1)	0.06	24.2 (22.2-26.5)	24.0 (22.1-26.3)	0.62
Diabetes	444 (32.9)	436 (32.3)	0.73	204 (36.2)	211 (37.5)	0.63
Hypertension	867 (64.3)	850 (63.0)	0.48	403 (71.5)	402 (71.5)	0.98
Hypercholesterolemia	537 (39.8)	530 (39.3)	0.77	192 (34.0)	198 (35.2)	0.68
Cigarette smoking			0.76			0.48
Current	552 (40.9)	541 (40.1)		22 (3.9)	27 (4.8)	
Former	271 (20.1)	264 (19.6)		13 (2.3)	18 (3.2)	
Never	526 (39.0)	545 (40.4)		529 (93.8)	517 (92.0)	
Previous myocardial infarction	152 (11.3)	150 (11.1)	0.90	27 (4.8)	29 (5.2)	0.77
Previous percutaneous coronary intervention	361 (26.8)	366 (27.1)	0.84	124 (22.0)	100 (17.8)	0.08
Previous coronary artery bypass grafting	3 (0.2)	3 (0.2)	1.00	2 (0.4)	1 (0.2)	1.00
Clinical presentation[a]			0.88			0.60
Asymptomatic ischemia	161 (11.9)	152 (11.3)		46 (8.2)	52 (9.3)	
Stable angina	330 (24.5)	345 (25.6)		163 (28.9)	148 (26.3)	
Unstable angina	776 (57.5)	774 (57.3)		335 (59.4)	336 (59.8)	
Post myocardial infarction (within 30 days)	82 (6.1)	79 (5.9)		20 (3.5)	26 (4.6)	
Estimated glomerular filtration rate (Cockcroft-Gault formula), mL/min/1.73 m^2	71.9 (60.0-84.3)	70.4 (58.7-84.2)	0.25	67.9 (55.1-80.2)	68.5 (56.9-83.6)	0.051
Left ventricular ejection fraction, %	63.0 (60.0-66.0)	63.0 (60.0-66.0)	0.13	64.0 (62.0-67.0)	64.0 (61.0-67.0)	0.92
Number of diseased vessels reported			0.96			0.35
1-vessel disease	607 (45.0)	611 (45.3)		283 (50.2)	258 (45.9)	
2-vessel disease	484 (35.9)	479 (35.5)		190 (33.7)	205 (36.5)	
3-vessel disease	228 (16.9)	226 (16.7)		78 (13.8)	90 (16.0)	
Left main disease	30 (2.2)	34 (2.5)		13 (2.3)	9 (1.6)	
Any vessel with ≥1 lesion with diameter stenosis >90% and TIMI flow grade <3	123 (9.1)	138 (10.2)	0.33	47 (8.3)	44 (7.8)	0.76
Anatomic SYNTAX score[b]	9.42 ± 6.08	9.62 ± 6.47	0.42	9.11 ± 5.62	9.45 ± 5.97	0.32
Functional SYNTAX score[c]	8.16 ± 6.39	8.15 ± 6.73	0.94	7.83 ± 5.95	7.71 ± 6.39	0.75

Values are mean ± SD, median (IQR), or n (%). [a]Consistent with clinical practice in China and the study protocol, creatine kinase-MB and non-high-sensitivity troponins were used to assess possible myocardial infarction at all participating centers. [b]The anatomic SYNTAX score is a scoring system that quantifies angiographic lesion extent and complexity. The SYNTAX score was calculated by the angiographic core laboratory. [c]The functional SYNTAX score was calculated by summing the segmental anatomic SYNTAX scores only in vessels with functional ischemia as defined by offline quantitative flow ratio of ≤0.80 as determined by the angiographic core laboratory.

QFR = quantitative flow ratio; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

The prerandomization vessel revascularization plan changed more for both women (25.5%) and men (22.3%) in the QFR-guided group, compared with women (5.9%) and men (6.4%) in the angiography-guided group, showing no sex interaction ($P_{\text{interaction}}$ = 0.27). Further analysis demonstrated that deferral of ≥1 originally intended vessel for PCI (in women: 21.1% vs 5.0% [P < 0.0001]; in men: 19.0% vs 5.3% [P < 0.0001]) and treatment of ≥1 vessel not originally deferred for PCI (in women: 5.5% vs 1.1% [P < 0.0001]; in men: 4.0% vs 1.6% [P = 0.0002]) occurred more frequently in QFR guidance than angiography guidance without sex interaction. Corresponding with the lower PCI frequency, the QFR-guided arm was less likely to receive antiplatelet agents (aspirin, $P2Y_{12}$ inhibitors, and dual antiplatelet therapy) than the angiography-guided arm at discharge, 6 months, 1 year, and 2 years after the procedure. Other medications were used similarly over 2 years of follow-up (Supplemental Table 3).

CLINICAL OUTCOMES. In this study, 2,652 2,699 men (98.3%) of and 1,107 of 1,126 women (98.3%) completed 2 years of follow-up. The 2-year rate of MACE was similar between women and men (10.3% vs 10.5%; P = 0.96) (Supplemental Table 4). Compared with men, more women experienced MI through 2 years (6.7% vs 4.9%; P = 0.02), whereas IDR tended to be more frequent in men (5.6% vs 3.5%; P = 0.007). The direction of sex differences in clinical outcomes was consistent before and after adjustment for

TABLE 2 Angiographic Findings and Procedural Results

	Men			Women			
	QFR Guided (n = 1,349)	Angiography Guided (n = 1,350)	*P* Value	QFR Guided (n = 564)	Angiography Guided (n = 562)	*P* Value	*P* Value for Interaction
Radial artery approach	1,330 (98.6)	1,324 (98.1)	0.29	555 (98.4)	545 (97.0)	0.11	0.5148
PCI performed	1,227 (91.0)	1,338 (99.1)	<0.0001	504 (89.4)	557 (99.1)	<0.0001	0.7490
Drug-eluting stents placed	1,172 (86.9)	1,276 (94.5)	<0.0001	495 (87.8)	536 (95.4)	<0.0001	0.7240
Drug-coated balloon angioplasty	47 (3.5)	42 (3.1)	<0.0001	8 (1.4)	16 (2.8)	<0.0001	0.0894
Non-drug-coated balloon angioplasty	8 (0.6)	20 (1.5)	<0.0001	1 (0.2)	5 (0.9)	<0.0001	0.5539
No. of stents placed per patient	1.60 ± 0.96	1.59 ± 0.96	0.64	1.59 ± 0.95	1.62 ± 0.99	0.66	0.2600
Stent length, mm	41.39 ± 27.35	39.90 ± 27.17	0.17	40.60 ± 26.25	40.52 ± 27.00	0.96	0.2500
Stent diameter, mm	2.91 ± 0.75	2.91 ± 0.76	0.96	2.92 ± 0.56	2.80 ± 0.66	0.002	0.0200
Use of intravascular imaging[a]	82 (6.1)	87 (6.4)	0.69	37 (6.6)	34 (6.0)	0.72	0.6108
Contrast medium used per patient, mL	163.7 ± 75.1	171.4 ± 75.8	0.009	161.2 ± 76.9	165.6 ± 70.0	0.33	0.5347
Fluoroscopy time, minutes	14.1 ± 8.1	15.0 ± 7.3	0.003	14.0 ± 7.8	14.7 ± 7.5	0.18	0.6103
Procedure time, minutes[b]	39.2 ± 26.2	40.8 ± 26.5	0.14	39.4 ± 26.2	38.0 ± 36.9	0.47	0.1540
Adjusted procedure time, minutes[b]	44.8 ± 28.7	50.3 ± 26.8	<0.0001	44.2 ± 29.1	47.6 ± 37.0	0.08	0.3140
PCI lesion success[c]	1,473/1,487 (99.1)	1,762/1,775 (99.3)	0.51	588/596 (98.7)	679/685 (99.1)	0.42	0.2179
PCI procedure success[d]	1,124/1,170 (96.1)	1,228/1,293 (95.0)	0.19	467/495 (94.3)	519/553 (93.9)	0.74	0.2234
Vessels intended to be treated before randomization			0.23			0.57	0.7688
Left main	22/1,774 (1.2)	33/1,812 (1.8)		11/748 (1.5)	8/770 (1.0)		
Left anterior descending	928/1,774 (52.3)	902/1,812 (49.8)		408/748 (54.5)	402/770 (52.2)		
Left circumflex	369/1,774 (20.8)	408/1,812 (22.5)		153/748 (20.5)	176/770 (22.9)		
Right coronary artery	455/1,774 (25.6)	469/1,812 (25.9)		176/748 (23.5)	184/770 (23.9)		
Vessels treated of those originally intended			0.05			0.12	0.7731
Left main	31/1,581 (2.0)	50/1,783 (2.8)		18/668 (2.7)	20/757 (2.6)		
Left anterior descending	857/1,581 (54.2)	896/1,783 (50.3)		371/668 (55.5)	374/757 (49.4)		
Left circumflex	308/1,581 (19.5)	393/1,783 (22.0)		143/668 (21.4)	179/757 (23.6)		
Right coronary artery	385/1,581 (24.4)	444/1,783 (24.9)		136/668 (20.4)	184/757 (24.3)		
Patients with intended vessel deferral or unintended vessel treatment	301 (22.3)	86 (6.4)	<0.0001	144 (25.5)	33 (5.9)	<0.0001	0.2741
Deferral (nontreatment) of ≥1 vessel originally intended for PCI	256 (19.0)	72 (5.3)	<0.0001	119 (21.1)	28 (5.0)	<0.0001	0.4323
Treatment of ≥1 vessel not originally intended for PCI	54 (4.0)	22 (1.6)	0.0002	31 (5.5)	6 (1.1)	<0.0001	0.1414
Residual anatomic SYNTAX score	2.51 ± 3.57	2.49 ± 4.18	0.85	2.24 ± 3.51	2.02 ± 3.36	0.28	0.4718
Residual functional SYNTAX score	0.67 ± 2.26	1.13 ± 3.06	<0.0001	0.66 ± 2.24	0.76 ± 2.22	0.45	0.0515
Residual functional SYNTAX score of 0	1,174/1,336 (87.9)	1,080/1,330 (81.2)	<0.0001	495/558 (88.7)	472/557 (84.7)	0.050	0.4156

Values are n (%), mean ± SD, or n/N (%). [a]Intravascular ultrasound examination or optical coherence tomography. [b]Procedure time was defined as the time between the first and last angiogram, including diagnostic coronary angiography, the randomization process, QFR calculation time, or 10-minute sham control time, and PCI time; in the adjusted procedure time, the mandated 10-minute delay for the real or sham QFR calculation was subtracted. [c]Defined as residual stenosis of <30% for patients treated with stents or <50% for patients treated with balloon angioplasty by visual estimation, with TIMI flow grade 3 in the treated vessel. [d]Defined as lesion success in all treated lesions without in-hospital major adverse cardiac events (up to a maximum of 7 days).

PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

differences in baseline risk factors (Supplemental Figure 2).

Clinical outcomes comparisons at 2 years between the QFR- and angiography-guided strategies according to sex are presented in **Table 3**. QFR guidance consistently decreased MACE in women (8.0% vs 12.7%; HR: 0.62; 95% CI: 0.42-0.90) and men (8.7% vs 12.4%; HR: 0.69; 95% CI: 0.54-0.87) without significant interaction ($P_{\text{interaction}} = 0.61$) (**Figures 1A and 1B**). There were also no significant sex interaction for the individual components of MACE endpoints. After excluding periprocedural MI, women (4.1% vs 8.3%, HR: 0.48; 95% CI: 0.29-0.80) and men (6.5% vs 9.0%, HR: 0.72; 95% CI: 0.54-0.94) experienced comparable benefits from a QFR-guided strategy ($P_{\text{interaction}} = 0.17$) (**Figures 1C and 1D**). In addition, among the other secondary endpoints, a significant interaction between the treatment effect and sex was found only for nonprocedural MI at 2 years (in women: 0.5% vs 3.8% [HR: 0.14; 95% CI: 0.04-0.47]; in men: 1.4% vs 2.3% [HR: 0.58; 95% CI: 0.32-1.04]; $P_{\text{interaction}} = 0.04$). According to vessel attribution analysis, no significant

JACC: ASIA, VOL. 4, NO. 3, 2024
MARCH 2024:201-212

TABLE 3 Clinical Outcomes at 2 Years Between QFR- and Angiography-Guided Strategies According to Sex

	Men (n = 26,99)				Women (n = 1,126)				
	QFR Guided (n = 1,349)	Angiography Guided (n = 1350)	HR (95% CI)	Log-Rank *P* Value	QFR Guided (n = 564)	Angiography Guided (n = 562)	HR (95% CI)	Log-Rank *P* Value	*P* Value for Interaction
MACE	116 (8.7)	166 (12.4)	0.69 (0.54-0.87)	0.002	45 (8.0)	71 (12.7)	0.62 (0.42-0.90)	0.01	0.61
All-cause death	14 (1.0)	12 (0.9)	1.17 (0.54-2.53)	0.69	6 (1.1)	9 (1.6)	0.66 (0.24-1.86)	0.43	0.38
Myocardial infarction	49 (3.7)	82 (6.1)	0.59 (0.42-0.85)	0.003	27 (4.8)	48 (8.6)	0.55 (0.35-0.89)	0.01	0.81
Ischemia-driven revascularization	63 (4.7)	87 (6.5)	0.72 (0.52-0.99)	0.045	16 (2.9)	23 (4.2)	0.68 (0.36-1.29)	0.23	0.88
MACE excluding periprocedural myocardial infarction	87 (6.5)	120 (9.0)	0.72 (0.54-0.94)	0.02	23 (4.1)	46 (8.3)	0.48 (0.29-0.80)	0.003	0.17
Other secondary endpoints									
Cardiovascular death	6 (0.4)	7 (0.5)	0.86 (0.29-2.56)	0.79	5 (0.9)	5 (0.9)	0.99 (0.29-3.43)	0.99	0.87
Noncardiovascular death	8 (0.6)	5 (0.4)	1.60 (0.52-4.90)	0.40	1 (0.2)	4 (0.7)	0.25 (0.03-2.20)	0.17	0.14
Periprocedural myocardial infarction	32 (2.4)	52 (3.9)	0.61 (0.40-0.95)	0.03	24 (4.3)	29 (5.2)	0.82 (0.48-1.41)	0.48	0.41
Nonprocedural myocardial infarction	18 (1.4)	31 (2.3)	0.58 (0.32-1.04)	0.06	3 (0.5)	21 (3.8)	0.14 (0.04-0.47)	<0.0001	0.04
Any revascularization	86 (6.5)	108 (8.1)	0.79 (0.60-1.05)	0.11	22 (4.0)	30 (5.4)	0.71 (0.41-1.24)	0.23	0.75
Target vessel revascularization[a]	37 (2.8)	49 (3.7)	0.75 (0.49-1.16)	0.19	9 (1.6)	16 (2.9)	0.55 (0.24-1.25)	0.15	0.51
Ischemia driven	27 (2.0)	40 (3.0)	0.68 (0.41-1.10)	0.11	7 (1.3)	13 (2.4)	0.53 (0.21-1.33)	0.17	0.65
Target lesion revascularization	26 (2.0)	37 (2.8)	0.70 (0.43-1.16)	0.17	5 (0.9)	16 (2.9)	0.31 (0.11-0.84)	0.02	0.15
Ischemia driven	22 (1.7)	31 (2.3)	0.71 (0.41-1.23)	0.22	5 (0.9)	13 (2.4)	0.38 (0.14-1.06)	0.06	0.29
Nontarget lesion revascularization	12 (0.9)	13 (1.0)	0.93 (0.42-2.03)	0.85	4 (0.7)	2 (0.4)	3.95 (0.44-35.4)	0.18	0.22
Ischemia driven	5 (0.4)	10 (0.8)	0.50 (0.17-1.47)	0.20	2 (0.4)	2 (0.4)	1.98 (0.18-21.8)	0.57	0.31
Nontarget vessel revascularization[b]	54 (4.1)	61 (4.6)	0.89 (0.61-1.28)	0.51	14 (2.5)	16 (2.9)	0.86 (0.42-1.75)	0.67	0.94
Ischemia driven	38 (2.9)	48 (3.6)	0.79 (0.52-1.21)	0.27	9 (1.6)	12 (2.2)	0.74 (0.31-1.74)	0.48	0.89
Stent thrombosis, definite or probable	2 (0.2)	6 (0.4)	0.33 (0.07-1.65)	0.16	4 (0.7)	4 (0.7)	0.99 (0.25-3.96)	0.99	0.31
Definite	0 (0)	3 (0.2)	-	0.08	1 (0.2)	1 (0.2)	0.99 (0.06-15.8)	0.99	0.93
Probable	2 (0.2)	3 (0.2)	0.67 (0.11-4.00)	0.66	3 (0.5)	3 (0.5)	0.99 (0.20-4.91)	0.99	0.75

Values are n (Kaplan-Meier estimated %) unless otherwise stated. The primary endpoint was the 1-year rate of MACE, defined as the composite of all-cause death, myocardial infarction, or ischemia-driven revascularization. [a]Revascularization of vessels that were treated with PCI after randomization. [b]Revascularization of vessels in which PCI was not previously performed.
Abbreviations as inTables 1 and 2.

difference in the effect of QFR-guided PCI strategy on specific vessel-related endpoints was observed at 2 years between the sexes (Supplemental Table 5).

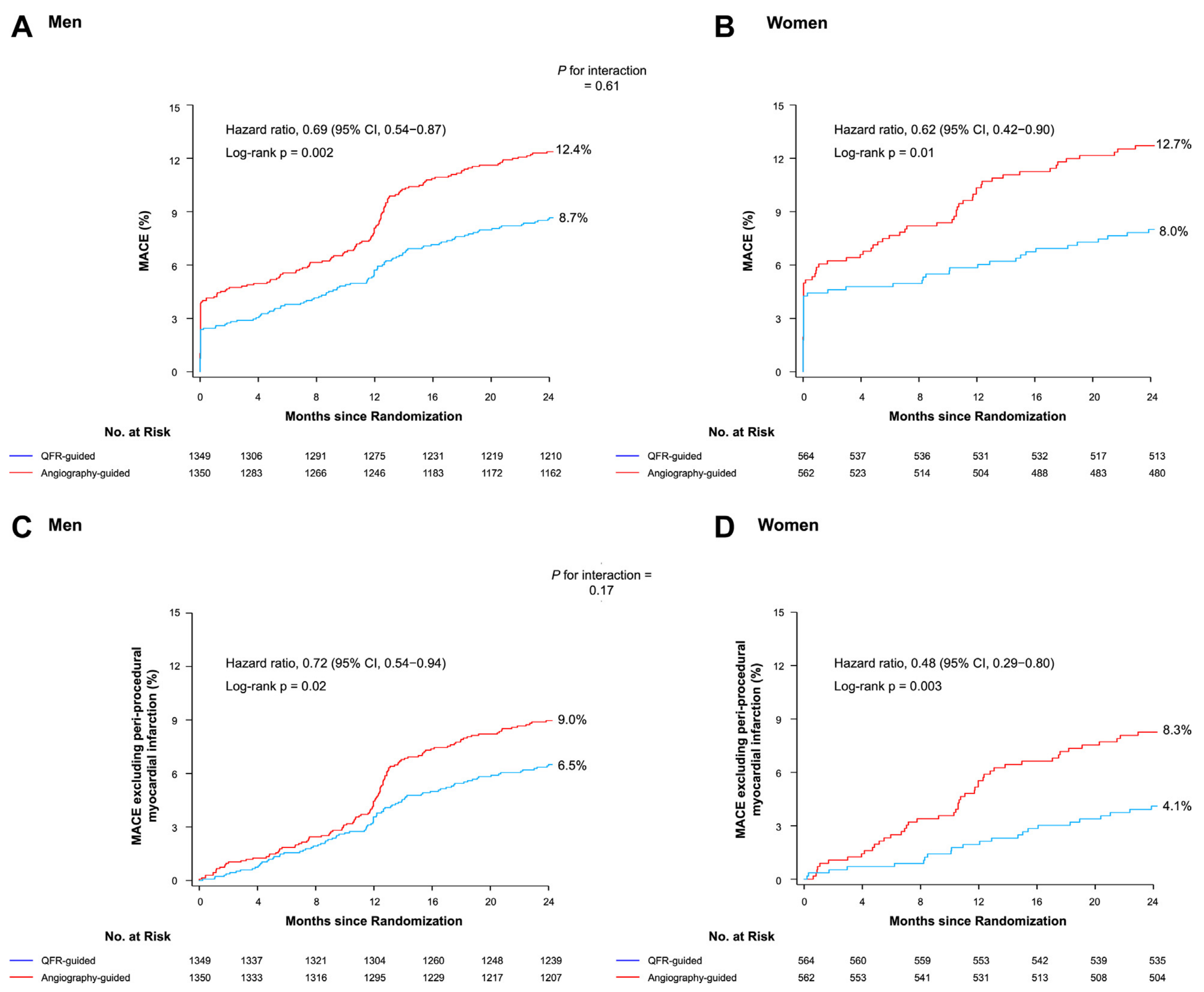
Landmark analyses at 1 year showed similar and consistent reduced risk by QFR guidance (as compared with angiographic guidance) in both men and women within 1 year and between 1 and 2 years on MACE (for men: HR: 0.70 [95% CI: 0.52-0.93] within 1 year; HR: 0.65 [95% CI: 0.44-0.96] from 1 to 2 years [$P_{interaction}$ = 0.78]; and for women: HR: 0.62 [95% CI: 0.42-0.90] within 1 year; HR: 0.64 [95% CI: 0.32-1.28] from 1 to 2 years [$P_{interaction}$ = 0.73]), MACE excluding periprocedural MI, and the individual components of MACE (**Figure 2**, Supplemental Figure 3).

QFR VALUES. QFR was successfully evaluated offline in 3,568 lesions in the male group and 1,494 in the female group, and no significant difference in mean QFR was found between the sexes (0.70 ± 0.15 vs 0.71 ± 0.15; P = 0.18). The lesions were divided into three groups according to angiographic severity of percent diameter stenosis by quantitative coronary angiographic. QFR values did not differ significantly between men and women with <50% stenosis (0.79 ± 0.12 vs 0.81 ± 0.12; P = 0.07), 50% to 70% stenosis (0.71 ± 0.14 vs 0.71 ± 0.14; P = 0.54), or >70% stenosis (0.61 ± 0.15 vs 0.60 ± 0.16; P = 0.70) (**Figure 3**).

DISCUSSION

FAVOR III China is the first randomized trial to compare the clinical outcomes of PCI guided by angiography-derived physiological lesion selection and standard angiography-guided lesion selection. This is the first subgroup analysis of a contemporary

FIGURE 1 **Kaplan-Meier Curves for 2-Year MACE and MACE Excluding Periprocedural MI**



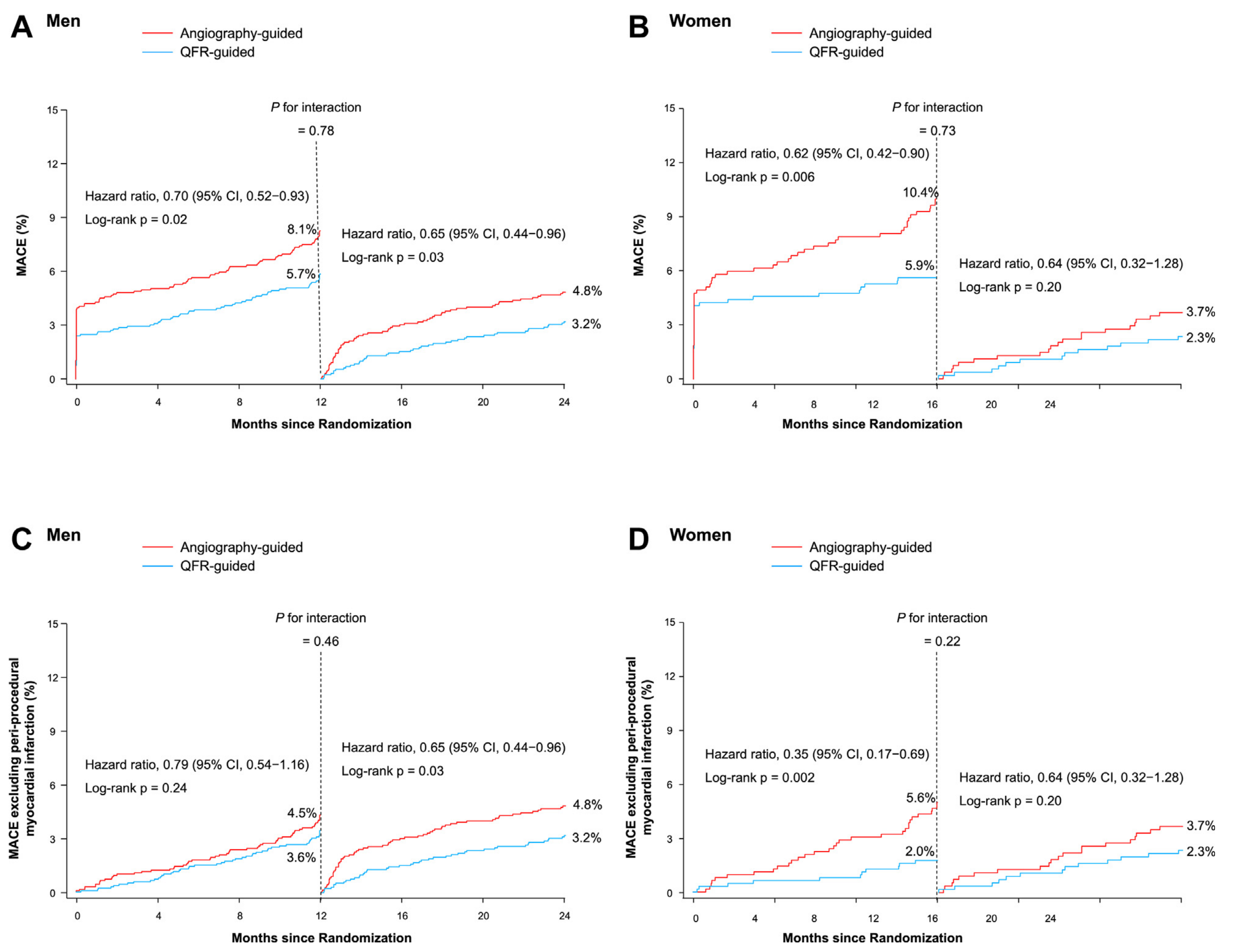
Kaplan-Meier cumulative event curves for (A) 2-year MACE in men, (B) 2-year MACE in women, (C) 2-year MACE excluding periprocedural MI in men, and (D) 2-year MACE excluding periprocedural MI in women. MACE = major adverse cardiac event(s); MI = myocardial infarction; QFR = quantitative flow ratio.

trial evaluating a QFR-guided PCI strategy to suggest that: 1) there were lower rates of PCI in women and men with the QFR- vs the angiography-guided strategy; 2) women and men benefited similarly from PCI guided by QFR vs angiography in terms of 2-year MACE endpoint with and without periprocedural MI; and 3) men and women showed similar QFR values according to different categories of angiographic stenosis (**Central Illustration**).

Consistent with the substudies of FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) and DEFINE-FLAIR (Functional Lesion Assessment of Intermediate stenosis to guide Revascularization) trials, the rates of MACE were not different according to sex in this study.[9,10] However, MI occurred more frequently in women than in men, and periprocedural MI contributed mainly to the discrepancy. Women with small vessel size, great tortuosity, and high propensity to dissection were considered to be independent risks factor for periprocedural MI.[12,13] In contrast, more men experienced IDR than women, possibly owing to poor living habits, higher risk factors for atherosclerosis (diabetes, hypercholesterolemia, etc), less protective

JACC: ASIA, VOL. 4, NO. 3, 2024
MARCH 2024:201–212

FIGURE 2 Landmark Analyses for 2-Year MACE and MACE Excluding Periprocedural MI



Landmark analyses for (A) 2-year MACE in men, (B) 2-year MACE in women, (C) 2-year MACE excluding periprocedural MI in men, and (D) 2-year MACE excluding periprocedural MI in women. Abbreviations as in Figure 1.

effects of estrogen, previous PCI, previous MI,[14] and other unmeasured biological factors, such as plaque vulnerability.[15]

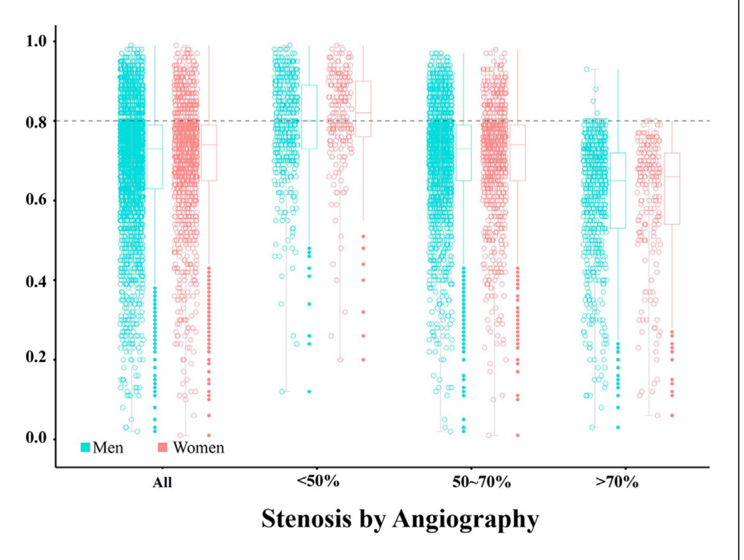
The improved clinical outcomes of QFR-guided PCI may be attributable to its optimization of clinical decision-making. Similar to previous literature,[6,16,17] we found that QFR enables better identification of lesions and vessels that require active intervention or safe deferral, resulting in a lower rate of 2-year MACE excluding periprocedural MI regardless of sex. QFR not only led to appropriate deferral of stenting and, therefore, decreased the attendant risks of periprocedural MI, but in fact also led to appropriate stenting of ischemic lesions that may have ultimately caused a future MI. A recent study[18] demonstrated a strong correlation between abnormal coronary physiology indices and pathological wall shear stress independent of angiographic severity, illustrating a potential mechanism by which QFR-guided PCI may have led to a decrease in spontaneous MI compared with angiography-guided PCI.

In the subgroup analysis of the FAME and DEFINE-FLAIR study, there was no significant difference in the incidence of MACE by treatment strategies between men and women,[9,10] which is consistent with our findings. FFR and instantaneous wave-free ratio require the invasive passage of an intracoronary wire capable of measuring distal coronary pressure and the former requires induction of maximal hyperemia (usually with adenosine). In this study, we adopted a novel wireless guide method QFR, which has emerged as a promising tool for the functional assessment of intermediate CAD. QFR does not require pharmacological hyperemia induction and can be calculated in a catheterization laboratory setting within minutes.[19,20] Previous studies showed that QFR had good correlation with FFR, with superior diagnostic accuracy compared with invasive coronary angiography when FFR was used as the benchmark.[21,22]

Landmark analysis demonstrated equivalent persistence of clinical benefit for MACE events between the sexes. Interestingly, however, females but not males benefited from QFR-guided PCI in terms of MACE, excluding periprocedural MI at 1 year. On the one hand, single-event analysis shown that the 1-year clinical benefit for men in the QFR-guided group was driven by the lower periprocedural MI, resulting in no longer a difference in 1-year MACE after excluding periprocedural MI. On the other hand, the clinical benefit of nonprocedural MI and nontarget vessel IDR continued to increase beyond 1 year after QFR-guided PCI, eventually leading to a gradual closing of the sex gap during 2 years of follow-up. In addition, an interaction between sex and guidance strategy was observed for nonprocedural MI at 2 years, in which women differed statistically but men differed only numerically between QFR and angiography guidance. Although nonprocedural MI can better reflect the clinical benefit of QFR in patients with vessels containing hemodynamic obstructive lesions with benign angiographic appearance,[23,24] the limited sample size and the lower incidence of MI in men than in women after PCI[12] may not meet the statistical power required for statistical significance, thus causing the sex discordance. Further studies with larger numbers and longer follow-up are required to evaluate whether the decrease in nonprocedural MI driven by QFR-guided PCI seen in women in this study is a sex-specific phenomenon.

We found comparable QFR values in men and women according to different categories of angiographic stenosis. In several studies, women, compared with men, showed a higher FFR value when having a similar angiographic stenosis lesion percentage,[25,26] which contrasts with the findings in our study. The finding of higher FFR in women compared with men with similar stenosis severity is most likely due to 2 key factors. First, women have smaller coronary arteries and smaller myocardial mass, therefore, leading to lower absolute flow and requiring more severe stenosis before a lesion becomes functionally significant. Second, women in the study are older with more hypertension, and are thus more likely to have microvascular dysfunction that may affect the degree of hyperemia achieved during adenosine infusion, which manifests as a higher FFR compared with men, despite similar stenosis severity. In contrast, QFR does not require induction of maximal hyperemia, which may render the higher incidence of microvascular dysfunction in women irrelevant; furthermore, QFR is heavily influenced by vessel geometry and, therefore, less likely to produce disparate results in lesions with similar stenosis severity regardless of sex.[27-30] In addition, it should be noted that some previous studies have shown that QFR values of similar stenosis were higher in women[31,32]; however, the results are not directly comparable given that they are both retrospective small sample studies for different populations with CAD. Despite these differences between FFR and QFR, it is reassuring that both approaches lead to improved outcomes when used to guide revascularization in women.

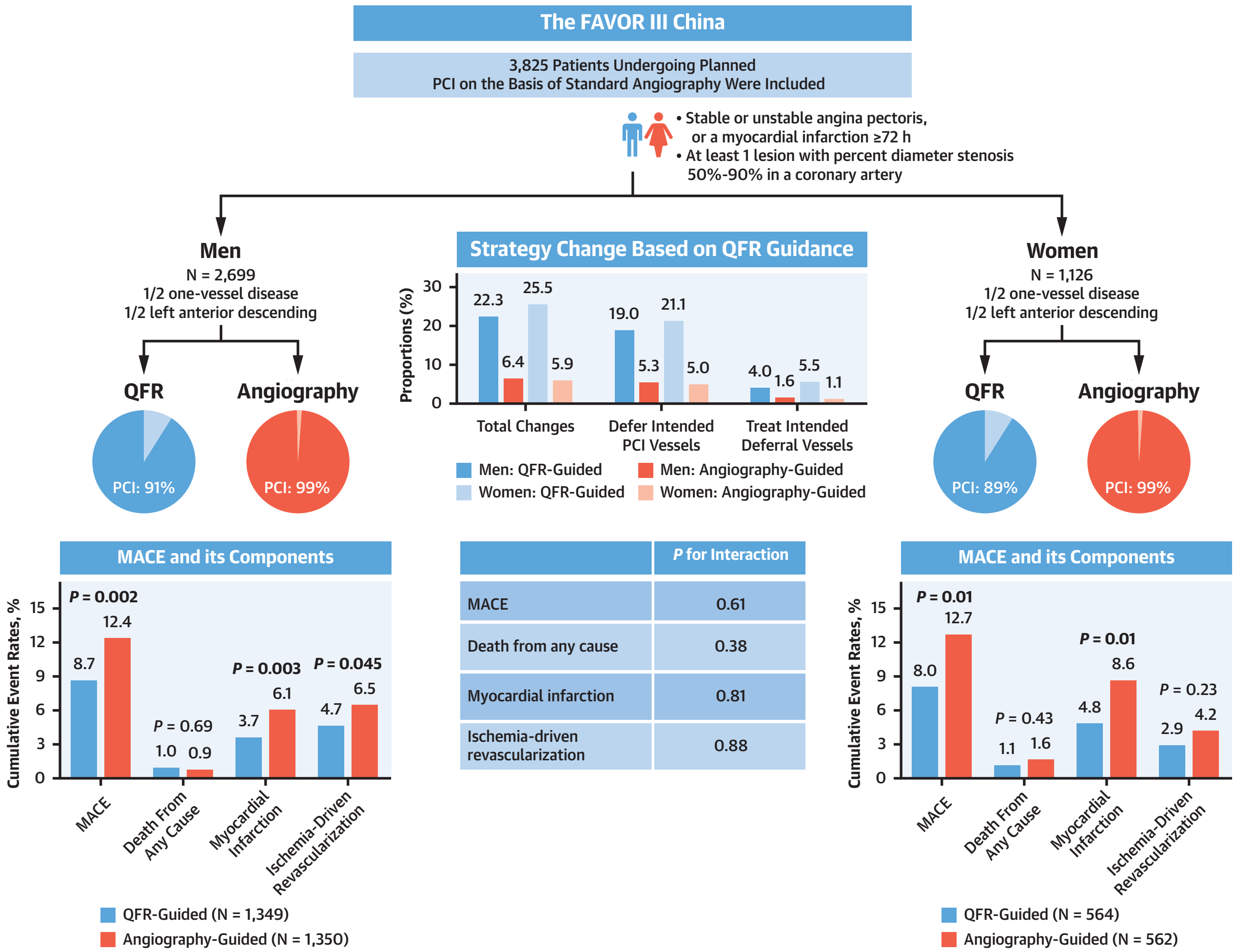
FIGURE 3 **Box Diagram of QFR Values**



There was no significant difference in mean QFR between the sexes among the 3 groups divided according to angiographic severity of diameter stenosis by QCA. QCA = quantitative coronary angiography; QFR = quantitative flow ratio.

STUDY LIMITATIONS. First, given that this study involved a prespecified subgroup analysis and that there was a limited sample size in each subgroup, the

CENTRAL ILLUSTRATION Sex Differences in Clinical Benefits of QFR- vs Angiography-Guided Strategy



Chen Y, et al. JACC: Asia. 2024;4(3):201-212.

Both men and women in the QFR-guided group were more likely to perform initially deferred revascularization and to defer initially intended revascularization. In terms of 2-year MACE and its components (death, MI, IDR), women and men benefited similarly from PCI guided by QFR versus angiography. Height of the bars indicates the proportions. IDR = ischemia-driven revascularization; MACE = major adverse cardiac event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; QFR = quantitative flow ratio.

results need to be interpreted with caution. Second, we used 2 projections for each vessel in QFR measurements, which limited the technique and quality of angiographic acquisition. The next-generation QFR system only requires 1 projection, allowing greater accuracy in evaluation and a shorter operating time.[33,34] Third, subject to the inclusion and exclusion criteria of the FAVOR III China study, our findings may only apply to the low- to intermediate-risk population, rather than those with higher clinical risks (eg, biomarker-positive unstable angina or acute MI) or more complex lesions (high SYNTAX score) which encountered in routine practice. Fourth, the current follow-up time of this study is 2 years, which is relatively short for the course of chronic disease; a longer observation time may be required. Finally, FAVOR III China was conducted in a predominantly Chinese population; whether these results can be generalizable to other ethnic groups should be validated further.

CONCLUSIONS

A QFR-guided PCI strategy improved 2-year MACE with and without periprocedural MI compared with standard angiography guidance in both men and women. The QFR values within different categories of angiographic stenosis were similar between women and men.

ACKNOWLEDGMENTS The authors appreciate all the participating patients for their contributions to the trial. They also thank all the physicians and nurses who cared for the patients, and all the clinical and research staff who assisted the study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences (NCRC2020001), the Beijing Municipal Science and Technology Commission (Z191100006619107), the National High Level Hospital Clinical Research Funding (2022-GSP-GG-20), and the National Natural Science Foundation of China (81827808). Dr Shengxian Tu is the co-founder of Pulse Medical and has received grants and consultancy from Pulse Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Yundai Chen, Department of Cardiology, the First Medical Center of Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. E-mail: cyundai@vip.163.com. OR Dr Lei Song, Department of Cardiology, State Key Laboratory of Cardiovascular Disease, FuWai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 167 Beilishi Road, Xicheng District, Beijing 100037, China. E-mail: drsong@vip.163.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In terms of 2-year MACE, a composite of all-cause death, myocardial infarction, or IDR, patients with coronary artery disease benefited similarly from PCI guided by QFR vs angiography regardless of sex.

TRANSLATIONAL OUTLOOK: Further randomized controlled trials with adequate representation of female patients and statistically powered to detect potential sex-related differences to evaluate the benefits of QFR-guided PCI strategy is warranted.

REFERENCES

1. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58:e44-122.

2. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35: 2541-2619.

3. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360(3):213-224.

4. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.

5. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan Study. *J Am Heart Assoc*. 2018;7:e009603.

6. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet*. 2021;398(10317): 2149-2159.

7. Song L, Xu B, Tu S, et al. 2-year outcomes of angiographic quantitative flow ratio-guided coronary interventions. *J Am Coll Cardiol*. 2022;80: 2089-2101.

8. Chichareon P, Modolo R, Kerkmeijer L, et al. Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the GLOBAL LEADERS Randomized Clinical Trial. *JAMA Cardiol*. 2020;5:21-29.

9. Kim HS, Tonino PA, De Bruyne B, et al. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. *J Am Coll Cardiol Intv*. 2012;5:1037-1042.

10. Kim CH, Koo BK, Dehbi HM, et al. Sex differences in instantaneous wave-free ratio or fractional flow reserve-guided revascularization strategy. *J Am Coll Cardiol Intv*. 2019;12:2035-2046.

11. Song L, Tu S, Sun Z, et al. Quantitative flow ratio-guided strategy versus angiography-guided strategy for percutaneous coronary intervention: rationale and design of the FAVOR III China trial. *Am Heart J*. 2020;223:72-80.

12. Gaudino M, Di Franco A, Cao D, et al. Sex-related outcomes of medical, percutaneous, and surgical interventions for coronary artery disease: JACC focus seminar 3/7. *J Am Coll Cardiol*. 2022;79:1407-1425.

13. Park DW, Kim YH, Yun SC, et al. Frequency, causes, predictors, and clinical significance of periprocedural myocardial infarction following percutaneous coronary intervention. *Eur Heart J*. 2013;34:1662-1669.

14. Abdel-Wahab M, Neumann FJ, Serruys P, et al. Incidence and predictors of unplanned non-target lesion revascularisation up to three years after drug-eluting stent implantation: insights from a pooled analysis of the RESOLUTE Global Clinical Trial Program. *EuroIntervention*. 2016;12: 465-472.

15. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol*. 2017;70:3077-3087.

16. Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *J Am Coll Cardiol Img*. 2012;5(3 Suppl):S62-S72.

17. Cortés C, Carrasco-Moraleja M, Aparisi A, et al. Quantitative flow ratio-meta-analysis and systematic review. *Catheter Cardiovasc Interv*. 2021;97:807-814.

18. Wong CCY, Javadzadegan A, Ada C, et al. Fractional flow reserve and instantaneous wave-free ratio predict pathological wall shear stress in coronary arteries: implications for understanding the pathophysiological impact of functionally significant coronary stenoses. *J Am Heart Assoc*. 2022;11:e023502.

19. Mejía-Rentería H, Lauri FM, Lee JM, et al. Interindividual variations in the adenosine-induced hemodynamics during fractional flow reserve evaluation: implications for the use of quantitative flow ratio in assessing intermediate coronary stenoses. *J Am Heart Assoc*. 2019;8:e012906.

20. Geng L, Yuan Y, Du P, et al. Association of quantitative flow ratio-derived microcirculatory indices with anatomical-functional discordance in intermediate coronary lesions. *Int J Cardiovasc Imaging*. 2021;37:2803–2813.

21. Cesaro A, Gragnano F, Di Girolamo D, et al. Functional assessment of coronary stenosis: an overview of available techniques. Is quantitative flow ratio a step to the future? *Expert Rev Cardiovasc Ther*. 2018;16:951–962. https://doi.org/10.1080/14779072.2018.1540303

22. Smit JM, Koning G, van Rosendael AR, et al. Referral of patients for fractional flow reserve using quantitative flow ratio. *Eur Heart J Cardiovasc Imaging*. 2019;20:1231–1238.

23. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379:250–259.

24. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

25. Lakhter V, Alkhouli M, Zack CJ, et al. Sex differences in fractional flow reserve-guided revascularization: a nationwide analysis. *J Womens Health (Larchmt)*. 2017;26:109–115.

26. Fineschi M, Guerrieri G, Orphal D, et al. The impact of gender on fractional flow reserve measurements. *EuroIntervention*. 2013;9:360–366.

27. Ties D, van Dijk R, Pundziute G, et al. Computational quantitative flow ratio to assess functional severity of coronary artery stenosis. *Int J Cardiol*. 2018;271:36–41.

28. Reis SE, Holubkov R, Conrad Smith AJ, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: results from the NHLBI WISE study. *Am Heart J*. 2001;141:735–741.

29. Ahmadi A, Stone GW, Leipsic J, et al. Association of coronary stenosis and plaque morphology with fractional flow reserve and outcomes. *JAMA Cardiol*. 2016;1:350–357.

30. Leonardi RA, Townsend JC, Patel CA, et al. Left ventricular end-diastolic pressure affects measurement of fractional flow reserve. *Cardiovasc Revasc Med*. 2013;14:218–222.

31. Zuo W, Sun R, Ji Z, et al. Sex differences in Murray law-based quantitative flow ratio among patients with intermediate coronary lesions. *J Am Heart Assoc*. 2023;12:e029330.

32. Hou H, Zhao Q, Qu C, et al. Sex differences in the non-infarct-related artery-based quantitative flow ratio in patients with ST-elevation myocardial infarction: a retrospective study. *Front Cardiovasc Med*. 2021;8:726307.

33. Tu S, Ding D, Chang Y, et al. Diagnostic accuracy of quantitative flow ratio for assessment of coronary stenosis significance from a single angiographic view: a novel method based on bifurcation fractal law. *Catheter Cardiovasc Interv*. 2021;97(Suppl 2):1040–1047.

34. Ding D, Tu S, Chang Y, et al. Quantitative flow ratio based on Murray fractal law: accuracy of single versus two angiographic views. *J Soc Cardiovasc Angiogr Interv*. 2022;1:100399.

KEY WORDS percutaneous coronary intervention, quantitative flow ratio, sex difference

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