



Original Investigation | Cardiology

Quantitative Flow Ratio– vs Angiography-Guided Percutaneous Coronary Intervention

A Secondary Analysis of the FAVOR III China Trial

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Abstract

IMPORTANCE Whether the association of quantitative flow ratio (QFR)–guided percutaneous coronary intervention (PCI) with long-term outcomes differs according to multivessel disease (MVD) status is uncertain.

OBJECTIVE To assess the association of QFR-guided vs angiography-guided PCI with 3-year outcomes according to MVD status.

DESIGN, SETTING, AND PARTICIPANTS In this prespecified secondary analysis of the FAVOR III China randomized clinical trial, patients were screened across 26 centers in China from December 25, 2018, to January 19, 2020. Eligible participants were adults undergoing PCI for stable or unstable angina or for myocardial infarction (MI) occurring at least 72 hours before screening who had at least 1 lesion with 50% to 90% diameter stenosis in a vessel of 2.5 mm or larger. The analysis compared QFR-guided with angiography-guided PCI according to MVD status. MVD was defined by involvement of at least 2 epicardial vessels or the left main coronary artery. The primary analyses of the current prespecified secondary analysis were completed in October 2024.

INTERVENTIONS Randomization 1:1 to QFR-guided PCI or angiography-guided PCI.

MAIN OUTCOMES AND MEASURES The primary end point of the FAVOR III China randomized clinical trial was 1-year major adverse cardiac events (MACE), defined as a composite of all-cause death, MI, and ischemia-driven revascularization. The current analysis evaluated 3-year MACE.

RESULTS Among 3825 patients in the intention-to-treat population (mean [SD] age, 62.7 [10.0] years; 2699 [70.6%] male), 2066 (54.0%) had MVD. In the MVD cohort, MACE occurred in 124 of 1023 patients (12.1%) in the QFR-guided group and 188 of 1043 patients (18.1%) in the angiography-guided group (hazard ratio, 0.65; 95% CI, 0.52–0.81; $P < .001$), driven by lower rates of MI and revascularization. In the non-MVD cohort, MACE occurred in 76 of 890 patients (8.6%) and 95 of 869 patients (11.0%), respectively (hazard ratio, 0.77; 95% CI, 0.57–1.04; $P = .09$). The treatment $\times$ MVD interaction was not statistically significant (P for interaction = .35). The findings of landmark, per-protocol, competing-risk, sensitivity, and hierarchical win-ratio analyses were directionally consistent with the main findings.

CONCLUSIONS AND RELEVANCE In this prespecified secondary analysis of a randomized clinical trial of patients undergoing PCI, QFR-guided PCI was associated with a lower 3-year MACE rate

Key Points

Question Does the association of quantitative flow ratio–guided vs angiography-guided percutaneous coronary intervention with 3-year outcomes differ by multivessel disease status?

Findings In this prespecified secondary analysis of 3825 patients in the FAVOR III China randomized clinical trial, the quantitative flow ratio–guided strategy reduced 3-year major adverse cardiac events significantly in the subgroup with multivessel disease (MVD), driven by fewer myocardial infarctions and ischemia-driven revascularizations. In the non-MVD subgroup, numerically fewer major adverse cardiac events were seen, but the interaction by MVD status was not significant.

Meaning These findings suggest support for quantitative flow ratio–guided percutaneous coronary across MVD strata but additional studies are needed.

+ Supplemental content

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Abstract (continued)

among patients with MVD; however, no significant interaction was observed between treatment effect and MVD status. These findings provide longer-term randomized evidence supporting QFR-guided PCI across MVD strata and warrant further confirmation.

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Introduction

Wire-based fractional flow reserve (FFR) is the most widely used invasive approach to identify flow-limiting coronary lesions requiring revascularization.^{1,2} Both European and American guidelines assign FFR-guided percutaneous coronary intervention (PCI) a class IA recommendation for patients with chronic coronary syndrome when noninvasive evidence of ischemia is lacking.^{3,4} Nevertheless, adoption of FFR-guided PCI remains limited, with most interventional cardiologists relying predominantly on angiographic assessment.^{5,6}

Quantitative flow ratio (QFR) is an angiography-derived computational physiologic index that simulates FFR without the need for a pressure wire or hyperemic agents.⁷ The diagnostic performance of online QFR has been validated against invasive FFR in the FAVOR (Functional Assessment by Various Flow Reconstructions) II Europe-Japan and China studies.^{8,9} By avoiding intracoronary procedures, adverse effects of hyperemic agents, and costs of pressure guidewires, QFR offers a pragmatic alternative for physiology-based decision-making in clinical practice.¹⁰ Recently, the landmark FAVOR III China randomized clinical trial demonstrated that a QFR-guided strategy improved clinical outcomes compared with a standard angiography-guided strategy.^{11,12}

Previous studies have confirmed the long-term safety and efficacy of FFR-guided PCI in high-risk patients with multivessel disease (MVD),¹³ strongly supporting the use of FFR guidance as a standard of care in this population.^{3,4} Although the current guidelines recognize QFR as an alternative to FFR, its long-term effectiveness in patients with MVD remains insufficiently characterized.³ Therefore, this prespecified secondary analysis of the FAVOR III China randomized clinical trial evaluated 3-year outcomes associated with QFR-guided PCI in patients with and without MVD.

Methods

Patients and Study Design

The FAVOR III China randomized clinical trial was a multicenter investigation conducted across 26 institutions from December 25, 2018, to January 19, 2020 (see trial protocol and statistical analysis plan in [Supplement 1](#)).^{11,12,14} Adults (aged ≥18 years) scheduled for PCI based on visual angiography estimation were assessed for eligibility. Further eligibility criteria were stable or unstable angina pectoris or a myocardial infarction (MI) at least 72 hours before screening, with at least 1 lesion demonstrating a visual diameter stenosis of 50% to 90% in a vessel 2.5 mm or larger in diameter. Detailed inclusion and exclusion criteria are listed in the eMethods in [Supplement 2](#). MVD was a prespecified stratified factor, defined as visual diameter stenosis 50% or greater in at least 2 epicardial vessels or 50% or greater in the left main coronary artery (equivalent to 2-vessel disease). The trial protocol was approved by the Ethics Committee of Fuwai Hospital and by the institutional review board or ethics committee at each participating center. All patients provided written informed consent before randomization. The study was conducted in accordance with the Declaration of Helsinki³² and Good Clinical Practice guidelines. This study is reported following the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline.³³

Randomization and Procedures

Eligible patients were randomized in a 1:1 ratio to QFR-guided or angiography-guided PCI, stratified by diabetes, MVD, the presence of any vessel with diameter stenosis greater than 90% with Thrombolysis in Myocardial Infarction (TIMI) flow less than 3, and study center. The patients and all postcatheterization laboratory physicians and research personnel were masked to the randomized allocation until the completion of the 1-year follow-up. The target vessels intended for treatment with standard angiography guidance were identified by the operator before randomization.

In the QFR-guided group, QFR was calculated in real time for all lesions with visually assessed diameter stenosis of 50% to 90% in vessels 2.5 mm or larger, using the AngioPlus system (Pulse Medical). PCI treatment was performed in all lesions with a QFR of 0.80 or less and was deferred in lesions with a QFR greater than 0.80. PCI was also performed in all lesions with angiographic diameter stenosis greater than 90%. If no lesions had a diameter stenosis greater than 90% and all interrogated vessels had a QFR greater than 0.80, the patient was treated with optimal medical therapy alone. In the angiography-guided group, PCI was performed based on visual angiographic assessment, in accordance with local standard practice. In both groups, a planned staged PCI procedure was allowed in patients with MVD within 60 days after the index procedure. Patients were followed up by telephone or clinic visits at 1 and 6 months and annually thereafter up to 5 years after randomization. Offline QFR assessment from the angiograms in both groups was performed by the independent angiographic core laboratory staff. Functionally complete revascularization (FCR) was defined as the absence of any vessel with a QFR of 0.80 or less after PCI.

Study End Points

The primary end point of the original trial was the 1-year rate of major adverse cardiac events (MACE), a composite of all-cause death, MI, or ischemia-driven revascularization (IDR). The major secondary end point was the 1-year rate of MACE excluding periprocedural MI.

In the current prespecified secondary analysis, we assessed the incidence of all end points at 3 years stratified by MVD status: MACE and the individual components as separate events, cardiovascular death, target vessel revascularization, target lesion revascularization, and stent thrombosis. Full definitions of end points have been previously described (eMethods in [Supplement 2](#)).¹¹ End point events were adjudicated by an independent committee blinded to randomization assignment.

Statistical Analysis

The primary analyses of the current prespecified secondary analysis were completed in October 2024. Categorical variables were summarized as numbers (percentages). Continuous variables were presented as mean (SD). Categorical variables were compared between the 2 groups using the likelihood ratio χ^2 test or Fisher exact test. Continuous variables with normal distributions were compared using 2-sample *t* tests, and nonnormal continuous data were compared with the Wilcoxon rank-sum test.

The presence of MVD was one of the stratified factors and prespecified subgroups. The principal analysis was performed on the ITT population. Logistic models were used to assess treatment $\times$ MVD interactions for procedural outcomes, including PCI strategy modification and FCR. Time-to-first-event rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards regression models. Treatment $\times$ MVD interactions for clinical outcomes were assessed using Cox proportional hazards regression models, including the randomized treatment group, MVD status, and their interaction term. Landmark analysis segmented outcomes at 1 year to examine time-dependent effects and treatment $\times$ period interaction. For survival analyses, patients without the end point were censored at the time of last follow-up; missing data were minimal and were not imputed.

Sensitivity analyses included per-protocol Cox proportional hazards regression analyses, Cox proportional hazards regression models adjusted for randomization stratification factors, and Fine-Gray competing-risk models for revascularization and stent thrombosis end points, with all-cause death treated as the competing event.¹⁵ Hierarchical win-ratio analyses were performed to evaluate the treatment effect across prioritized clinical outcomes, including all-cause death, nonprocedural MI, and IDR.¹⁶ Additional post hoc analyses evaluated treatment × vessel number interactions across 1-, 2-, and 3-vessel disease strata.

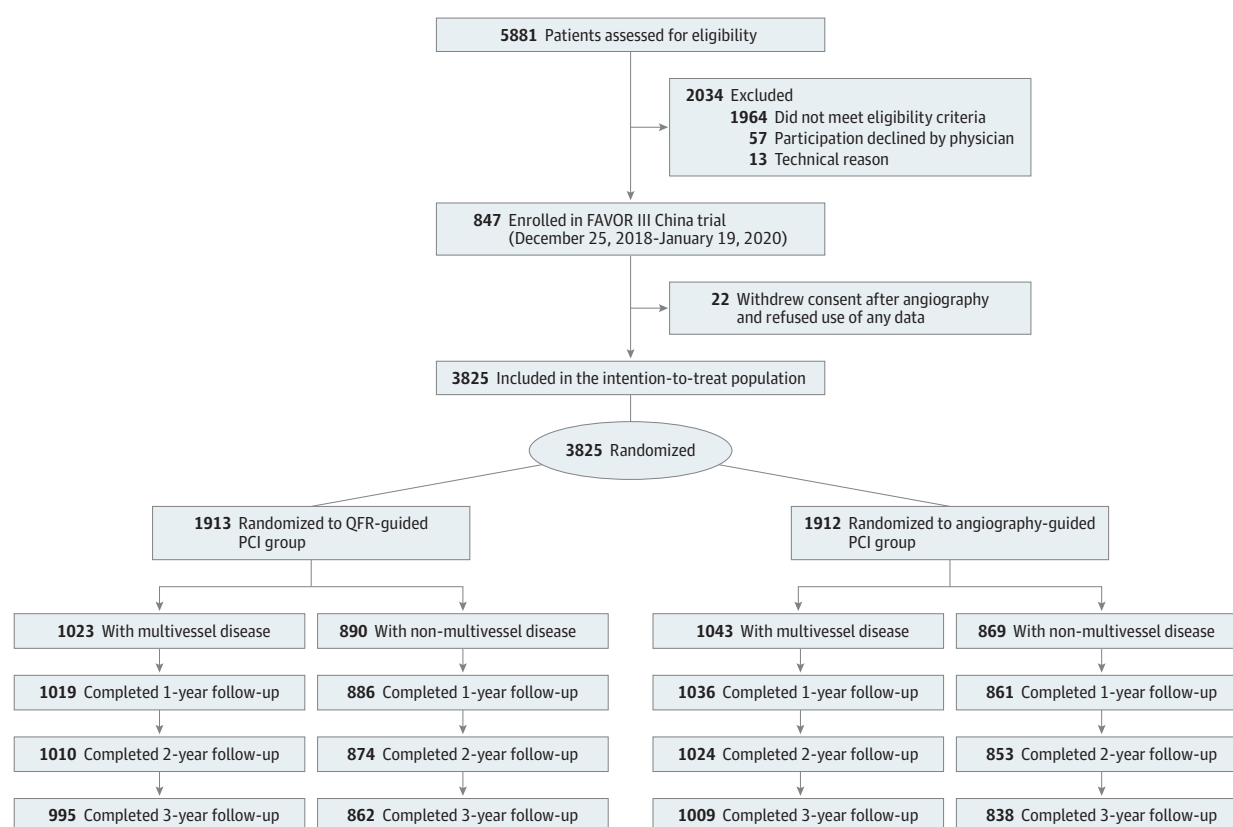
A 2-sided $P < .05$ was considered statistically significant. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Patient Characteristics

Between December 25, 2018, and January 19, 2020, 5881 patients were assessed for eligibility, 3847 were enrolled and randomized, and 3825 were included in the intention-to-treat population after 22 patients withdrew consent after angiography and refused use of any data. Of the 3825 study patients (mean [SD] age, 62.7 [10.0] years; 2699 [70.6%] male and 1126 [29.4%] female), 1759 (46.0%) did not have MVD, whereas 2066 (54.0%) had MVD. Within the MVD subgroup, the prevalence of 2-vessel, 3-vessel, and left main disease was 65.7% ($n = 1358$), 30.1% ($n = 622$), and 4.2% ($n = 86$), respectively. Three-year clinical follow-up was completed for 1857 of 1913 patients (97.1%) in the QFR-guided group and 1847 of 1912 patients (96.6%) in the angiography-guided group (**Figure 1**).

Figure 1. Study Flowchart



PCI indicates percutaneous coronary intervention; QFR, quantitative flow ratio.

During 3-year follow-up, 115 participants were unavailable for follow-up and 6 participants withdrew; details are provided in eTable 1 in [Supplement 2](#).

The MVD cohort exhibited a higher prevalence of diabetes, hypertension, hypercholesterolemia, current smoking, and lower left ventricular ejection fraction compared with their counterparts. Baseline clinical characteristics were generally well balanced between the QFR- and angiography-guided arms in both the MVD and non-MVD cohorts (**Table 1**), and overall differences between patients with and without MVD are given in eTable 2 in [Supplement 2](#).

Angiographic and Procedural Characteristics

The mean (SD) number of diseased vessels per patient was 2.30 (0.46). Mean (SD) anatomical and functional SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) scores were 11.8 (6.6) and 10.1 (7.0), respectively, and were higher than those observed in patients without MVD. Baseline angiographic characteristics were comparable between the QFR-guided and angiography-guided arm (eTable 2 in [Supplement 2](#)).

Patients with MVD in the QFR-guided group underwent fewer interventions than those in the angiography-guided group. Additionally, procedural duration, number of stents deployed, and radiation exposure were lower in the QFR-guided group. Modifications to revascularization strategies after randomization occurred more frequently in the QFR-guided group than in the angiography-guided group (301 [29.4%] vs 105 [10.1%]; $P < .001$), including deferral of at least 1 vessel originally intended for PCI (231 [22.6%] vs 88 [8.4%]; $P < .001$) and treatment of at least 1 vessel not originally intended for PCI (83 [8.1%] vs 25 [2.4%]; $P < .001$). In the non-MVD cohort, QFR guidance was also associated with more frequent strategy modification and deferral of intended PCI, whereas treatment of vessels not originally intended for PCI did not differ between groups (2 [0.2%] vs 3 [0.3%]; $P = .68$). FCR was achieved more often in the QFR-guided group than the angiography-guided group among patients with MVD (831 [82.5%] vs 743 [72.6%]; $P < .001$), with no significant difference in the non-MVD cohort (94.5% vs 93.7%; $P = .51$) (**Table 2**; eTable 3 in [Supplement 2](#)). Interactions by MVD status were significant for any PCI strategy modification and deferral of intended PCI, whereas interactions for PCI performance and FCR achievement were nonsignificant (eTable 4 in [Supplement 2](#)).

According to offline core laboratory QFR analysis, a higher proportion of vessels with a QFR of 0.80 or less were treated in the QFR-guided group compared with the angiography-guided group among patients with MVD (1277 [95.4%] vs 1177 [87.6%]; $P < .001$), whereas no difference was observed in the patients without MVD (713 [99.2%] vs 666 [98.1%]; $P = .08$). Conversely, more vessels with a QFR greater than 0.80 were treated in the angiography-guided group compared with the QFR-guided group, in both the MVD (294 [57.2%] vs 44 [9.0%]; $P < .001$) and non-MVD cohorts (194 [90.2%] vs 43 [21.4%]; $P < .001$) (eTable 5 in [Supplement 1](#)).

Clinical Outcomes

Overall 3-year outcomes according to MVD status are given in eTable 6 in [Supplement 2](#). In the MVD cohort, the incidence of MACE was lower in the QFR-guided group compared with the angiography-guided group (124 [12.1%] vs 188 [18.1%]; HR, 0.65; 95% CI, 0.52-0.81; $P < .001$), driven by fewer MIs (56 [5.5%] vs 99 [9.5%]; $P = .001$) and IDRs (66 [6.5%] vs 95 [9.2%]; $P = .02$). In the non-MVD cohort, no statistical difference between the 2 strategies was observed (76 [8.6%] vs 95 [11.0%]; HR, 0.77; 95% CI, 0.57-1.04; $P = .09$). However, the treatment $\times$ MVD interaction was not statistically significant (P for interaction = .35). Similar patterns were observed for secondary end points, with no statistically significant treatment $\times$ MVD interactions (**Table 3** and **Figure 2**; eFigure 1 in [Supplement 2](#)).

A prespecified 1-year landmark analysis in the ITT population showed that, among the MVD cohort, QFR-guided PCI was associated with a lower incidence of MACE within the first year (HR, 0.59; 95% CI, 0.44-0.79; $P < .001$) but not beyond 1 year (HR, 0.74; 95% CI, 0.52-1.05; $P = .10$); however, treatment $\times$ period interaction for MACE was nonsignificant (P for interaction = .31). Similar

Table 1. Baseline Clinical and Angiographic Characteristics of Treatment Groups Stratified by MVD Status

Characteristic	No. (%) of patients ^a		Non-MVD group (n = 1759)	
	MVD group (n = 2066)	Angiography-guided group (n = 1043)	QFR-guided group (n = 890)	Angiography-guided group (n = 869)
Age, mean (SD), y	62.5 (9.9)	62.8 (10.1)	63.0 (10.3)	62.5 (10.2)
Sex				
Male	742 (72.5)	739 (70.9)	607 (68.2)	611 (70.3)
Female	281 (27.5)	304 (29.1)	283 (31.8)	258 (29.7)
BMI, mean (SD)	25.2 (3.1)	25.1 (3.1)	25.1 (3.2)	24.8 (3.3)
Diabetes	363 (35.5)	378 (36.2)	285 (32.0)	269 (31.0)
Hypertension	696 (68.0)	707 (67.8)	574 (64.5)	545 (62.7)
Hypercholesterolemia	420 (41.1)	454 (43.5)	309 (34.7)	274 (31.5)
Current smoker	325 (31.8)	333 (31.9)	249 (28.0)	235 (27.0)
Family history of coronary artery disease	82 (8.0)	75 (7.2)	65 (7.3)	74 (8.5)
Previous myocardial infarction	105 (10.3)	112 (10.7)	74 (8.3)	67 (7.7)
Previous percutaneous coronary intervention	264 (25.8)	266 (25.5)	221 (24.8)	200 (23.0)
Previous coronary artery bypass grafting	5 (0.5)	3 (0.3)	0 (0)	1 (0.1)
Previous stroke	103 (10.1)	105 (10.1)	81 (9.1)	70 (8.1)
Peripheral artery disease	30 (2.9)	44 (4.2)	25 (2.8)	27 (3.1)
Clinical presentation ^b				
Asymptomatic ischemia	104 (10.2)	118 (11.3)	103 (11.6)	86 (9.9)
Stable angina	267 (26.1)	281 (26.9)	226 (25.4)	212 (24.4)
Unstable angina	586 (57.3)	577 (55.3)	525 (59.0)	533 (61.3)
Postmyocardial infarction (within 30 days)	66 (6.5)	67 (6.4)	36 (4.0)	38 (4.4)
Acute coronary syndrome	652 (63.7)	644 (61.7)	561 (63.0)	571 (65.7)
Stable angina CCS class ^b				
I	103/267 (38.6)	120/281 (42.7)	73/226 (32.3)	71/212 (33.5)
II	89/267 (33.3)	84/281 (29.9)	75/226 (33.2)	62/212 (29.2)
III	55/267 (20.6)	50/281 (17.8)	48/226 (21.2)	43/212 (20.3)
IV	20/267 (7.5)	27/281 (9.6)	30/226 (13.3)	36/212 (17.0)
Unstable angina Braunwald class ^b				
I	254/586 (43.3)	244/577 (42.3)	257/525 (49.0)	267/533 (50.1)
II	277/586 (47.3)	275/577 (47.7)	233/525 (44.4)	228/533 (42.8)
III	55/586 (9.4)	58/577 (10.1)	35/525 (6.7)	38/533 (7.1)
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m ^{2c}	73.8 (64.3)	71.9 (35.7)	73.4 (25.1)	73.9 (27.8)
Left ventricular ejection fraction, mean (SD), %	62.9 (6.4)	62.4 (7.1)	63.5 (6.8)	63.4 (6.7)
No. of diseased vessels ^d				
1	0	0	890 (100.0)	869 (100.0)
2	674 (65.9)	684 (65.6)	0	0
3	306 (29.9)	316 (30.3)	0	0
Left main disease	43 (4.2)	43 (4.1)	0	0
No. of diseased vessels per patient, mean (SD)	2.30 (0.46)	2.30 (0.46)	1.00 (0.00)	1.00 (0.00)
Any vessel with ≥1 lesions with diameter stenosis >90% and TIMI flow <3	166 (16.2)	176 (16.9)	4 (0.4)	6 (0.7)
Patients with moderate to severe coronary lesions ^e	777 (76.0)	786 (75.4)	494 (55.5)	493 (56.7)
Anatomical SYNTAX score, mean (SD) ^e	11.6 (6.3)	11.9 (6.8)	6.7 (4.2)	6.7 (4.2)
Functional SYNTAX score, mean (SD) ^f	10.0 (6.8)	10.1 (7.3)	5.9 (4.8)	5.6 (4.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCS, Canadian Cardiovascular Society; MVD, multivessel coronary disease; QFR, quantitative flow ratio; TIMI, Thrombolysis in Myocardial Infarction.

^a Unless otherwise indicated.

^b Consistent with clinical practice in China and the study protocol, non-high-sensitivity troponins were used to assess possible myocardial infarction at all participating centers. Stable angina was classified according to the CCS functional classification and unstable angina according to the Braunwald classification.

^c Estimated glomerular filtration rate was calculated with the Cockcroft-Gault formula.

^d Site reported.

^e The anatomical SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score is a scoring system that quantifies angiographic lesion extent and complexity. The SYNTAX score was calculated by the angiographic core laboratory.

^f The functional SYNTAX score was calculated by summing the segmental anatomical SYNTAX scores only in vessels with functional ischemia as defined by an offline quantitative flow ratio of 0.80 or less as determined by the angiographic core laboratory.

patterns were observed for MACE excluding periprocedural MI (HR, 0.58 [95% CI, 0.39-0.87] within 1 year vs 0.72 [95% CI, 0.50-1.03] beyond 1 year). In the non-MVD subgroup, no statistically significant differences were observed in either interval (eFigure 2 in Supplement 2). Component-level landmark analyses showed no treatment × period interactions for all components (eFigure 3 in Supplement 2).

Table 2. Procedural Characteristics of the Treatment Groups Stratified by MVD Status

Characteristic	No./total No. (%) of patients ^a		P value	Non-MVD group (n = 1759)		P value
	MVD group (n = 2066)	Angiography-guided group (n = 1043)		QFR-guided group (n = 890)	Angiography-guided group (n = 869)	
Radial artery approach	1004 (98.1)	1019 (97.7)	.48	881 (99.0)	850 (97.8)	.047
PCI performed	980 (95.8)	1036 (99.3)		751 (84.4)	859 (98.8)	
Drug-eluting stents placed	950 (92.9)	997 (95.6)	<.001	717 (80.6)	815 (93.8)	<.001
Drug-coated balloon angioplasty	26 (2.5)	26 (2.5)		29 (3.3)	32 (3.7)	
Non-drug-coated balloon angioplasty	4 (0.4)	13 (1.2)		5 (0.6)	12 (1.4)	
No. of stents placed per patient, mean (SD)	1.81 (1.11)	1.91 (1.10)	.04	1.03 (0.71)	1.18 (0.59)	<.001
Stent length, mean (SD), mm	46.8 (31.1)	48.7 (30.9)	.17	26.2 (20.0)	28.9 (16.7)	.002
Stent diameter, mean (SD), mm	2.75 (0.85)	2.83 (0.72)	.03	2.50 (1.29)	2.88 (0.85)	<.001
Use of intravascular imaging ^b	71 (6.9)	68 (6.5)	.70	48 (5.4)	53 (6.1)	.52
Contrast medium used per patient, mean (SD), mL	173.1 (76.6)	180.5 (77.7)	.03	151.4 (72.7)	156.7 (67.4)	.12
Fluoroscopy time, mean (SD), min	15.8 (8.2)	16.5 (7.6)	.07	12.2 (7.4)	13.2 (6.7)	.004
Procedure time, mean (SD), min ^c	50.8 (29.5)	54.9 (28.8)	.002	37.5 (26.3)	43.1 (30.6)	<.001
Adjusted procedure time, mean (SD), min ^c	43.0 (28.1)	45.2 (28.5)	.08	34.4 (22.6)	33.6 (30.4)	.55
PCI lesion success ^d	1480/1498 (98.8)	1672/1687 (99.1)	.39	765/769 (99.5)	889/893 (99.6)	>.99
PCI procedure success ^e	927/980 (94.6)	959/1036 (92.6)	.06	730/751 (97.2)	837/859 (97.4)	.77
Vessels intended to be treated before randomization						
Left main	33/1613 (2.0)	40/1690 (2.4)	.53	0/890 (0)	0/869 (0)	NA
Left anterior descending	702/1613 (43.5)	703/1690 (41.6)	.26	615/890 (69.1)	578/869 (66.5)	.25
Left circumflex	427/1613 (26.5)	472/1690 (27.9)	.35	95/890 (10.7)	113/869 (13.0)	.13
Right coronary artery	451/1613 (28.0)	475/1690 (28.1)	.93	180/890 (20.2)	178/869 (20.5)	.89
Vessels actually treated of those originally intended	1365/1613 (84.6)	1592/1690 (94.2)	<.001	747/890 (83.9)	857/869 (98.6)	<.001
Left main	29/1365 (2.1)	38/1592 (2.4)	.63	0/747 (0)	0/857 (0)	NA
Left anterior descending	634/1365 (46.4)	669/1592 (42.0)	.02	540/747 (72.3)	570/857 (66.5)	.03
Left circumflex	344/1365 (25.2)	445/1592 (28.0)	.09	74/747 (9.9)	112/857 (13.1)	.002
Right coronary artery	358/1365 (26.2)	440/1592 (27.6)	.39	133/747 (17.8)	175/857 (20.4)	.004
Patients with intended vessel deferral or unintended vessel treatment	301 (29.4)	105 (10.1)	<.001	144 (16.2)	14 (1.6)	<.001
Deferral (nontreatment) of at least 1 vessel originally intended for PCI	231 (22.6)	88 (8.4)	<.001	144 (16.2)	12 (1.4)	<.001
Treatment of at least 1 vessel not originally intended for PCI	83 (8.1)	25 (2.4)	<.001	2 (0.2)	3 (0.3)	.68
Residual anatomical SYNTAX score, mean (SD)	3.39 (3.99)	3.45 (4.61)	.77	1.34 (2.57)	1.03 (2.43)	.01
Residual functional SYNTAX score, mean (SD)	1.00 (2.68)	1.61 (3.50)	<.001	0.29 (1.55)	0.32 (1.51)	.71
Residual functional SYNTAX score of 0	831 (82.5)	743 (72.6)	<.001	838 (94.5)	809 (93.7)	.51

Abbreviations: MVD, multivessel coronary disease; NA, not applicable; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio.

^a Unless otherwise indicated.

^b Intravascular ultrasonography or optical coherence tomography.

^c 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.

^d Defined as residual stenosis less than 30% for patients treated with stents or less than 50% for patients treated with balloon angioplasty by visual estimation, with Thrombolysis in Myocardial Infarction flow grade 3 in the treated vessel.

^e Defined as lesion success in all treated lesions without in-hospital major adverse cardiac events (though a maximum of 7 days).

Sensitivity and Subgroup Analyses

Per-protocol analyses were consistent with the ITT findings. In the MVD cohort, the 3-year incidence of MACE was lower in the QFR-guided group than in the angiography-guided group (118 [12.1%] vs 159 [17.0%]; HR, 0.69; 95% CI, 0.55-0.88; *P* = .002). In the non-MVD group, between-group differences were not statistically significant (76 [8.6%] vs 93 [10.9%]; HR, 0.78; 95% CI, 0.58-1.06; *P* = .11) (eTable 7 in Supplement 2). Furthermore, hierarchical win-ratio analyses of prioritized clinical outcomes favored QFR-guided PCI within both the MVD and non-MVD cohorts in the ITT and per-protocol populations (eFigures 4 and 5 in Supplement 2).

Sensitivity analyses adjusted for randomization stratification factors were also consistent with the primary analysis, with adjusted HRs for 3-year MACE of 0.64 (95% CI, 0.51-0.81) in the MVD cohort and 0.77 (95% CI, 0.57-1.04) in the non-MVD cohort and no significant treatment × MVD interaction (*P* for interaction = .35) (eTable 8 in Supplement 2). Fine-Gray competing-risk analyses showed lower revascularization-related end points with QFR guidance in the MVD cohort, whereas no between-group differences were observed in the non-MVD cohort (eTable 9 in Supplement 2). The association between QFR guidance and 3-year MACEs was not statistically significant across 1-, 2-, and 3-vessel disease strata (*P* for interaction = .59) (eTable 10 in Supplement 2). Subgroup analyses demonstrated consistent benefit of QFR-guided PCI across most subgroups in the MVD cohort, whereas in the non-MVD cohort, treatment effects varied by age, sex, or clinical presentation (eFigures 6 and 7 in Supplement 2).

Discussion

The prespecified secondary analysis of the large-scale randomized FAVOR III China randomized clinical trial found that (1) QFR guidance was associated with a higher rate of FCR compared with

Table 3. Three-Year Clinical Outcomes of Treatment Groups Stratified by MVD Status^a

Outcome	MVD group (n = 2066)				Non-MVD group (n = 1759)				
	QFR-guided group (n = 1023)	Angiography-guided group (n = 1043)	Hazard ratio (95% CI)	P value	QFR-guided group (n = 890)	Angiography-guided group (n = 869)	Hazard ratio (95% CI)	P value	P value for Interaction
MACE	124 (12.1)	188 (18.1)	0.65 (0.52-0.81)	<.001	76 (8.6)	95 (11.0)	0.77 (0.57-1.04)	.09	.35
All-cause death	19 (1.9)	25 (2.4)	0.77 (0.43-1.40)	.40	10 (1.1)	9 (1.0)	1.09 (0.44-2.67)	.86	.54
Myocardial infarction	56 (5.5)	99 (9.5)	0.57 (0.41-0.79)	.001	31 (3.5)	47 (5.4)	0.64 (0.41-1.01)	.052	.66
Ischemia-driven revascularization	66 (6.5)	95 (9.2)	0.69 (0.51-0.95)	.02	40 (4.5)	46 (5.4)	0.85 (0.55-1.92)	.44	.46
MACE excluding PMI	90 (8.8)	136 (13.1)	0.66 (0.50-0.86)	.002	60 (6.8)	78 (9.0)	0.74 (0.53-1.04)	.08	.57
Other secondary end points									
Cardiovascular death	9 (0.9)	14 (1.4)	0.65 (0.28-1.51)	.32	4 (0.4)	4 (0.5)	0.98 (0.24-3.91)	.97	.63
PMI	39 (3.8)	63 (6.0)	0.79 (0.65-0.97)	.02	17 (1.9)	18 (2.1)	0.96 (0.69-1.34)	.81	.33
Non-PMI	18 (1.8)	39 (3.8)	0.47 (0.27-0.81)	.006	14 (1.6)	29 (3.4)	0.47 (0.25-0.88)	.02	.99
Any revascularization	85 (8.4)	110 (10.7)	0.77 (0.58-1.03)	.07	54 (6.1)	60 (7.0)	0.87 (0.61-1.26)	.47	.60
Target vessel revascularization ^b	40 (4.0)	58 (5.6)	0.70 (0.47-1.04)	.08	26 (3.0)	25 (2.9)	1.02 (0.59-1.76)	.96	.27
Ischemia-driven	30 (3.0)	51 (5.0)	0.59 (0.38-0.93)	.02	21 (2.4)	20 (2.3)	1.03 (0.56-1.90)	.93	.15
Target lesion revascularization	27 (2.7)	48 (4.7)	0.57 (0.35-0.91)	.02	17 (1.9)	21 (2.4)	0.79 (0.42-1.50)	.47	.41
Ischemia-driven	24 (2.4)	44 (4.3)	0.55 (0.33-0.90)	.02	16 (1.8)	16 (1.9)	0.98 (0.49-1.96)	.95	.18
Stent thrombosis, definite or probable	5 (0.5)	12 (1.2)	0.42 (0.15-1.20)	.10	2 (0.2)	2 (0.2)	0.98 (0.14-6.93)	.98	.46

Abbreviations: MACE, major adverse cardiovascular event; MVD, multivessel coronary disease; PMI, periprocedural myocardial infarction; QFR, quantitative flow ratio.

^a Event rates are shown as the number of events, with Kaplan-Meier-estimated time-to-first-event rates in parentheses. MACEs are defined as the composite of death from any cause, myocardial infarction, or ischemia-driven revascularization.

^b Revascularization of vessels that were actually treated with percutaneous coronary intervention after randomization.

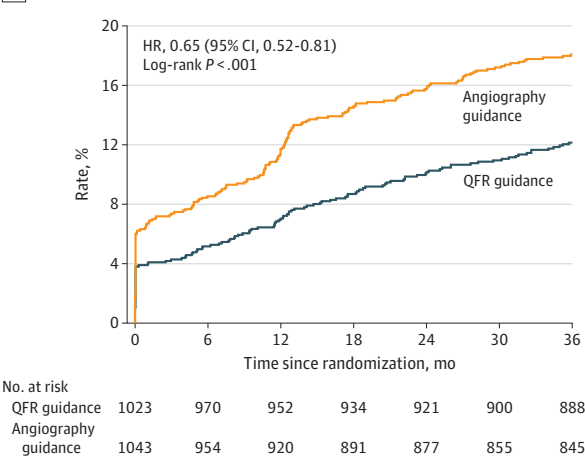
angiography guidance in patients with MVD; (2) QFR guidance altered PCI strategy, primarily through deferral of intervention, particularly in the MVD cohort; and (3) QFR-guided PCI was associated with lower 3-year MACE rate in the MVD cohort, whereas the difference in the non-MVD cohort was not statistically significant. However, no significant interaction by MVD status was observed.

Strategy Reclassification and Functional Revascularization

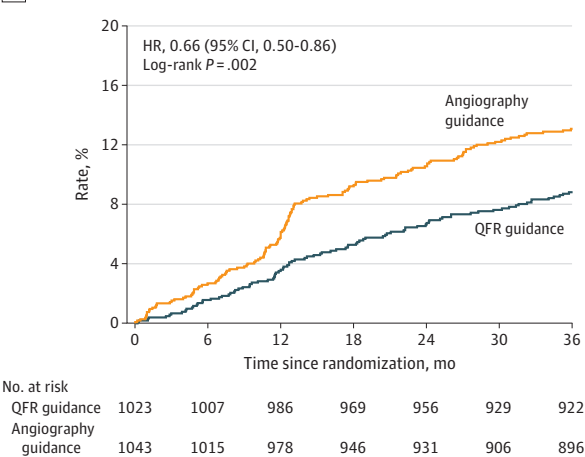
MVD represents a high-risk phenotype of atherosclerosis and is associated with adverse outcomes.¹⁷ Previous studies^{13,17-19} have demonstrated that physiology-guided PCI using wire-based indexes, such as FFR and instantaneous wave-free ratio, can reclassify treatment strategies, facilitate FCR, and improve long-term clinical outcomes in this setting. In the FAME (Fractional Flow Reserve vs Angiography for Multivessel Evaluation) trial, FFR-guided PCI reduced MACEs at 1 year by approximately 30% compared with angiography-guided PCI (HR, 0.72), driven by fewer MIs and revascularizations.^{13,17} Our findings suggest a similar risk reduction of QFR-guided PCI in patients with MVD (HR, 0.65), extend this body of evidence to angiography-derived physiology, and thus offer a practical, wire-free, and less invasive alternative.¹⁰

Figure 2. Kaplan-Meier Curves for the 3-Year Outcomes

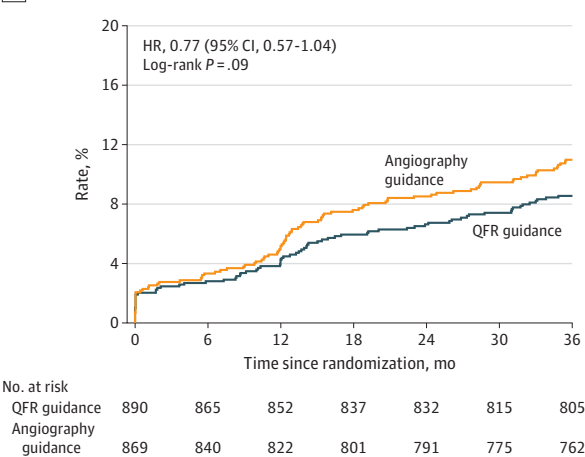
A 3-y MACE rate in MVD cohort



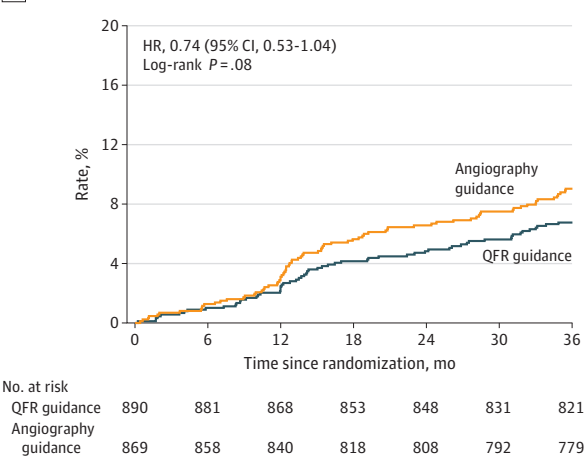
B 3-y MACE rate excluding PMI in MVD cohort



C 3-y MACE rate in non-MVD cohort



D 3-y MACE rate excluding PMI in non-MVD cohort



Analyses were performed in the intention-to-treat population. HR, hazard ratio; MACE, major adverse cardiac event; MVD, multivessel coronary disease; PMI, periprocedural myocardial infarction; QFR, quantitative flow ratio.

Two observations may help contextualize these findings. First, QFR guidance led to a high rate of modifications to initial angiography-based PCI plans, particularly in the MVD cohort. Specifically, QFR guidance was associated with more frequent deferral of at least 1 intended vessel (22.6%) and treatment of at least 1 unintended vessel (8.1%). This pattern is consistent with prior physiology-guided studies, reporting reclassification rates ranging from 26% to 45% in patients with MVD.^{20,21} Notably, deferral of PCI in functionally nonsignificant lesions (FFR >0.80) is safe, whereas treatment of ischemic lesions reduces adverse events.²²⁻²⁵ These findings reinforce the physiology over anatomy paradigm, highlighting the limitations of angiography alone in the context of MVD.^{13,26} Second, previous studies^{13,17} have shown that FCR is associated with improved long-term outcomes. Residual functional SYNTAX score is a strong predictor of adverse outcomes,²⁷ whereas residual anatomical SYNTAX score was not associated with clinical outcomes if FCR was achieved.²⁸ In the current study, QFR guidance in the MVD cohort achieved a higher rate of FCR (82.5% vs 72.6%), whereas FCR rates were high and similar between QFR and angiography groups (94.5% vs 93.7%), leaving little scope for QFR guidance to further improve this procedural outcome.

Landmark, Per-Protocol, and Hierarchical Analyses

The prespecified 1-year landmark analysis showed that the lower risk of QFR guidance in the MVD population was numerically more evident within the first year.^{13,29} However, treatment × period interaction testing did not support a statistically significant time-dependent treatment association. In prior work,¹³ the early advantage of physiology-guided over angiography-guided PCI appeared to attenuate during longer-term follow-up, potentially reflecting the progression of nontarget vessel disease and the influence of systemic risk factors over time. The 3-year follow-up in the current subgroup analysis may be insufficient to determine whether the early benefit in patients with MVD will persist. Per-protocol analysis and hierarchical win-ratio analyses were also broadly consistent with previous findings: QFR guidance is more likely to impact ischemia-related outcomes than mortality within the observed follow-up period.^{13,30}

Contextualizing Conflicting Evidence

Contemporary guidelines support the use of physiologic assessment to guide revascularization in patients with MVD (class IA).^{3,4} At the same time, the FAVOR III Europe trial did not demonstrate noninferiority of QFR compared with FFR-guided PCI.³¹ This is important when interpreting the results of the current study: the current analysis evaluates QFR against angiography-guided PCI according to MVD status rather than comparing QFR with FFR. Within this context, QFR guidance was associated with lower event rates in the MVD subgroup, and no significant interaction by MVD status was observed. Rather, these findings suggest that QFR may be useful when revascularization decisions would otherwise be based on angiography alone.

Limitations

Our study has several limitations. First, although MVD status was a prespecified subgroup, the current analysis was underpowered and should be interpreted with caution. The lower event rate in the non-MVD cohort may have limited the precision of treatment-effect estimates within this stratum. In addition, secondary end points and subgroup, landmark, and win-ratio analyses should also be considered exploratory and hypothesis-generating. Second, QFR measurements depend on the technique and quality of angiographic acquisition. Third, PCI operators were not blind to the group assignments, which could have introduced procedural bias. Patients and follow-up personnel were also unblinded after 1 year, as per the protocol; subsequent management, particularly repeat revascularization, may have been influenced by knowledge of treatment assignment. Fourth, the MVD cohort had relatively low-to-moderate anatomical complexity, with a mean SYNTAX score of 12 and a lower proportion of left main disease than other MVD studies.^{20,28} The generalizability of these findings to patients with highly complex MVD may be limited.

Conclusions

In this prespecified secondary analysis of the FAVOR III China randomized clinical trial, QFR-guided PCI was associated with lower 3-year MACE rate in patients with MVD, although no statistically significant differential treatment effects by MVD status were observed. These findings provide longer-term randomized evidence supporting QFR-guided PCI across MVD strata and warrant further confirmation.

ARTICLE INFORMATION

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Data Sharing Statement: See [Supplement 4](#).

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SUPPLEMENT 1.

Trial Protocol

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SUPPLEMENT 3.

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SUPPLEMENT 4.

Data Sharing Statement