

# Lesion length-dependent effects of quantitative flow ratio-guided percutaneous coronary intervention

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## ABSTRACT

**Background** The FAVOR III China trial previously revealed that quantitative flow ratio (QFR)-guided percutaneous coronary intervention (PCI) achieved superior outcomes compared with angiography guidance. This predefined subgroup analysis was conducted to examine whether coronary lesion length modifying the clinical effect of QFR based revascularization strategy.

**Methods** Overall, 3,825 patients were randomly assigned to either QFR-guided PCI (PCI performed only when QFR  $\leq$  0.80) or angiography-guided PCI. Lesions were categorized as long ( $\geq$  20 mm) or short ( $<$  20 mm), based on measurements from an independent imaging core laboratory. The primary study endpoint consisted of the composite of major adverse cardiac events (MACE), including myocardial infarction, ischemia-associated revascularization, and all-cause mortality over three years of follow-up.

**Results** A total of 1,877 patients were classified into the long-lesion group (931 QFR-guided and 946 angiography-guided), and 1,925 into the short-lesion group (974 QFR-guided, 951 angiography-guided). After three years, patients with longer lesions had a greater incidence of MACE relative to those with shorter lesions (15.5% vs. 9.8%;  $P < 0.0001$ ). Relative to angiography, QFR guidance led to a reduction in PCI procedures in both strata 14.8% in the short-lesion group and 2.4% in the long-lesion group. Relative risk reduction in MACE with QFR guidance was consistent regardless of lesion length: 7.1% versus 12.6% (HR = 0.55; 95% CI: 0.41–0.74) in the short-lesion group and 13.9% versus 17.0% (HR = 0.79; 95% CI: 0.63–1.00) in the long-lesion group ( $P_{\text{interaction}} = 0.06$ ).

**Conclusions** QFR-guided PCI was linked to fewer MACE relative to PCI guided by angiography after three years. The relative benefit was most pronounced in patients with shorter lesions.

Coronary artery disease (CAD) remains a key contributor to death and disability worldwide, and percutaneous coronary intervention (PCI) represents a cornerstone of treatment for affected individuals.<sup>[1]</sup> In patients presenting with symptoms of ischemic heart disease (IHD), invasive coronary angiography (ICA) is frequently recommended. Clinical guidelines also support adjunctive physiological assessment with fractional flow reserve (FFR) determined by pressure guidewire, especially when optimal medical therapy fails to control symptoms and revascularization is under consideration.<sup>[2]</sup> Despite advances in devices, stents, and procedural techniques that have improved PCI outcomes, many patients still experience recurrent angina or adverse cardiovascular events following angiography-guided PCI. These persistent problems highlight the limitations of anatomical assessment alone and underscore the potential value of functional evaluation for guiding revascularization.<sup>[3]</sup> Quantitative flow ratio (QFR) is a new angiography-based method for estimating FFR that eliminates the need for pressure wires and hyperemic agents. QFR is derived from three-dimensional quantitative coronary angiography and computational modeling of contrast flow. Previous studies have confirmed its accuracy as a means of detecting physiologically significant stenoses relative to invasive guidewire-measured FFR, as well as its prognostic relevance in patients with ischemic cardiomyopathy.<sup>[4,5]</sup> Large-scale evaluations across populations in Europe, Asia, and North America have validated its diagnostic performance and clinical applicability.<sup>[6]</sup>

The FAVOR III China trial (NCT03656848), a prospective, multicenter randomized study, compared QFR-guided versus angiography-guided PCI and reported that QFR-based lesion selection was associated with improved outcomes at both one and two years of follow-up.<sup>[7,8]</sup> However, it has not been fully determined whether the advantage of QFR guidance extends equally to both short and long coronary lesions.

Lesion length has long been recognized as an important anatomical determinant of PCI success. Longer lesions are traditionally linked to greater procedural complexity and higher event rates, particularly when treated with first-generation drug-eluting stents (DES). With the advent of newer-generation DES and refined procedures, the efficacy and safety of PCI for long lesions have improved substantially, although risks may still exceed those of shorter lesions.<sup>[9-11]</sup> Against this backdrop, the

current analysis aimed to investigate whether lesion length modifies the benefit of QFR guidance over a 3-year horizon and to provide lesion length-specific insights into outcomes in the era of modern PCI procedures.

## METHODS

### Study Design

Data from FAVOR III China, a prospective, multicenter randomized controlled trial conducted at 26 hospitals across China, were analyzed using prespecified subgroups. The overall design, protocol, and main findings have been described. In this analysis, we specifically examined whether outcomes associated with QFR- versus angiography-guided PCI varied in terms of lesion length (Supplemental Figure 1).

Eligible patients were over the age of 18 years with an indication for PCI based on angiographic findings and clinical presentation of myocardial infarction > 72 h before assessment or stable/unstable angina. Inclusion required a minimum of one coronary lesion with stenosis of 50%–90% diameter in a vessel with reference diameter  $\geq 2.5$  mm, as visually assessed. The exclusion criteria included moderate-to-severe chronic kidney disease (serum creatinine > 150 mmol/L or eGFR < 45 mL/min per 1.73 m<sup>2</sup> per the Cockcroft-Gault formula), severe vessel tortuosity, overlapping stenoses, or poor image quality precluding QFR analysis. Full eligibility details are available in prior publications. The trial received institutional review boards approval for all study sites, with all participants having received written informed consent.

### Participants and Procedures

Following operator-determined eligibility for angiography-guided treatment, patients were randomly assigned in a 1: 1 ratio to either the QFR-guided or angiography-guided group. QFR measurements were obtained using the AngioPlus system (Pulse Medical), adhering to standardized protocols. Two angiographic projections with at least a 25° separation were acquired and transmitted via the local network. Anatomical data were then processed to generate pullback curves. PCI was performed only when the QFR value was  $\leq 0.80$ ; otherwise, revascularization was deferred and patients received medical therapy alone.

In the angiography-guided group, PCI was carried out



based solely on the operator's visual interpretation, consistent with standard clinical practice. To ensure blinding, patients and outcome assessors were kept unaware of treatment assignment. During the procedure, patients in both arms wore headphones with music, and a standardized 10-minute delay was applied to mask whether QFR calculations were real or sham. The success of blinding and patient perception of allocation were assessed at discharge and at 6 and 12 months using structured questionnaires. Further details of the blinding strategy are described in the original FAVOR III China trial protocol. All randomized lesions subsequently underwent offline QFR reassessment and quantitative coronary angiographic analysis at an independent core laboratory.

### Clinical Outcomes

The primary study endpoint consisted of the cumulative incidence of major adverse cardiac events (MACE) over three years, which was determined based on the composite of all-cause mortality, myocardial infarction (MI), and ischemia-driven revascularization (IDR). To account for procedural influences, sensitivity analyses were also undertaken, excluding periprocedural MIs resulting from the index procedure or planned staged interventions. The secondary outcomes were each component of the composite endpoint, cardiovascular versus non-cardiovascular death, periprocedural and spontaneous MI, target-vessel and overall revascularization, and stent thrombosis at 3 years. In addition, variables such as the number of implanted stents and alterations in the revascularization approach prompted by QFR findings were assessed. All endpoints adhered to standardized definitions published previously, and an independent Clinical Events Committee, whose members had no involvement in the trial, adjudicated all suspected events. Periprocedural myocardial infarction was defined according to the FAVOR III China trial protocol. In stable patients with normal baseline CK-MB, periprocedural myocardial infarction was diagnosed when post-PCI CK-MB increased to > 3 times the upper limit of normal. Consistent with clinical practice in China and the study protocol, CK-MB and non-high-sensitivity troponins were used to assess possible myocardial infarction at all participating centers.

In this prespecified subgroup analysis of FAVOR III China, lesions were categorized as short (< 20 mm) or long ( $\geq$  20 mm) based on quantitative measurements

from an independent core laboratory. The 20 mm threshold was prespecified, guided by the ACC/AHA lesion classification, which defines diffuse or complex lesions as  $\geq$  20 mm in length.<sup>[12]</sup> For vessels with multiple lesions, each lesion was assessed individually, and the longest lesion per vessel was used for patient- or vessel-level classification, ensuring a consistent and clinically meaningful stratification.

### Statistical Analysis

Continuous data are summarized as mean  $\pm$  SD or median with interquartile range, depending on distribution. Between-group comparisons were performed using Student's *t*-tests for normally distributed data and the Mann-Whitney *U* tests for skewed data, with normality verified by the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages and were analyzed via chi-square tests or Fisher's exact test when expected counts were low. Analyses comparing outcomes by lesion length were stratified according to treatment strategy. The distributions of QFR values and angiographic lesion severity were illustrated with box-and-whisker plots.

Time-to-event analyses were conducted using Kaplan-Meier curves and log-rank tests. Hazard ratios (HRs) with 95% confidence intervals (CIs) were determined through Cox proportional hazards regression. Interaction effects between treatment assignment (QFR-guided vs. angiography-guided) and lesion length were evaluated using multiplicative terms within Cox models. All tests were two-tailed, with  $P < 0.05$  being deemed significant for both main and interaction analyses. All computations were undertaken using SAS v9.4.

## RESULTS

### Baseline Characteristics

3,802 participants included in the present analysis, 1,925 (50.6%) were classified into the short-lesion group, and 1,877 (49.4%) into the long-lesion group (Supplemental Table 1). Patients with long lesions more frequently had a history of coronary artery bypass grafting, whereas hypercholesterolemia was more prevalent among those with short lesions. In terms of presentation, unstable angina was observed more often in the short-lesion group, while silent ischemia was more frequent in the long-lesion group. In addition, patients with longer



lesions exhibited a lower left ventricular ejection fraction at baseline. Within each lesion-length subgroup, clinical characteristics were comparable between the QFR-guided and angiography-guided cohorts (Table 1).

### Procedural Characteristics and Medication Use

Overall procedural and angiographic findings differed between lesion-length categories, though the frequency of radial access, the number of vessels originally inter-

**Table 1** Baseline characteristics.

|                                                                                            | Short lesion group      |                                    |         | Long lesion group       |                                    |         |
|--------------------------------------------------------------------------------------------|-------------------------|------------------------------------|---------|-------------------------|------------------------------------|---------|
|                                                                                            | QFR Guided<br>(n = 974) | Angiography<br>Guided<br>(n = 951) | P-value | QFR Guided<br>(n = 931) | Angiography<br>Guided<br>(n = 946) | P-value |
| Age, yrs                                                                                   | 62.33 ± 9.76            | 62.76 ± 10.20                      | 0.343   | 63.20 ± 10.40           | 62.60 ± 10.14                      | 0.209   |
| Female                                                                                     | 282 (29.0%)             | 290 (30.5%)                        | 0.460   | 279 (30.0%)             | 268 (28.3%)                        | 0.435   |
| Body mass index, kg/m <sup>2</sup>                                                         | 25.24 ± 3.07            | 25.11 ± 3.45                       | 0.2376  | 25.08 ± 3.20            | 24.89 ± 3.05                       | 0.220   |
| Diabetes                                                                                   | 336 (34.5%)             | 319 (33.5%)                        | 0.659   | 310 (33.3%)             | 325 (34.4%)                        | 0.628   |
| Hypertension                                                                               | 640 (65.7%)             | 618 (65.0%)                        | 0.739   | 625 (67.1%)             | 627 (66.3%)                        | 0.695   |
| Hypercholesterolemia                                                                       | 399 (41.0%)             | 375 (39.4%)                        | 0.493   | 327 (35.1%)             | 347 (36.7%)                        | 0.482   |
| Cigarette smoking                                                                          |                         |                                    | 0.857   |                         |                                    | 0.835   |
| Current                                                                                    | 295 (30.3%)             | 280 (29.4%)                        |         | 277 (29.8%)             | 283 (29.9%)                        |         |
| Former                                                                                     | 130 (13.3%)             | 134 (14.1%)                        |         | 152 (16.3%)             | 145 (15.3%)                        |         |
| Never                                                                                      | 549 (56.4%)             | 537 (56.5%)                        |         | 502 (53.9%)             | 518 (54.8%)                        |         |
| Previous myocardial infarction                                                             | 89 (9.1%)               | 90 (9.5%)                          | 0.805   | 86 (9.1%)               | 88 (9.5%)                          | 0.787   |
| Previous percutaneous coronary intervention                                                | 230 (23.6%)             | 230 (24.2%)                        | 0.769   | 252 (27.1%)             | 232 (24.5%)                        | 0.208   |
| Previous coronary artery bypass grafting                                                   | 0 (0.0%)                | 0 (0.0%)                           | NA      | 5 (0.5%)                | 4 (0.4%)                           | 0.752   |
| Clinical presentation <sup>a</sup>                                                         |                         |                                    | 0.880   |                         |                                    | 0.946   |
| Asymptomatic ischemia                                                                      | 102 (10.5%)             | 96 (10.1%)                         |         | 105 (11.3%)             | 104 (11.0%)                        |         |
| Stable angina                                                                              | 256 (26.3%)             | 250 (26.3%)                        |         | 235 (25.2%)             | 241 (25.5%)                        |         |
| Unstable angina                                                                            | 578 (59.3%)             | 561 (59.0%)                        |         | 527 (56.6%)             | 542 (57.3%)                        |         |
| Post myocardial infarction (within 30 days)                                                | 38 (3.9%)               | 44 (4.6%)                          |         | 64 (6.9%)               | 59 (6.2%)                          |         |
| Estimated glomerular filtration rate (Cockcroft-Gault formula), mL/min/1.73 m <sup>2</sup> | 71.64 ± 20.77           | 69.84 ± 29.33                      | 0.099   | 72.77 ± 71.82           | 71.95 ± 40.37                      | 0.135   |
| Left ventricular ejection fraction, %                                                      | 63.71 ± 6.40            | 63.13 ± 6.54                       | 0.188   | 62.86 ± 6.84            | 62.81 ± 7.20                       | 0.945   |
| Number of diseased vessels reported                                                        |                         |                                    | 0.532   |                         |                                    | 0.911   |
| 1-vessel disease                                                                           | 549 (56.4%)             | 505 (53.1%)                        |         | 341 (36.6%)             | 356 (37.6%)                        |         |
| 2-vessel disease                                                                           | 295 (30.3%)             | 309 (32.5%)                        |         | 373 (40.1%)             | 369 (39.0%)                        |         |
| 3-vessel disease                                                                           | 113 (11.6%)             | 117 (12.3%)                        |         | 191 (20.5%)             | 198 (20.9%)                        |         |
| Left main disease                                                                          | 17 (1.7%)               | 20 (2.1%)                          |         | 26 (2.8%)               | 23 (2.4%)                          |         |
| Any vessel with ≥1 lesion with diameter stenosis >90% and TIMI flow grade < 3              | 67 (6.9%)               | 72 (7.6%)                          | 0.558   | 99 (10.6%)              | 102 (10.8%)                        | 0.917   |
| Anatomic SYNTAX score <sup>b</sup>                                                         | 7.30 ± 4.83             | 7.59 ± 5.35                        | 0.682   | 11.47 ± 6.15            | 11.63 ± 6.51                       | 0.586   |
| Functional SYNTAX score <sup>c</sup>                                                       | 6.00 ± 5.17             | 6.01 ± 5.65                        | 0.410   | 10.31 ± 6.40            | 10.32 ± 6.80                       | 0.255   |

Data are presented as mean ± SD or n (%). <sup>a</sup>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. <sup>b</sup>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. <sup>c</sup>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.



ded for treatment, and the number of patients who underwent PCI on vessels not initially planned were comparable (Supplemental Table 2).

Adopting a QFR-guided approach led to a substantial

decrease in PCI utilization, with 14.8% fewer interventions in the short-lesion subgroup and 2.4% fewer in the long-lesion subgroup relative to angiographic guidance (Table 2). Consequently, the short-lesion group also

**Table 2** Procedural characteristics of the treatment groups classified by the lesion type.

|                                                                       | Short lesion group      |                                    |          | Long lesion group       |                                    |         |
|-----------------------------------------------------------------------|-------------------------|------------------------------------|----------|-------------------------|------------------------------------|---------|
|                                                                       | QFR Guided<br>(n = 974) | Angiography<br>Guided<br>(n = 951) | P-value  | QFR Guided<br>(n = 931) | Angiography<br>Guided<br>(n = 946) | P-value |
| Radial artery approach                                                | 962 (98.8%)             | 934 (98.2%)                        | 0.316    | 916 (98.4%)             | 920 (97.3%)                        | 0.090   |
| PCI performed                                                         | 819 (84.1%)             | 941 (98.9%)                        | < 0.001  | 904 (97.1%)             | 941 (99.5%)                        | < 0.001 |
| Drug-eluting stents placed                                            | 779 (80.0%)             | 879 (92.4%)                        |          | 881 (94.6%)             | 920 (97.3%)                        |         |
| Drug-coated balloon angioplasty                                       | 38 (3.9%)               | 46 (4.8%)                          |          | 16 (1.7%)               | 12 (1.3%)                          |         |
| Non-drug-coated balloon angioplasty                                   | 2 (0.2%)                | 16 (1.7%)                          |          | 7 (0.8%)                | 9 (1.0%)                           |         |
| No. of stents placed per patient                                      | 1.22 ± 0.63             | 1.21 ± 0.69                        | < 0.001  | 1.85 ± 1.00             | 1.86 ± 0.99                        | 0.015   |
| Stent length, mm                                                      | 24.89 ± 21.23           | 27.45 ± 19.47                      | 0.006    | 49.98 ± 28.97           | 52.08 ± 28.41                      | 0.114   |
| Stent diameter, mm                                                    | 2.45 ± 1.29             | 2.81 ± 0.92                        | < 0.001  | 2.84 ± 0.76             | 2.91 ± 0.61                        | 0.026   |
| Use of intravascular imaging <sup>a</sup>                             | 40 (4.1%)               | 55 (5.8%)                          | 0.089    | 79 (8.5%)               | 66 (7.0%)                          | 0.221   |
| Contrast medium used per patient, mL                                  | 167.03 ± 70.09          | 166.36 ± 71.73                     | < 0.001  | 170.74 ± 73.53          | 171.40 ± 72.40                     | 0.216   |
| Fluoroscopy time, minutes                                             | 13.65 ± 6.89            | 13.92 ± 6.78                       | < 0.001  | 16.60 ± 7.61            | 16.16 ± 7.63                       | 0.418   |
| Procedure time, minutes <sup>b</sup>                                  | 34.60 ± 23.78           | 35.09 ± 23.24                      | 0.365    | 40.01 ± 24.38           | 40.64 ± 25.50                      | 0.858   |
| Adjusted procedure time, minutes <sup>b</sup>                         | 44.60 ± 23.78           | 45.09 ± 23.24                      | < 0.001  | 50.01 ± 24.38           | 50.64 ± 25.50                      | 0.287   |
| PCI lesion success <sup>c</sup>                                       | 975/983 (99.2%)         | 1163/1176 (98.9%)                  | 0.489    | 1256/1270 (98.9%)       | 1383/1389 (99.6%)                  | 0.043   |
| PCI procedure success <sup>d</sup>                                    | 798/819 (97.4%)         | 909/941 (96.6%)                    | 0.303    | 851/904 (94.1%)         | 874/941 (92.9%)                    | 0.273   |
| Vessels intended to be treated before randomization                   |                         |                                    | 0.298    |                         |                                    | 0.542   |
| Left main                                                             | 15/1171 (1.3%)          | 19/1185 (1.6%)                     |          | 18/1320 (1.4%)          | 21/1357 (1.5%)                     |         |
| Left anterior descending                                              | 621/1171 (53.0%)        | 583/1185 (49.2%)                   |          | 691/1320 (52.3%)        | 689/1357 (50.8%)                   |         |
| Left circumflex                                                       | 255/1171 (21.8%)        | 281/1185 (23.7%)                   |          | 264/1320 (20.0%)        | 301/1357 (22.2%)                   |         |
| Right coronary artery                                                 | 280/1171 (23.8%)        | 302/1185 (25.3%)                   |          | 347/1320 (26.3%)        | 346/1357 (25.5%)                   |         |
| Vessels treated of those originally intended                          |                         |                                    | 0.014    |                         |                                    | 0.135   |
| Left main                                                             | 13/928 (1.4%)           | 19/1136 (1.7%)                     |          | 16/1173 (1.4%)          | 19/1299 (1.5%)                     |         |
| Left anterior descending                                              | 524/928 (56.5%)         | 562/1136 (49.5%)                   |          | 646/1173 (55.1%)        | 669/1299 (51.5%)                   |         |
| Left circumflex                                                       | 197/928 (21.2%)         | 266/1136 (23.4%)                   |          | 218/1173 (18.6%)        | 289/1299 (22.2%)                   |         |
| Right coronary artery                                                 | 194/928 (20.9%)         | 289/1136 (25.4%)                   |          | 293/1173 (25.0%)        | 322/1299 (24.8%)                   |         |
| Patients with intended vessel deferral or unintended vessel treatment | 268/974 (27.5%)         | 51/951 (5.4%)                      | < 0.0001 | 174/931 (18.7%)         | 66/946 (7.0%)                      | < 0.001 |
| Deferral (nontreatment) of ≥1 vessel originally intended for PCI      | 235/974 (24.1%)         | 45/951 (4.7%)                      | < 0.0001 | 139/931 (14.9%)         | 53/946 (5.6%)                      | < 0.001 |
| Treatment of ≥1 vessel not originally intended for PCI                | 45/974 (4.6%)           | 14/951 (1.5%)                      | 0.0001   | 38/931 (4.1%)           | 14/946 (1.5%)                      | 0.001   |
| Residual anatomic SYNTAX score                                        | 1.63 ± 3.03             | 1.73 ± 3.35                        | 0.006    | 2.64 ± 3.56             | 2.57 ± 4.05                        | 0.085   |
| Residual functional SYNTAX score                                      | 0.52 ± 2.08             | 0.82 ± 2.51                        | < 0.0001 | 0.80 ± 2.27             | 1.03 ± 2.86                        | 0.049   |
| Residual functional SYNTAX score of 0                                 | 893/974 (91.7%)         | 787/951 (82.8%)                    | < 0.0001 | 775/931 (83.2%)         | 757/946 (80.0%)                    | 0.072   |

<sup>a</sup>Intravascular ultrasound examination or optical coherence tomography. <sup>b</sup>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. <sup>c</sup>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. <sup>d</sup>Defined as lesion success in all treated lesions without in-hospital major adverse cardiac events (up to a maximum of 7 days).

demonstrated reduced use of drug-eluting stents as well as fewer drug-coated and plain balloon procedures, with a highly significant connection between lesion length and treatment approach ( $P_{\text{interaction}} < 0.0001$ ). In addition to reducing the proportion of patients undergoing PCI, QFR-guided strategy was associated with fewer stents implanted per patient in both lesion-length categories. QFR-based decisions also resulted in smaller mean stent diameters for both short lesions and long lesions (short lesions:  $2.45 \pm 1.29$  mm vs.  $2.81 \pm 0.92$  mm,  $P < 0.001$ ; long lesions:  $2.84 \pm 0.76$  mm vs.  $2.91 \pm 0.61$  mm,  $P = 0.0258$ ).

QFR assessment prompted modifications to the pre-randomization PCI plan more frequently than angiographic evaluation alone, affecting 27.5% of short-lesion cases and 18.7% of long-lesion cases compared with 5.4% and 7.0% in the angiography-guided arms, respectively ( $P_{\text{interaction}} = 0.001$ ). Specifically, deferral of at least one initially intended PCI vessel was markedly more frequent under QFR guidance than under angiography guidance in both lesion-length categories (short lesions: 24.1% vs. 4.7%,  $P < 0.0001$ ; long lesions: 14.9% vs. 5.6%,  $P < 0.0001$ ). Conversely, initiation of PCI in vessels not previously targeted occurred more often in the QFR-guided group for both lesion-length categories (short lesions: 4.6% vs. 1.5%; long lesions: 4.1% vs. 1.5%), though this was not significantly influenced by lesion length. Consistent with the lower rate of PCI procedures, patients randomized to QFR guidance were discharged on dual antiplatelet therapy (aspirin plus a P2Y<sub>12</sub> inhibitor) less often and continued to receive such therapy less frequently at 6 months, 1 year, 2 years, and 3 years of follow-up. Use of other cardiovascular medications did not differ between groups during the study period (Supplemental Table 3).

## Outcomes

At 3 years, patients with longer lesions exhibited significantly greater cumulative risk of MACE compared with those with shorter lesions (15.5% vs. 9.8%,  $P < 0.0001$ ) (Supplemental Table 4). Rates of MI were more than double in the long-lesion cohort (8.34% vs. 3.87%,  $P < 0.0001$ ), whereas IDR occurred somewhat more frequently albeit without significance (7.34% vs. 5.72%,  $P = 0.490$ ). These differences persisted after adjustment for baseline clinical characteristics (Supplemental Figure 2).

Table 3 and Figures 1A–B present the treatment-strategy comparisons. Across both lesion-length categories, QFR guidance conferred lower rates of MACE:

7.10% vs. 12.57% in short lesions (HR = 0.55, 95% CI: 0.41–0.74) and 13.89% vs. 17.04% in long lesions (HR = 0.79, 95% CI: 0.63–1.00). There was no marked interaction with lesion length ( $P_{\text{interaction}} = 0.0584$ ). For individual components of MACE, the treatment effects of QFR guidance were generally directionally consistent across lesion-length categories; however, a significant interaction was observed for all-cause death ( $P_{\text{interaction}} = 0.0358$ ). When periprocedural MIs were excluded, the benefit of QFR remained evident in the short-lesion group (5.76% vs. 10.79%, HR = 0.52, 95% CI: 0.38–0.72), but did not reach significance in the long-lesion group (9.92% vs. 11.55%, HR = 0.85, 95% CI: 0.64–1.12), with a marked interaction by lesion length ( $P < 0.05$ ) (Figures 2A–D). For non-target lesion revascularization, event rates were low, and no significant difference was observed between QFR-guided and angiography-guided strategies in either short lesions or long lesions (short lesions: 1.04% vs. 0.74%, HR = 1.38, 95% CI: 0.53–3.64; long lesions: 1.53% vs. 1.07%, HR = 1.43, 95% CI: 0.64–3.22). Therefore, this endpoint should not be interpreted as showing a lesion length-dependent benefit of QFR guidance.

## DISCUSSION

FAVOR III China is the first randomized controlled trial incorporating direct comparisons of outcomes between PCI procedures guided by angiography-derived functional assessment and those guided solely by standard angiographic imaging. This pre-specified subgroup analysis provides new insights into the role of QFR-based guidance in PCI, highlighting three key findings: (1) patients with both short and long lesions underwent fewer PCI procedures when guided by QFR rather than angiography alone; (2) the reduction in 3-year MACE incidence, both including and excluding periprocedural MI, varied by lesion length; and (3) QFR values were broadly comparable between short and long lesions across different angiographic severities. However, the lesion length-dependent treatment effect of QFR guidance was more evident after excluding periprocedural MI, suggesting that procedural events may have partly obscured differences in ischemia-driven outcomes between short and long lesions. Simulated residual QFR derived from three-dimensional angiography and augmented reality technology has demonstrated strong agreement with post-PCI QFR, offering predictive value for functional recovery and 2-year prognosis after PCI.<sup>[13]</sup>



Table 3 Clinical outcomes at 3 years between QFR- and angiography-guided strategies classified by the lesion type.

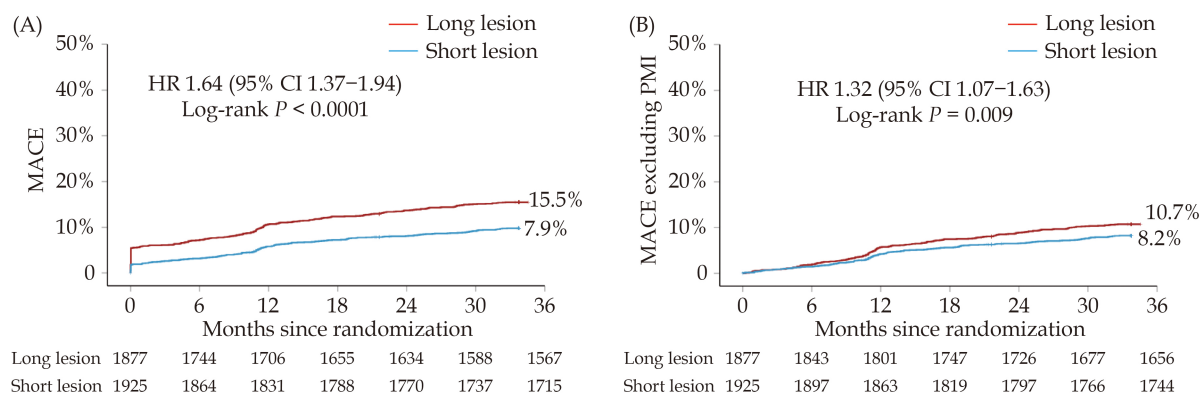
|                                                     | Short lesion group   |                              |                   |                  | Long lesion group    |                              |                   |                  | P-Interaction |
|-----------------------------------------------------|----------------------|------------------------------|-------------------|------------------|----------------------|------------------------------|-------------------|------------------|---------------|
|                                                     | QFR guided (n = 974) | Angiography Guided (n = 951) | HR (95% CI)       | Log-Rank P-value | QFR Guided (n = 931) | Angiography Guided (n = 946) | HR (95% CI)       | Log-Rank P-value |               |
| MACE                                                | 69 (7.10%)           | 119 (12.57%)                 | 0.55 (0.41, 0.74) | 0.001            | 129 (13.89%)         | 161 (17.04%)                 | 0.79 (0.63, 1.00) | 0.050            | 0.058         |
| All-cause death                                     | 8 (0.82%)            | 18 (1.91%)                   | 0.43 (0.19, 0.99) | 0.043            | 21 (2.26%)           | 16 (1.70%)                   | 1.34 (0.70, 2.56) | 0.379            | 0.036         |
| Myocardial infarction                               | 24 (2.47%)           | 50 (5.30%)                   | 0.46 (0.28, 0.75) | 0.002            | 61 (6.58%)           | 95 (10.07%)                  | 0.64 (0.47, 0.89) | 0.006            | 0.274         |
| Ischemia-driven revascularization                   | 42 (4.35%)           | 67 (7.13%)                   | 0.60 (0.41, 0.88) | 0.009            | 64 (6.98%)           | 72 (7.69%)                   | 0.90 (0.64, 1.26) | 0.530            | 0.116         |
| MACE excluding periprocedural myocardial infarction | 56 (5.76%)           | 102 (10.79%)                 | 0.52 (0.38, 0.72) | 0.001            | 92 (9.92%)           | 109 (11.55%)                 | 0.85 (0.64, 1.12) | 0.234            | 0.026         |
| Other secondary endpoints                           |                      |                              |                   |                  |                      |                              |                   |                  |               |
| Cardiovascular death                                | 4 (0.41%)            | 10 (1.06%)                   | 0.39 (0.12, 1.24) | 0.110            | 9 (0.97%)            | 8 (0.85%)                    | 1.15 (0.44, 2.97) | 0.779            | 0.158         |
| Non-cardiovascular death                            | 4 (0.41%)            | 8 (0.86%)                    | 0.48 (0.15, 1.61) | 0.237            | 12 (1.30%)           | 8 (0.86%)                    | 1.53 (0.63, 3.74) | 0.352            | 0.132         |
| Periprocedural myocardial infarction                | 15 (1.5%)            | 19 (2.0%)                    | 0.77 (0.39, 1.52) | 0.450            | 41 (4.4%)            | 62 (6.6%)                    | 0.67 (0.45, 0.99) | 0.040            | 0.701         |
| Nonprocedural myocardial infarction                 | 9 (0.93%)            | 31 (3.30%)                   | 0.28 (0.13, 0.58) | 0.001            | 21 (2.29%)           | 36 (3.83%)                   | 0.59 (0.34, 1.01) | 0.0540           | 0.110         |
| Any revascularization                               |                      |                              |                   |                  |                      |                              |                   |                  |               |
| Target vessel revascularization <sup>a</sup>        | 25 (2.59%)           | 41 (4.37%)                   | 0.59 (0.36, 0.96) | 0.036            | 41 (4.48%)           | 42 (4.48%)                   | 0.99 (0.65, 1.53) | 0.962            | 0.115         |
| Ischemia driven                                     | 17 (1.76%)           | 33 (3.52%)                   | 0.50 (0.28, 0.89) | 0.019            | 34 (3.72%)           | 38 (4.06%)                   | 0.91 (0.57, 1.45) | 0.693            | 0.110         |
| Target lesion revascularization                     | 16 (1.65%)           | 36 (3.84%)                   | 0.43 (0.24, 0.77) | 0.004            | 28 (3.06%)           | 33 (3.52%)                   | 0.86 (0.52, 1.43) | 0.553            | 0.076         |
| Ischemia driven                                     | 14 (1.45%)           | 29 (3.09%)                   | 0.47 (0.25, 0.88) | 0.019            | 26 (2.84%)           | 31 (3.31%)                   | 0.85 (0.51, 1.44) | 0.553            | 0.149         |
| Nontarget lesion revascularization                  | 10 (1.04%)           | 7 (0.74%)                    | 1.38 (0.53, 3.64) | 0.500            | 14 (1.53%)           | 10 (1.07%)                   | 1.43 (0.64, 3.22) | 0.390            | 0.003         |
| Ischemia driven                                     | 4 (0.41%)            | 5 (0.53%)                    | 0.78 (0.21, 2.89) | 0.706            | 8 (0.88%)            | 8 (0.86%)                    | 1.02 (0.38, 2.72) | 0.969            | 0.532         |
| Nontarget vessel revascularization <sup>b</sup>     | 34 (3.52%)           | 47 (5.00%)                   | 0.70 (0.45, 1.08) | 0.110            | 47 (5.11%)           | 44 (4.70%)                   | 1.09 (0.72, 1.65) | 0.692            | 0.143         |
| Ischemia driven                                     | 25 (2.59%)           | 37 (3.93%)                   | 0.65 (0.39, 1.08) | 0.096            | 33 (3.59%)           | 35 (3.74%)                   | 0.96 (0.60, 1.54) | 0.862            | 0.272         |
| Stent thrombosis, definite or probable              | 1 (0.10%)            | 6 (0.64%)                    | 0.16 (0.02, 1.35) | 0.092            | 6 (0.65%)            | 8 (0.85%)                    | 0.76 (0.26, 2.20) | 0.617            | 0.120         |
| Definite                                            | 0 (0.00%)            | 2 (0.21%)                    | NA                | 0.152            | 2 (0.22%)            | 3 (0.32%)                    | 0.68 (0.11, 4.06) | 0.667            | 0.957         |
| Probable                                            | 1 (0.10%)            | 4 (0.43%)                    | 0.24 (0.03, 2.17) | 0.171            | 4 (0.43%)            | 5 (0.53%)                    | 0.81 (0.22, 3.03) | 0.758            | 0.353         |

Data are presented as n (%) unless other indicated. <sup>a</sup>Revascularization of vessels that were treated with PCI after randomization. <sup>b</sup>Revascularization of vessels in which PCI was not previously performed. MACE: major adverse cardiac events; NA: not available; QFR: quantitative flow ratio; PCI: percutaneous coronary intervention.

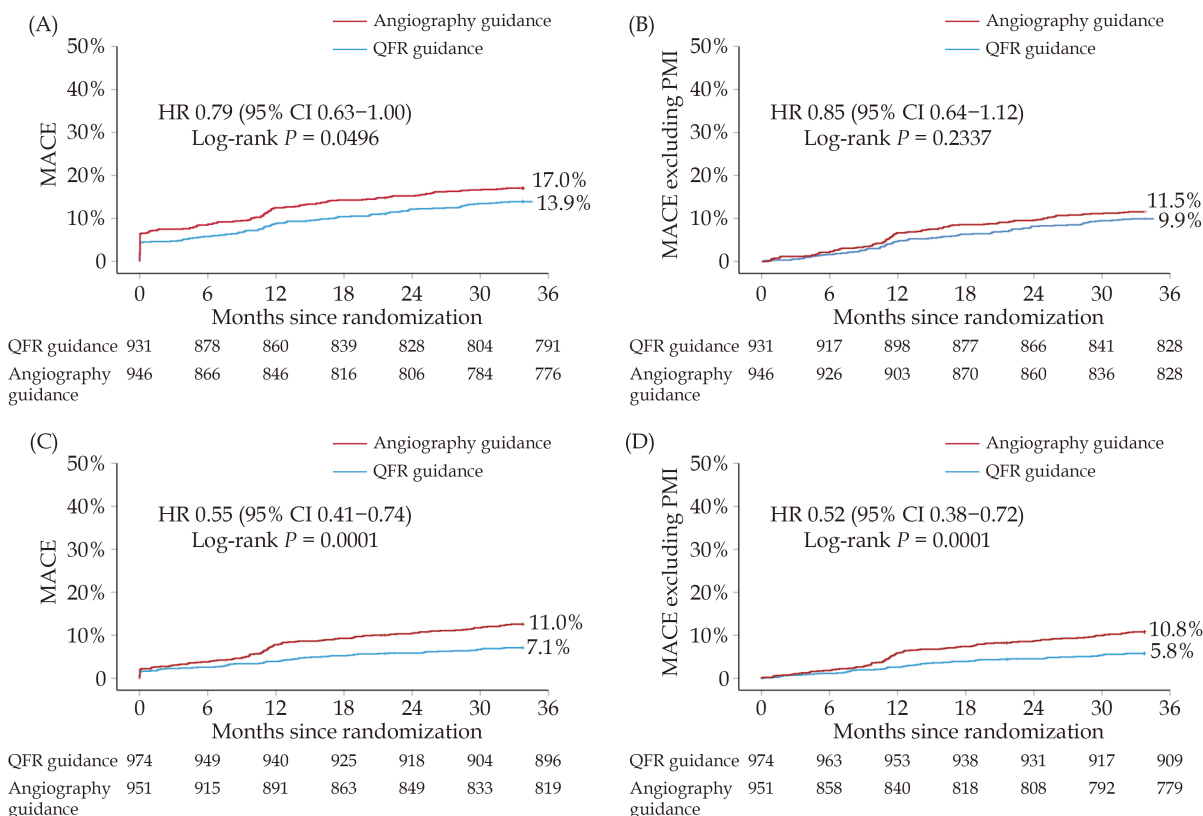
Beyond stable coronary artery disease, QFR has proven informative in patients with atrial fibrillation, where remodeling-related reductions in flow velocity and altered

vessel geometry contribute to relatively higher QFR values despite angiographic stenosis.<sup>[14]</sup> Similarly, in valvular disease, coronary QFR has shown prognostic value:





**Figure 1** Kaplan-Meier Curves for 3-year MACE and MACE Excluding Periprocedural MI. Kaplan-Meier cumulative event curves for (A) 3-year MACE in short lesion and long lesion group, (B) 3-year MACE excluding periprocedural MI in short lesion and long lesion group. MACE: major adverse cardiac event(s); MI: myocardial infarction; QFR: quantitative flow ratio.



**Figure 2** Subgroup analyses for 3-year MACE and MACE Excluding Periprocedural MI. Subgroup analyses for (A) 3-year MACE in long lesion group, (B) 3-year MACE excluding periprocedural MI in long lesion group, (C) 3-year MACE in short lesion group, and (D) 3-year MACE excluding periprocedural MI in short lesion group. Abbreviations as in Figure 1.

in severe aortic stenosis, QFR can predict death after transcatheter aortic valve replacement (TAVR),<sup>[15]</sup> demonstrates good diagnostic performance against FFR and invasive pressure indices,<sup>[16]</sup> and can serve as a safe and convenient pre-TAVR assessment tool.<sup>[17]</sup> In surgical populations, preoperative QFR influences intraoperative flow dynamics of graft conduits such as the left internal

thoracic artery (LITA),<sup>[18]</sup> predicts the long-term patency of grafts after coronary artery bypass grafting (CABG),<sup>[19]</sup> and provides discriminative value for bypass function in the PRIDE-METAL trial, where a threshold of 0.76 yielded strong predictive accuracy.<sup>[20]</sup> Moreover, combined valve replacement and CABG procedures guided by QFR have been associated with optimized surgical plan-



ning and reduced one-year MACCE compared with angiography-only strategies.<sup>[21]</sup> The discrepancy between the primary endpoint including periprocedural MI and the sensitivity endpoint excluding periprocedural MI deserves further consideration. Periprocedural MI is influenced not only by lesion-specific ischemic significance but also by procedural complexity, plaque burden, side-branch compromise, distal embolization, lesion preparation, and the extent of stent implantation. These factors are more common in long and diffuse lesions and may partly dilute or obscure the lesion length-dependent effect of QFR-guided lesion selection when periprocedural MI is included in the composite endpoint. After excluding periprocedural MI, the endpoint may better reflect spontaneous ischemic events and the longer-term clinical consequences of avoiding functionally unnecessary PCI. Therefore, the more apparent benefit of QFR guidance in short lesions may be related to the greater likelihood that short lesions represent focal, physiologically targetable disease. However, because this finding emerged from a subgroup/sensitivity analysis, it should be interpreted as hypothesis-generating rather than definitive evidence of a true biological difference.

The present results are aligned with prior studies examining the influence of lesion length and stent strategy on outcomes. The SPOT trial, for instance, suggested that spot stenting for lesions  $\geq 25$  mm was not inferior to complete lesion coverage in terms of target vessel failure.<sup>[22]</sup> However, angiographic assessment alone cannot always reliably distinguish physiologically significant segments, particularly in borderline lesions. QFR offers a rapid, non-invasive alternative that correlates closely with FFR and provides an objective functional perspective for revascularization decisions. While longer stents are sometimes essential to ensure full coverage, contemporary trials such as EVOLVE 48 and BioMime Morph have demonstrated that extended stents can be used safely when necessary.<sup>[23,24]</sup> Nevertheless, longer implants inherently carry higher risks of restenosis, thrombosis, and technical complexity attributable to extensive metal implantation. The present findings suggest that QFR may help to avoid unnecessary stenting in angiographically suspicious, but functionally insignificant, segments.

The apparent interaction between lesion length and clinical outcomes reflects a lesion-length-dependent effect of QFR-guided PCI. In short lesions, QFR guidance may prevent overtreatment, reducing stent numbers,

vascular trauma, and complication risk, thus translating into superior outcomes. In contrast, in long lesions where diffuse disease produces complex hemodynamics, QFR still offers benefit but may be less able to offset the procedural requirements for extended stenting. Taken together, these data argue for a tailored approach to PCI in which anatomical and physiological information are integrated to optimize therapy. QFR-guided decision-making appears especially advantageous in shorter lesions, enabling more selective and appropriate stent use. Further research is warranted to refine QFR thresholds and lesion-specific criteria to optimize PCI outcomes across varying lesion lengths.

Of note, a significant interaction between treatment strategy and lesion length was observed for all-cause death. This finding should be interpreted cautiously because all-cause death was not the primary endpoint, the number of death events was relatively limited, and all-cause mortality may be influenced by non-cardiovascular factors that are not directly related to lesion physiology or the revascularization strategy. Therefore, this finding should be considered hypothesis-generating rather than definitive.

### Study limitations

Several limitations to this study should be considered. First, as a prespecified subgroup analysis, the sample size within each lesion-length category was relatively modest, and findings should therefore be interpreted cautiously. In addition, although the QFR-guided and angiography-guided groups were well balanced in size within the long-lesion subgroup, the number of events for several individual endpoints was relatively small. Consequently, some hazard ratio estimates had wide confidence intervals, reflecting limited statistical precision. These findings, especially those based on individual components of MACE or subgroup-specific analyses, should therefore be interpreted cautiously and considered hypothesis-generating. Second, QFR measurements were derived from two angiographic projections per vessel, which may have limited image quality; newer systems requiring only a single projection could enhance accuracy and procedural efficiency. Third, the eligibility criteria of FAVOR III China restricted enrollment to patients at low-to-intermediate clinical risk, limiting generalizability to higher-risk populations such as acute MI, biomarker-positive unstable angina, or individuals with complex coronary anatomy. Finally, as the trial co-



hort was predominantly Chinese, external validation is required to assess the applicability of these findings across different ethnic populations. In addition, lesion phenotype based on the pullback pressure gradient was not systematically assessed in the present analysis. Although lesion length was measured by an independent angiographic core laboratory, anatomical lesion length does not fully capture the physiological distribution of coronary artery disease. Short lesions are more likely to represent focal disease, whereas long lesions may more frequently reflect diffuse or mixed disease patterns. Therefore, the absence of pullback pressure gradient (PPG)-based lesion phenotyping limited our ability to determine whether the lesion length-dependent treatment effect of QFR-guided PCI was partly mediated by the underlying physiological disease pattern. Future studies incorporating standardized QFR-derived PPG analysis are warranted to clarify the incremental value of physiological lesion phenotype beyond anatomical lesion length alone.

## Conclusions

A QFR-guided PCI strategy resulted in improved 3-year MACE outcomes, with a more pronounced benefit observed in short coronary lesions.

## DISCLOSURE

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