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# Performance of angiographic quantitative flow ratio in guiding coronary interventions across different age groups: prespecified subgroup analysis of the FAVOR III China trial

Xin-Ye XU[1], Li-Yun HE[1], Chang-Dong GUAN[2], Ming CUI[1], Yu-Peng WANG[1], Yu-Jie ZHOU[3], Jian-An WANG[4], Jun BU[5], Liang-Long CHEN[6], Xin-Kai QU[7], Jun-Qing YANG[8], Yan-Yan ZHAO[9], Xue-Bo LIU[10], Cheng-Xing SHEN[11], Sheng-Xian TU[12], Gregg STONE[13], Li-Jun GUO[1,✉], Lei SONG[2,✉]

1. Department of Cardiology, Peking University Third Hospital, NHC Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Beijing, China; 2. Department of Cardiology, Fuwai Hospital, National Centre for Cardiovascular Diseases, National Clinical Research Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; 3. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; 4. Department of Cardiology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 5. Department of Cardiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; 6. Department of Cardiology, Fujian Medical University Union Hospital, Fuzhou, China; 7. Department of Cardiology, Huadong Hospital Affiliated to Fudan University, Shanghai, China; 8. Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; 9. Medical Research and Biometrics Centre, National Centre for Cardiovascular Diseases, Beijing, China; 10. Department of Cardiology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China; 11. Department of Cardiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China; 12. Biomedical Instrument Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China; 13. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, United States

✉ Correspondence to: guo_li_jun@126.com (GUO LJ); drsong@vip.163.com (SONG L)
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**ABSTRACT**

**Background** Quantitative flow ratio (QFR) based lesion selection for percutaneous coronary intervention (PCI) treatment has shown clinical benefits in terms of reduced risk for myocardial infarction and repeat revascularization. Whether this benefit is consistent across different age groups still needs further investigation.

**Methods** In this prespecified subgroup study of FAVOR III China trial, we compared long-term clinical outcomes between QFR-guided and angiography-guided PCI among different age groups among 3825 enrolled subjects. The primary endpoint was major adverse cardiac events (MACEs), a composite of all-cause death, myocardial infarction, and ischemia-driven revascularization.

**Results** Of the 3825 patients, 1717 (44.9%) were aged ≥ 65 years. At baseline, patients ≥ 65 had higher rates of hypertension, hyperlipidaemia, stroke history ($P$ < 0.0001), and peripheral vascular disease ($P$ = 0.024) and had higher SYNTAX scores ($P$ = 0.0095). Compared with standard angiography guidance, the QFR-guided strategy consistently reduced the 1-year (≥ 65 years, 6.04% *vs.* 9.19%, HR = 0.65, 95% CI: 0.46–0.92; < 65 years, 5.53% *vs.* 8.43%, HR = 0.65, 95% CI: 0.47–0.91) and 3-year MACE rates in both age groups (≥ 65 years, 11.8% *vs.* 15.2%, HR: 0.75, 95% CI: 0.58–0.98; < 65 years, 9.5% *vs.* 14.6%, HR = 0.63; 95% CI: 0.49–0.81), without a significant interaction ($P_{interaction}$ = 0.99). Within the QFR-guided group, the 3-year MACE rate in patients with deferred vessels was numerically greater in patients aged ≥ 65 years than in those aged < 65 years (8.3% *vs.* 3.0%, $P$ = 0.10).

**Conclusions** Although with higher rate of comorbidities and more complex coronary anatomy, the long-term benefit of the QFR-guided PCI strategy remained consistent in patients ≥ 65 years, compared with those < 65 years.

Age is an unmodifiable risk factor for coronary artery disease (CAD). As individuals age, the prevalence of CAD risk factors such as diabetes, hypertension, and hyperlipidaemia increases. These risk factors persist for longer periods, leading to greater target organ damage.[1] Elderly patients often present with more complex coronary anatomy features, including multivessel diseases, diffuse or calcified lesion. Additionally, the risk of procedural complications is also higher among the elderly.[2-4] In addition to maladaptive age-related vascular changes, changes in coagulation can also increase the risk in elderly patients received percutaneous coronary intervention (PCI).[5,6] Consequently, elderly patients undergoing PCI typically have a poorer prognosis than their younger counterparts.[7] Therefore, optimizing PCI strategies for elderly patients is critical for improving their clinical prognosis and overall health outcomes.

Fractional flow reserve (FFR) with adenosine-induced hyperaemia is the gold standard for assessing the presence of coronary lesion-induced ischaemia.[8,9] FFR-guided PCI yields better clinical outcomes than conventional coronary angiography, particularly for multivessel lesions, tandem lesions, and diffuse lesions.[10] Moreover, delayed PCI guided by FFRs does not increase the risk in elderly patients.[11] The adoption of pressure wire-based invasive FFRs is limited by suboptimal manipulation of pressure guidewires, contraindications and side effects of adenosine/adenosine triphosphate, and increased procedure time and cost. The use of non-vasodilator-dependent invasive detection methods based on pressure wires (e.g., iFRs and RFRs) has also failed to fully overcome these challenges.[12]

The angiography-based quantitative flow ratio (QFR) is an imaging-based method for the functional assessment of coronary arteries that has demonstrated very high consistency with FFR in preliminary studies, as an alternative to FFR that does not rely on pressure guidewires or vasodilators.[13,14] In the Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients With Coronary Artery Disease (FAVOR III) China trial, we demonstrated that the QFR is superior to coronary angiography alone in improving patient prognosis, without incurring additional time or cost.[15] There is still a lack of evidence on the effectiveness of the QFR in elderly patients. Hence, we conducted a prespecified substudy of the FAVOR III China trial to compare the outcomes of QFR-guided versus angiography-guided PCI in elderly patients.

## METHODS

### FAVOR Ⅲ China Trial

This study is a prespecified subgroup analysis of the FAVOR III China trial (NCT03656848), an investigator-initiated, multi-center, randomized, blinded, and sham-controlled clinical trial involving 26 hospitals in China. A total of 3825 patients who present with angina pectoris or ≥ 72 h post myocardial infarction scheduled for PCI, and identified with at least one lesion with a percentage of diameter stenosis of 50% to 90% in a coronary vessel with a reference diameter of ≥ 2.5 mm, were successfully randomized. The study design was published before.[15,16] In brief, patients were randomly assigned at a 1: 1 ratio to either the QFR-guided treatment group or the standard angiography-guided treatment group. All patients and laboratory investigators were blinded to the grouping. For the QFR-guided group, data from two angiographic images with angles differing by ≥ 25 degrees were transmitted to the AngioPlus system (Pulse Medical) for real-time QFR calculation. Lesions with a QFR ≤ 0.80 or diameter stenosis ≥ 90% were treated with PCI, and staged PCI was allowed within 60 days if multiple vessels met the criteria. The PCIs of lesions with a QFR > 0.80 and diameter stenosis < 90% were deferred (not treated).

The study protocol was approved by the ethics committee at each participating site, and this study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the China National Medical Products Administration. Before enrolment, all patients provided written informed consent.

### Procedure and Medication

Coronary angioplasty and PCI procedures were performed according to standard protocol. Intravascular imaging utilization were left to the discretion of the operators based on their clinical experience. All patients were required a loading dose of 300 mg of aspirin at least 24 h before the procedure, along with either 300-600 mg of clopidogrel or 180 mg of ticagrelor administered at least 6 h prior, unless the patient had been on chronic P2Y12 inhibitor therapy for more than 6 days beforehand. During the procedure, intravenous unfractionated heparin is administered as needed to maintain a clotting

time of 250-350 s (using the HemoTec method) once stent implantation is required. After the procedure, patients without PCI receive optimal medical therapy, including aspirin (or clopidogrel if aspirin can't be tolerated), a beta-1 receptor blocker, calcium channel blocker, nitrates, statins, and other necessary medications. Diabetic patients also receive focused diabetes management. For those who underwent PCI, they are prescribed aspirin (100 mg daily indefinitely) along with clopidogrel (75 mg daily) for a minimum of 12 months. Other medical therapy remains the same as for patients without PCI.

### Groups

In this subgroup analysis, we primarily compared the long-term prognosis between the QFR-guided strategy and the standard angiography-only guided strategy in patient subgroups aged < 65 years and ≥ 65 years. In the sensitivity analysis, we also compared clinical outcomes among study groups in the following age subgroups: < 55 years and ≥ 55 years; < 75 years and ≥ 75 years.

### Follow-up and outcomes

All patients enrolled in FAVOR III China trial were followed up at 1 month, 6 months, 1 year and annually up to 5 years after randomization either by telephone or clinic visits. All the adverse events were collected and adjudicated by the independent committee.

The primary outcome of the study was major adverse cardiac events (MACEs), a composite of all-cause death, myocardial infarction (MI), or ischemia-driven revascularization (IDR). Secondary outcomes included MACE excluding periprocedural MI, death, MI, any revascularization, target vessel revascularization due to ischemic or non-ischemic reasons, and stent thrombosis. Target vessels were defined as vessels that were actually treated with PCI after randomization.

### Statistical Analysis

All our analyses were conducted in the intent-to-treat population. Continuous variables are presented as the mean ± SD or median (IQR) and were compared using the 2-sample Student's t test or the Wilcoxon rank-sum test, as appropriate. Categorical variables are presented as *n* (%) and were compared using the likelihood ratio chi-squared test or Fisher's exact test, as appropriate. The time-to-first-event rates for each group were estimated with the Kaplan–Meier method and were compared by the log-rank test. Between-group risks were estimated by hazard ratios (HRs) with 95% confidence intervals (CIs) using the Cox proportional hazards model. $P < 0.05$ were considered to indicate statistical significance. All analyses were performed with SAS software, version 9.4 (SAS Institute Inc.).

## RESULTS

### Baseline Characteristics

A total of 3,825 patients were randomly assigned to either the QFR-guided or angiography-guided PCI group. Among them, the average age was 61.3 ± 10.4 years. 406 (10.61%) were aged ≥ 75 years, 1311 (34.27%) were aged ≥ 65 and < 75 years, 1246 (32.58%) were aged ≥ 55 and < 65 years, 862 (22.54%) were aged ≤ 55 years (Figure 1 and Figure 2). The group aged ≥ 65 years was predominantly female, had a lower body mass index, and had a lower proportion of smokers. This group of patients also had a greater prevalence of comorbidities, such as hypertension, chronic kidney disease, and a history of stroke, and a lower incidence of hyperlipidaemia. The SYNTAX score and functional SYNTAX score were greater in the ≥ 65-year-old group than in the < 65-year-old group, while the incidence of diabetes mellitus did not differ (Supplementary Table 1). As shown in Table 1, the baseline characteristics were well balanced between the randomized treatment arms in both the ≥ 65 and the < 65 age group.

### Procedure and Medication Use

The procedural details and results are shown in Table 2 and Supplement Table 2. More treatment changes were observed in both the ≥ 65 year (216 (25.0%) *vs.* 60 (5.7%); $P < 0.0001$) and < 65 year groups (229 (21.8%) *vs.* 60 (5.7%); $P < 0.0001$). Complete deferral (i.e., not implementing) of PCI was more common under QFR guidance than under angiography guidance in both the ≥ 65 patients (10.2% *vs.* 1.1%; $P < 0.0001$) and < 65 patients (9.0% *vs.* 0.8%; $P < 0.0001$). As shown in Table 2, PCI patients who received QFR guidance had fewer stents, received stents that were smaller in diameter, and received less contrast agent per patient. In the ≥ 65 year patients who received QFR-guided PCI, the stent length was shorter (37.77 ± 28.93 *vs.* 40.82 ± 28.99, $P = 0.0292$), but there was no such difference in the < 65 year patients. In terms of the success rate of PCI, the success rate of PCI in the ≥ 65 year group was similar under QFR and an-

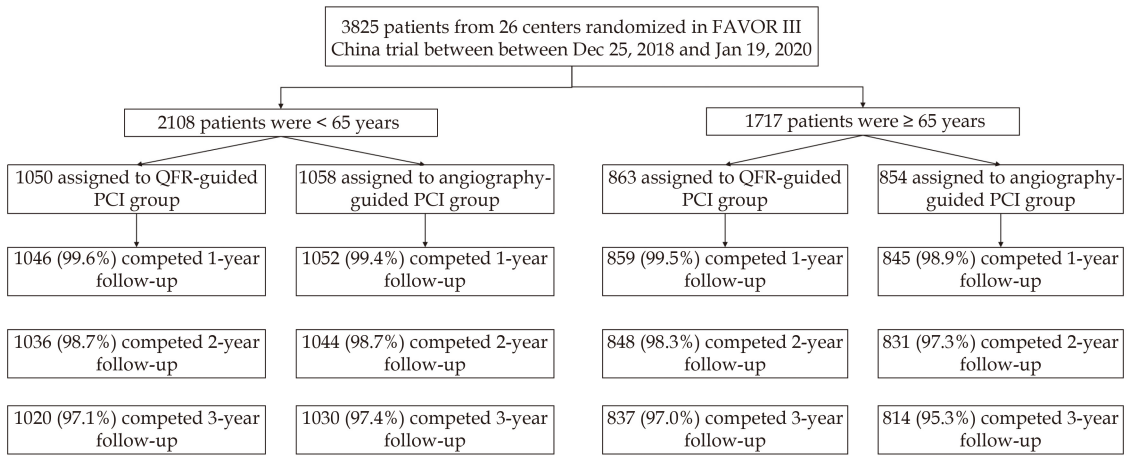


**Figure 1 Research involvement and baseline follow-up situation of the age subgroup analysis in the FAVOR-III China study.**

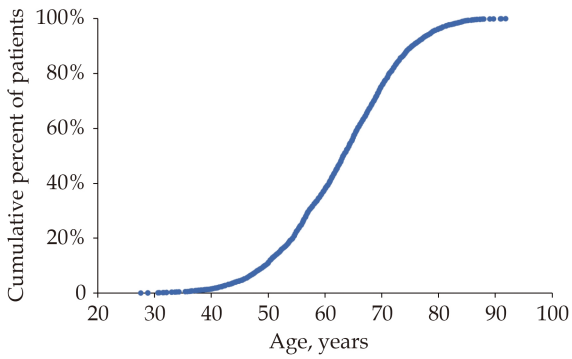


**Figure 2 The age distribution of patients in the FAVOR III China study is shown.**

giography guidance, but in the < 65 year group, the success rate under QFR guidance was slightly lower than that under angiography guidance (98.8% *vs.* 99.6%; $P$ = 0.0297). Regardless of whether the patients were < 65 year or ≥ 65 year, the remaining anatomical SYNTAX scores of the QFR-guided and angiography-guided patients after PCI were similar (< 65 year group, 2.42 ± 3.43 *vs.* 2.24 ± 3.88; $P$ = 0.276; and ≥ 65 year group, 2.45 ± 3.70 *vs.* 2.48 ± 4.06; $P$ = 0.890). However, in both the ≥ 65 year patients (87.3% *vs.* 82.5%; $P$ = 0.051) and < 65 year patients (88.8% *vs.* 82.1%; $P$ < 0.0001), complete functional reconstruction was more often achieved under QFR

**Table 1 Baseline characteristics of the treatment groups stratified by age.**

| | < 65 yrs | | ≥ 65 yrs | |
|---|---|---|---|---|
| | QFR-Guided (*n* = 1050) | Angio-Guided (*n* = 1058) | QFR-Guided (*n* = 863) | Angio-Guided (*n* = 854) |
| Age, yrs | 55.43 ± 6.63 | 55.42 ± 6.89 | 71.63 ± 5.26 | 71.63 ± 5.18 |
| Female | 206 (19.6%) | 227 (21.5%) | 358 (41.5%) | 335 (39.2%) |
| Body mass index, kg/m | 25.65 ± 3.12 | 25.44 ± 3.22 | 24.51 ± 3.05 | 24.34 ± 3.10 |
| Diabetes mellitus | 346 (33.0%) | 349 (33.0%) | 302 (35.0%) | 298 (34.9%) |
| Insulin requiring | 85 (8.1%) | 91 (8.6%) | 81 (9.4%) | 90 (10.5%) |
| Hypertension | 641 (61.0%) | 634 (59.9%) | 629 (72.9%) | 618 (72.4%) |
| Hyperlipidemia | 471 (44.9%) | 476 (45.0%) | 258 (29.9%) | 252 (29.5%) |
| Smoking | | | | |
| Never smoked | 482 (45.9%) | 514 (48.6%) | 573 (66.4%) | 548 (64.2%) |
| Current smoker | 404 (38.5%) | 383 (36.2%) | 170 (19.7%) | 185 (21.7%) |
| Former smoker | 164 (15.6%) | 161 (15.2%) | 120 (13.9%) | 121 (14.2%) |
| Family history of CAD | 106 (10.1%) | 96 (9.1%) | 41 (4.8%) | 53 (6.2%) |
| Previous MI | 107 (10.2%) | 98 (9.3%) | 72 (8.3%) | 81 (9.5%) |
| Prior PCI | 235 (22.4%) | 243 (23.0%) | 250 (29.0%) | 223 (26.1%) |
| Prior CABG | 2 (0.2%) | 1 (0.1%) | 3 (0.3%) | 3 (0.4%) |
| Prior stroke | 81 (7.7%) | 76 (7.2%) | 103 (11.9%) | 99 (11.6%) |

Continued

| | < 65 yrs | | ≥ 65 yrs | |
|---|---|---|---|---|
| | QFR-Guided (*n* = 1050) | Angio-Guided (*n* = 1058) | QFR-Guided (*n* = 863) | Angio-Guided (*n* = 854) |
| Peripheral vascular disease | 25 (2.4%) | 32 (3.0%) | 30 (3.5%) | 39 (4.6%) |
| Clinical presentation | | | | |
| Silent ischemia | 120 (11.4%) | 113 (10.7%) | 87 (10.1%) | 91 (10.7%) |
| STABLE | 276 (26.3%) | 274 (25.9%) | 217 (25.1%) | 219 (25.6%) |
| UnsTABLE | 590 (56.2%) | 601 (56.8%) | 521 (60.4%) | 509 (59.6%) |
| Post-AMI | 64 (6.1%) | 70 (6.6%) | 38 (4.4%) | 35 (4.1%) |
| CCS class | | | | |
| N (Nmiss) | 276 (774) | 274 (784) | 217 (646) | 219 (635) |
| I | 99 (35.9%) | 98 (35.8%) | 77 (35.5%) | 93 (42.5%) |
| II | 93 (33.7%) | 84 (30.7%) | 71 (32.7%) | 62 (28.3%) |
| III | 52 (18.8%) | 57 (20.8%) | 51 (23.5%) | 36 (16.4%) |
| IV | 32 (11.6%) | 35 (12.8%) | 18 (8.3%) | 28 (12.8%) |
| Braunwald class | | | | |
| N (Nmiss) | 590 (460) | 601 (457) | 521 (342) | 509 (345) |
| I | 264 (44.7%) | 279 (46.4%) | 247 (47.4%) | 232 (45.6%) |
| II | 285 (48.3%) | 273 (45.4%) | 225 (43.2%) | 230 (45.2%) |
| III | 41 (6.9%) | 49 (8.2%) | 49 (9.4%) | 47 (9.2%) |
| Estimated glomerular | 83.25 ± 61.77 | 80.14 ± 18.94 | 61.72 ± 26.17 | 63.49 ± 42.02 |
| LVEF (%) | 63.11 ± 6.38 | 63.07 ± 6.52 | 63.15 ± 6.76 | 62.50 ± 7.36 |
| Angiographic | | | | |
| 1-vessel | 472 (45.0%) | 492 (46.5%) | 418 (48.4%) | 377 (44.1%) |
| 2-vessel | 382 (36.4%) | 369 (34.9%) | 292 (33.8%) | 315 (36.9%) |
| 3-vessel | 179 (17.0%) | 179 (16.9%) | 127 (14.7%) | 137 (16.0%) |
| Concomitant LM disease | 17 (1.6%) | 18 (1.7%) | 26 (3.0%) | 25 (2.9%) |
| SYNTAX score | 9.21 ± 5.76 | 9.22 ± 6.00 | 9.48 ± 6.17 | 10.00 ± 6.68 |
| Functional SYNTAX score[a] | 7.92 ± 6.09 | 7.78 ± 6.28 | 8.24 ± 6.47 | 8.31 ± 7.03 |
| Existence of any lesion with DS% > 90% and TIMI flow < 3 | 99 (9.4%) | 93 (8.8%) | 71 (8.2%) | 89 (10.4%) |

Values are mean ± SD or *n* (%). [a]The functional SYNTAX score was calculated by summing the segmental anatomic SYNTAX scores only in vessels with functional ischemia as defifined by of flfline QFR ≤ 0.80 assessed by the angiographic core laboratory. QFR: quantitative flow rate; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIMI: thrombolysis in myocardial infarction.

guidance. In terms of the treatment process, the radiation exposure time and contrast agent dosage in the < 65 year patients in the QFR-guided group were significantly lower than those in the angiography-guided group, but these benefits were not observed in the ≥ 65 year patients.

## Clinical Outcomes

At the 1-year follow-up, the QFR-guided group had a significantly lower incidence of MACEs with PMI in both age groups than did the angiography-guided group (≥ 65 years, 6.04% *vs.* 9.19%; HR = 0.65; 95% CI: 0.46–0.92; < 65 years, 5.53% *vs.* 8.43%; HR = 0.65; 95% CI: 0.47–0.91). In patients < 65 years old, the QFR-guided group had a lower incidence of MACEs without PMI (2.58% *vs.* 4.46%; HR = 0.57; 95% CI: 0.36–0.92), but there was no significant difference between the two guidance strategies in patients ≥ 65 year (3.72% *vs.* 5.20%; HR = 0.71; 95% CI: 0.45–1.12, Table 3). For patients < 65 years old, the benefits of the QFR-guided strategy at one year can be sustained until three years, but for patients ≥ 65, no sustained benefits were observed at 3 years of follow-up (Figure 3).

At 3 years of follow-up, the incidence of MACE did not differ between patients aged ≥ 65 year and those aged < 65 year. MACEs occurred in 9.5% of the 1050 pa-

**Table 2 Procedural characteristics of the treatment groups stratified by age.**

| | < 65 yrs | | | ≥ 65 yrs | | |
|---|---|---|---|---|---|---|
| | QFR-Guided (*n* = 1050) | Angio-Guided (*n* = 1058) | *P*-value | QFR-Guided (*n* = 863) | Angio-Guided (*n* = 854) | *P*-value |
| Radial-artery approach | 1030 (98.1%) | 1036 (97.9%) | 0.7742 | 855 (99.1%) | 833 (97.5%) | 0.0122 |
| PCI performed (patient level) | 956 (91.0%) | 1050 (99.2%) | < 0.0001 | 775 (89.8%) | 845 (98.9%) | < 0.0001 |
| Treatment strategy (patient level) | | | < 0.0001 | | | < 0.0001 |
| Balloon angioplasty | 7 (0.7%) | 10 (0.9%) | | 2 (0.2%) | 15 (1.8%) | |
| Drug-eluting balloon | 34 (3.2%) | 37 (3.5%) | | 21 (2.4%) | 21 (2.5%) | |
| Drug-eluting stent | 915 (87.1%) | 1003 (94.8%) | | 752 (87.1%) | 809 (94.7%) | |
| No treatment | 94 (9.0%) | 8 (0.8%) | | 88(10.2%) | 9 (1.1%) | |
| PCI performed (lesion level) | 1259 (74.5%) | 1423 (88.1%) | < 0.0001 | 1008 (74.5%) | 1157 (86.9%) | < 0.0001 |
| Treatment strategy (lesion level) | | | < 0.0001 | | | < 0.0001 |
| Balloon angioplasty | 30 (1.8%) | 48 (3.0%) | | 31 (2.3%) | 50 (3.8%) | |
| Drug-eluting balloon | 54 (3.2%) | 65 (4.0%) | | 36 (2.7%) | 40 (3.0%) | |
| Drug-eluting stent | 1175 (69.5%) | 1310 (81.1%) | | 941 (69.5%) | 1067 (80.1%) | |
| No treatment | 432 (25.5%) | 193 (11.9%) | | 345 (25.5%) | 175 (13.1%) | |
| No.of stents placed per patient | 1.44 ± 1.01 | 1.56 ± 0.92 | 0.0046 | 1.46 ± 1.04 | 1.61 ± 1.03 | 0.0027 |
| Stent length per patient, mm | 36.81 ± 27.97 | 38.84 ± 25.75 | 0.0827 | 37.77 ± 28.93 | 40.82 ± 28.99 | 0.0292 |
| Stent diameter per patient, mm | 2.66 ± 1.10 | 2.88 ± 0.79 | < 0.0001 | 2.60 ± 1.07 | 2.83 ± 0.77 | < 0.0001 |
| Intravascular imaging evaluation | 58 (5.5%) | 59 (5.6%) | 0.9578 | 61 (7.1%) | 62 (7.3%) | 0.8777 |
| Contrast material used per patient, mL | 159.70 ± 70.99 | 168.26 ± 72.95 | 0.0067 | 167.06 ± 80.76 | 171.49 ± 75.62 | 0.2444 |
| Fluoroscopy time, min | 13.70 ± 7.87 | 14.68 ± 7.17 | 0.0051 | 14.55 ± 8.14 | 15.24 ± 7.56 | 0.0929 |
| Adjusted procedural duration, min | 44.19 ± 28.35 | 48.54 ± 32.45 | 0.0011 | 45.09 ± 29.34 | 50.72 ± 27.09 | < 0.0001 |
| Procedural duration, min | 38.54 ± 25.91 | 38.91 ± 32.29 | 0.7787 | 40.21 ± 26.48 | 41.26 ± 26.72 | 0.4244 |
| Lesion success (PCI performed) | 1145 (98.8%) | 1353 (99.6%) | 0.0297 | 916 (99.1%) | 1088 (98.8%) | 0.4831 |
| Procedural success (PCI performed) | 878 (95.2%) | 968 (95.0%) | 0.8124 | 713 (96.0%) | 779 (94.2%) | 0.1058 |
| No.of vessels intended to treat | | | 0.5873 | | | 0.2675 |
| LAD | 733 (52.8%) | 709 (50.2%) | | 603 (53.1%) | 595 (50.8%) | |
| LCX | 298 (21.5%) | 318 (22.5%) | | 224 (19.7%) | 266 (22.7%) | |
| LM | 14 (1.0%) | 16 (1.1%) | | 19 (1.7%) | 25 (2.1%) | |
| RCA | 342 (24.7%) | 368 (26.1%) | | 289 (25.5%) | 285 (24.3%) | |
| No.of vessels actually treated | | | 0.0908 | | | 0.1786 |
| LAD | 685 (54.8%) | 695 (50.0%) | | 543 (54.4%) | 575 (50.0%) | |
| LCX | 252 (20.2%) | 309 (22.2%) | | 199 (19.9%) | 263 (22.9%) | |
| LM | 22 (1.8%) | 32 (2.3%) | | 27 (2.7%) | 38 (3.3%) | |
| RCA | 291 (23.3%) | 354 (25.5%) | | 230 (23.0%) | 274 (23.8%) | |
| Patients with all originally intended vessels treated | 821 (78.2%) | 998 (94.3%) | < 0.0001 | 647 (75.0%) | 795 (93.1%) | < 0.0001 |
| Patients with at least one unintended vessel treated | 43 (4.1%) | 13 (1.2%) | < 0.0001 | 42 (4.9%) | 15 (1.8%) | 0.0002 |
| Patients with deferral of at least one vessel that was originally intended to be treated | 192 (18.3%) | 51 (4.8%) | < 0.0001 | 183 (21.2%) | 49 (5.7%) | < 0.0001 |
| Patients with unintended vessel treatment OR intended vessel deferral | 229 (21.8%) | 60 (5.7%) | < 0.0001 | 216 (25.0%) | 59 (6.9%) | < 0.0001 |
| Residual SYNTAX score | 2.42 ± 3.43 | 2.24 ± 3.88 | 0.2763 | 2.45 ± 3.70 | 2.48 ± 4.06 | 0.8900 |
| Residual Functional SYNTAX score | 0.56 ± 1.93 | 1.00 ± 2.75 | < 0.0001 | 0.80 ± 2.59 | 1.04 ± 2.95 | 0.0703 |
| Residual Functional SYNTAX score=0 | 925 (88.8%) | 856 (82.1%) | < 0.0001 | 744 (87.3%) | 696 (82.5%) | 0.0051 |

Data are presented as mean ± SD or *n* (%). Categorical data will be compared between the two groups using likelihood ratio Chi-square test or Fisher's exact test. Continuous variables will be compared between the two groups using two sample *t*-test. The 95% CIs of the difference between two groups will be calculated by normal approximation for continuous variables and by the continuity correction asymptotic wald method for binary variables.

**Table 3 1-year clinical outcomes of the treatment groups stratified by age.**

| | < 65 yrs | | | ≥ 65 yrs | | |
|---|---|---|---|---|---|---|
| | QFR-Guided (*n* = 1050) | Angio-Guided (*n* = 1058) | Hazard Ratio and 95% CI | QFR-Guided (*n* = 863) | Angio-Guided (*n* = 854) | Hazard Ratio and 95% CI |
| MACE at 1 year | 58 (5.53%) | 89 (8.43%) | 0.65 (0.47,0.91) | 52 (6.04%) | 78 (9.19%) | 0.65 (0.46,0.92) |
| All cause death | 4 (0.38%) | 3 (0.28%) | 1.34 (0.30,6.00) | 9 (1.05%) | 6 (0.71%) | 1.48 (0.53,4.14) |
| Myocardial infarction | 40 (3.81%) | 62 (5.87%) | 0.65 (0.44,0.97) | 25 (2.90%) | 47 (5.53%) | 0.52 (0.32,0.85) |
| Ischemia-driven revascularization | 18 (1.72%) | 31 (2.95%) | 0.58 (0.33,1.04) | 20 (2.34%) | 28 (3.33%) | 0.70 (0.39,1.24) |
| MACE without PMI | 27 (2.58%) | 47 (4.46%) | 0.57 (0.36,0.92) | 32 (3.72%) | 44 (5.20%) | 0.71 (0.45,1.12) |
| Cardiovascular death | 2 (0.19%) | 2 (0.19%) | 1.01 (0.14,7.16) | 7 (0.81%) | 5 (0.59%) | 1.38 (0.44,4.34) |
| Non-cardiovascular death | 2 (0.19%) | 1 (0.09%) | 2.01 (0.18,22.21) | 2 (0.23%) | 1 (0.12%) | 1.97 (0.18,21.68) |
| Periprocedural myocardial infarction | 34 (3.24%) | 45 (4.25%) | 0.76 (0.49,1.19) | 22 (2.55%) | 36 (4.22%) | 0.60 (0.35,1.02) |
| Spontaneous myocardial infarction | 7 (0.67%) | 18 (1.71%) | 0.39 (0.16,0.94) | 3 (0.35%) | 12 (1.43%) | 0.24 (0.07,0.87) |
| Revascularization | 25 (2.39%) | 35 (3.33%) | 0.72 (0.43,1.20) | 24 (2.81%) | 32 (3.81%) | 0.73 (0.43,1.25) |
| Target vessel revascularization | 14 (1.34%) | 11 (1.05%) | 1.29 (0.59,2.84) | 8 (0.94%) | 14 (1.67%) | 0.56 (0.24,1.34) |
| Ischemia-driven Target vessel revascularization | 12 (1.15%) | 9 (0.86%) | 1.35 (0.57,3.20) | 6 (0.70%) | 12 (1.43%) | 0.49 (0.18,1.31) |
| Target Lesion revascularization | 11 (1.05%) | 11 (1.05%) | 1.01 (0.44,2.33) | 6 (0.70%) | 12 (1.43%) | 0.49 (0.18,1.31) |
| Ischemia-driven Target Lesion revascularization | 10 (0.96%) | 9 (0.86%) | 1.12 (0.46,2.76) | 6 (0.70%) | 10 (1.19%) | 0.59 (0.21,1.63) |
| Target vessel non-target Lesion revascularization | 3 (0.29%) | 1 (0.10%) | 3.03 (0.31,29.10) | 2 (0.23%) | 3 (0.36%) | 0.66 (0.11,3.93) |
| Ischemia-driven Target vessel non-target Lesion revascularization | 2 (0.19%) | 1 (0.10%) | 2.02 (0.18,22.25) | 0 (0.00%) | 3 (0.36%) | NA |
| Non-target vessel revascularization | 14 (1.34%) | 25 (2.37%) | 0.56 (0.29,1.08) | 18 (2.11%) | 20 (2.38%) | 0.88 (0.47,1.67) |
| Ischemia-driven Non-target vessel revascularization | 8 (0.77%) | 22 (2.09%) | 0.36 (0.16,0.82) | 14 (1.64%) | 18 (2.14%) | 0.76 (0.38,1.53) |
| Definite/probable stent thrombosis | 2 (0.19%) | 3 (0.28%) | 0.67 (0.11,4.02) | 1 (0.12%) | 3 (0.35%) | 0.33 (0.03,3.16) |
| Definite stent thrombosis | 1 (0.10%) | 1 (0.10%) | 1.01 (0.06,16.13) | 0 (0.00%) | 2 (0.24%) | NA |
| Probable stent thrombosis | 1 (0.10%) | 2 (0.19%) | 0.50 (0.05,5.56) | 1 (0.12%) | 1 (0.12%) | 0.65 (0.46,0.92) |

Values are *n* (%) unless other indicated. PMI: Peri-procedural myocardial injury.

tients randomized to the QFR-guided group and in 14.6% of the 1058 patients randomized to the angiography-guided group among patients < 65 year (HR and 95% CI: 0.75 (0.58-0.98)), whereas in patients ≥ 65 year, MACEs occurred in 11.8% of the 863 patients randomized to the QFR-guided group and in 15.2% of the 854 patients randomized to the angiography-guided group (HR and 95% CI: 0.63 (0.49-0.81), Table 4).

We also looked at the patients who were < 55 years old and ≥ 75 years old. Among the patients who were < 55 years, there was no significant difference in 3-year MACEs between the QFR-guided group and the angiography-guided group (9.4% *vs.* 13.0%; HR = 0.84; 95% CI 0.69–1.03). Among the patients who were ≥ 75 year, there was also no significant difference in 3-year MACE between the QFR-guided group and the angiography-guided group (13.1% *vs.* 15.1%; HR: 0.92; 95% CI 0.71–1.20). These results suggested that the benefit of the QFR-guided strategy was limited in both the young and the very old, a result that may be related to the small number of patients who were < 55 years old or ≥ 75 years old (Supplementary Tables 9, 12).

## QFR-guided PCI Deferral

Among the 1913 patients of the QFR guidance group, 375 (19.6%) had at least one vessel that was initially planned for treatment but did not undergo PCI because the QFR of the lesion was greater than 0.80. This deferral rate was comparable between patients aged ≥ 65 years (21.2%) and those aged < 65 years (18.3%) ($P$ = 0.46, Table 2).

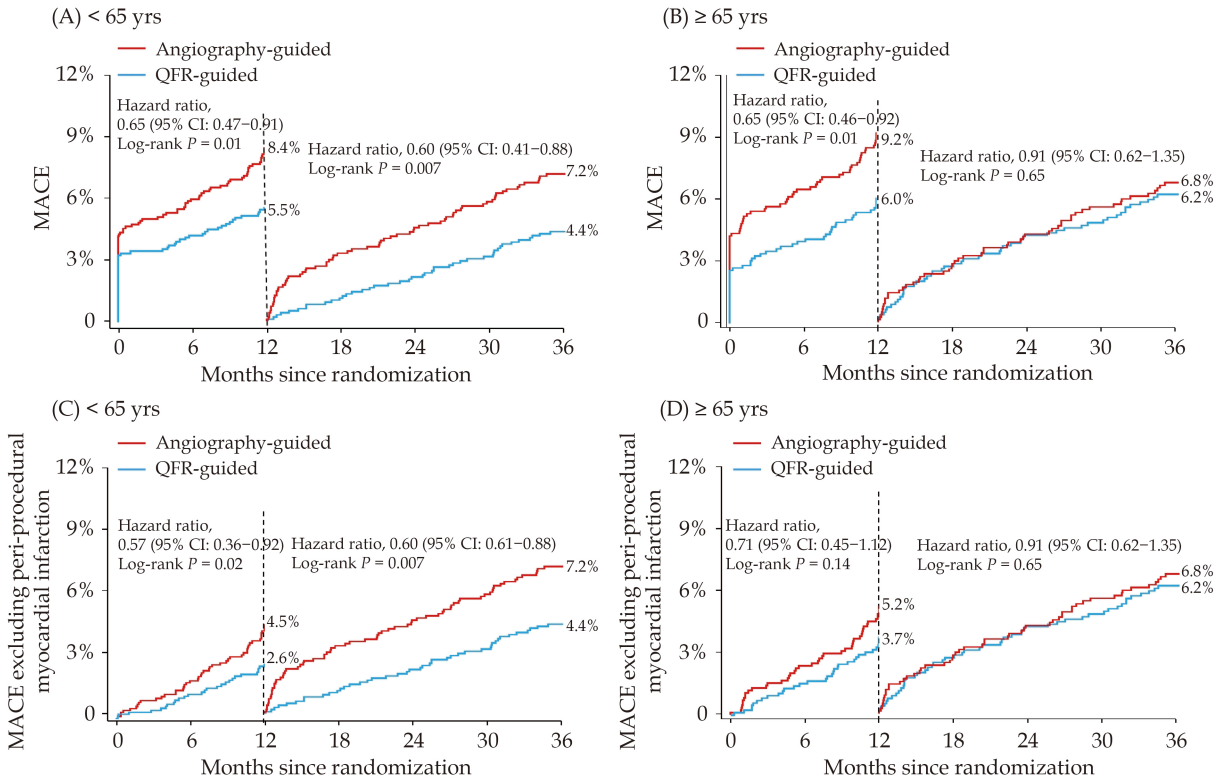


**Figure 3 Prognosis up to 36 months of follow-up.** The patients' age is 61.3 ± 10.4 years old, which conforms to the normal distribution. The preset age subgroup in this study is defined as 65 years old. (A & C): In patients < 65 years old, both the total MACE rate and the MACE rate excluding PMI were significantly lower in the QFR-guided PCI group than in the angiography-guided PCI group at 12 months of follow-up, and this effect persisted at 36 months of follow-up; (B & D): in patients ≥ 65 years old, the total MACE rate and the MACE rate excluding PMI were significantly lower in the QFR-guided PCI group than in the angiography-guided PCI group at 12 months of follow-up, but no continued benefit was observed at 36 months of follow-up. MACE: major adverse cardiac events; PCI: percutaneous coronary intervention; PMI: periprocedural myocardial injury.

Within the QFR-guided group, the 1-year MACE rate in patients with deferred vessels was similar between those aged ≥ 65 year and those aged < 65 year (5.32% *vs.* 0.98%, respectively; $P = 0.12$, Table 5). Similarly, the 3-year MACE rate in patients with deferred vessels was also similar between those aged ≥ 65 year and those aged < 65 year (8.3% *vs.* 3.0%, respectively; $P = 0.10$, Table 6).

## Multivariable Correction for Three-year Clinical Outcomes of the Treatment Groups Stratified by Age

In patients < 65 years old, after multivariable adjustment, the QFR-guided group still showed a significantly lower risk of MACE compared to the angiography-guided group, with an adjusted hazard ratio of 0.64 (95% CI: 0.48–0.85) and a *P*-value of 0.002. Similarly, in patients ≥ 65 years old, the adjusted hazard ratio was 0.62 (95% CI: 0.46–0.84), also indicating a significant benefit of the QFR-guided strategy. This shows that even after considering various factors, the QFR-guided PCI strategy remains associated with better outcomes (Supplementary Table 13).

## Primary Endpoint Subgroup Analysis Across Different Age Groups

In the primary endpoint subgroup analysis across different age groups, the QFR-guided PCI strategy showed differential benefits. Among patients ≥ 65 years, QFR guidance significantly reduced events in females (HR = 0.61, 95%CI: 0.38–0.97), those with hypertension (HR = 0.70, 95%CI: 0.52–0.94), and hypercholesterolemia (HR = 0.59, 95%CI: 0.36-0.95), while other subgroups showed non-significant trends. In patients < 65 years, males (HR = 0.61, 95% CI: 0.46-0.81), individuals with diabetes mellitus (HR = 0.59, 95%CI: 0.39-0.89), hypertension (HR = 0.54, 95%CI: 0.39–0.74), and hypercholesterolemia (HR = 0.61, 95%CI: 0.42–0.89) benefited significantly from QFR guidance, with more pronounced effects in lower-to-moderate SYNTAX score tiers (e.g., 5.0–9.0: HR =

**Table 4 3-year clinical outcomes of the treatment groups stratified by age.**

| | < 65 yrs | | | ≥ 65 yrs | | |
|---|---|---|---|---|---|---|
| | QFR-Guided (*n* = 1050) | Angio-Guided (*n* = 1058) | Hazard Ratio and 95% CI | QFR-Guided (*n* = 863) | Angio-Guided (*n* = 854) | Hazard Ratio and 95% CI |
| MACE | 99 (9.5%) | 154 (14.6%) | 0.63 (0.49, 0.81) | 101 (11.8%) | 129 (15.2%) | 0.75 (0.58, 0.98) |
| All cause death | 7 (0.7%) | 11 (1.0%) | 0.64 (0.25, 1.65) | 22 (2.6%) | 23 (2.7%) | 0.95 (0.53, 1.70) |
| Myocardial infarction | 49 (4.7%) | 82 (7.8%) | 0.60 (0.42, 0.85) | 38 (4.4%) | 64 (7.6%) | 0.58 (0.39, 0.86) |
| Ischemia-driven revascularization | 55 (5.3%) | 78 (7.5%) | 0.70 (0.50, 0.99) | 51 (6.0%) | 63 (7.5%) | 0.79 (0.55, 1.15) |
| MACE without PMI | 60 (6.6%) | 113 (10.8%) | 0.60 (0.44, 0.81) | 81 (9.4%) | 101 (11.9%) | 0.78 (0.58, 1.04) |
| Cardiovascular death | 2 (0.2%) | 6 (0.6%) | 0.34 (0.07, 1.66) | 11 (1.3%) | 12 (1.4%) | 0.91 (0.40, 2.05) |
| Non-cardiovascular death | 5 (0.5%) | 5 (0.5%) | 1.01 (0.29, 3.47) | 11 (1.3%) | 11 (1.3%) | 0.99 (0.43, 2.28) |
| Periprocedural myocardial infarction | 34 (3.2%) | 45 (4.3%) | 0.76 (0.49, 1.19) | 22 (2.5%) | 36 (4.2%) | 0.60 (0.35, 1.02) |
| Spontaneous myocardial infarction | 16 (1.5%) | 38 (3.6%) | 0.42 (0.23, 0.75) | 16 (1.9%) | 30 (3.6%) | 0.52 (0.28, 0.96) |
| Revascularization | 75 (7.2%) | 94 (9.0%) | 0.79 (0.59, 1.07) | 64 (7.6%) | 76 (9.1%) | 0.82 (0.59, 1.15) |
| Target vessel revascularization | 40 (3.9%) | 41 (3.9%) | 0.98 (0.63, 1.52) | 26 (3.1%) | 42 (5.0%) | 0.61 (0.37, 0.99) |
| Ischemia-driven target vessel revascularization | 33 (3.2%) | 34 (3.3%) | 0.98 (0.61, 1.58) | 18 (2.1%) | 37 (4.4%) | 0.48 (0.27, 0.84) |
| Target lesion revascularization | 29 (2.8%) | 33 (3.2%) | 0.88 (0.54, 1.45) | 15 (1.8%) | 36 (4.3%) | 0.41 (0.22, 0.74) |
| Ischemia-driven target lesion revascularization | 26 (2.5%) | 29 (2.8%) | 0.90 (0.53, 1.53) | 14 (1.7%) | 31 (3.7%) | 0.44 (0.24, 0.83) |
| Target vessel non-target lesion revascularization | 13 (1.3%) | 10 (1.0%) | 1.31 (0.57, 2.98) | 11 (1.3%) | 7 (0.8%) | 1.56 (0.60, 4.01) |
| Ischemia-driven target vessel non-target lesion revascularization | 8 (0.8%) | 6 (0.6%) | 1.34 (0.47, 3.87) | 4 (0.5%) | 7 (0.8%) | 0.56 (0.17, 1.93) |
| Non-target vessel revascularization | 40 (3.9%) | 55 (5.3%) | 0.73 (0.48, 1.09) | 41 (4.8%) | 38 (4.5%) | 1.07 (0.69, 1.66) |
| Ischemia-driven non-target vessel revascularization | 25 (2.4%) | 45 (4.3%) | 0.55 (0.34, 0.90) | 33 (3.9%) | 29 (3.5%) | 1.12 (0.68, 1.85) |
| Definite/probable stent thrombosis | 4 (0.4%) | 6 (0.6%) | 0.67 (0.19, 2.38) | 3 (0.4%) | 8 (1.0%) | 0.37 (0.10, 1.40) |
| Definite stent thrombosis | 99 (9.5%) | 154 (14.6%) | 0.63 (0.49, 0.81) | 101 (11.8%) | 129 (15.2%) | 0.75 (0.58, 0.98) |
| Probable stent thrombosis | 7 (0.7%) | 11 (1.0%) | 0.64 (0.25, 1.65) | 22 (2.6%) | 23 (2.7%) | 0.95 (0.53, 1.70) |

Values are *n* (%) unless other indicated. MACE: major adverse cardiac events; PMI: periprocedural myocardial injury.

0.51, 95%CI: 0.33–0.79). Subgroups with reduced left ventricular ejection fraction (≤ 45%) in both age groups showed no clear trends, potentially due to limited sample size. Overall, these results reinforce the general efficacy of QFR-guided PCI across various comorbidities and age groups, with some subgroup-specific nuances, and the lack of significant interaction effects across most subgroups indicates the generalizability of QFR guidance in clinical practice (Supplementary Figure 1 and 2).

## DISCUSSION

The FAVOR III study demonstrated that the QFR, a physiological assessment method based on coronary angiography, is superior to standard coronary angiography in guiding PCI. The main results of this sub-study show that: (1) Although with higher rate of co-morbidities and more complex coronary anatomy, the QFR-guided strategy can significantly reduce 1-year and 3-year MACE in patients ≥ 65 years, compared with those < 65 years. (2) For patients < 65 years, the QFR-guided strategy can reduce the rate of MACEs within 3 years. (3) For patients ≥ 65 years, the reduction in MACEs caused by the QFR-guided strategy mainly occurred within the first year after the index procedure, and the benefit was not significant over 3-years. By using QFR guidance, we can recognize coronary lesions from a physiological perspective, delaying PCI for physiologically nonobstructive lesions with a QFR greater than 0.80. These results are consistent with the main results of the FAVOR III study.[16]

**Table 5 One-year clinical outcomes of the age groups in deferred PCI.**

| Indicator | < 65 (*n* = 102) | ≥ 65 (*n* = 97) | Estimated Difference and 95% CI | Hazard Ratio and 95% CI | *P*-value |
|---|---|---|---|---|---|
| MACE at 1 year | 1 (0.98%) | 5 (5.32%) | −4.34% (−9.26%, 0.58%) | 0.18 (0.02, 1.56) | 0.1205 |
| All cause death | 0 | 2 (2.13%) | −2.13% (−5.04%, 0.79%) | NA | 0.9964 |
| Myocardial infarction | 0 | 2 (2.13%) | −2.13% (−5.04%, 0.79%) | NA | 0.9964 |
| Ischemia-driven revascularization | 1 (0.98%) | 3 (3.25%) | −2.27% (−6.36%, 1.82%) | 0.30 (0.03, 2.91) | 0.3009 |
| MACE without PMI | 1 (0.98%) | 5 (5.32%) | −4.34% (−9.26%, 0.58%) | 0.18 (0.02, 1.56) | 0.1205 |
| Cardiovascular death | 0 | 2 (2.13%) | −2.13% (−5.04%, 0.79%) | NA | 0.9964 |
| Non-cardiovascular death | 0 | 0 | NA | NA | NA |
| Periprocedural myocardial infarction | 0 | 0 | NA | NA | NA |
| Spontaneous myocardial infarction | 0 | 0 | NA | NA | NA |
| Revascularization | 1 (0.98%) | 4 (4.34%) | −3.36% (−7.93%, 1.22%) | 0.23 (0.03, 2.02) | 0.1831 |
| Target vessel revascularization | 0 | 0 | NA | NA | NA |
| Ischemia-driven target vessel revascularization | 0 | 0 | NA | NA | NA |
| Target lesion revascularization | 0 | 0 | NA | NA | NA |
| Ischemia-driven target lesion revascularization | 0 | 0 | NA | NA | NA |
| Target vessel non-target lesion revascularization | 0 | 0 | NA | NA | NA |
| Ischemia-driven target vessel non-target lesion revascularization | 0 | 0 | NA | NA | NA |
| Non-target vessel revascularization | 1 (0.98%) | 4 (4.34%) | −3.36% (−7.93%, 1.22%) | 0.23 (0.03, 2.02) | 0.1831 |
| Ischemia-driven non-target vessel revascularization | 1 (0.98%) | 3 (3.25%) | −2.27% (−6.36%, 1.82%) | 0.30 (0.03, 2.91) | 0.3009 |
| Definite/probable stent thrombosis | 0 | 0 | NA | NA | NA |
| Definite stent thrombosis | 0 | 0 | NA | NA | NA |
| Probable stent thrombosis | 0 | 0 | NA | NA | NA |

Data are presented as *n* (%) unless other indicated. Kaplan-Meier survival analysis will be used to calculate event rate in each group. Cox proportional hazards model will be used to calculate hazard ratio and corresponding 2-sided 95% CI between test and control group. If the MACE at 1 year is "No" or "Missing", it will be counts as "Censored" in Kaplan-Meier survival analysis or Cox proportional hazards model analysis. The difference time between the earliest date of the event and the start date of operation will be used if the subject occurs MACE at 1 year,the difference time between the date of last visit and the start date of operation will be used for the censored subject. The *P* value of superiority test between test and control group. MACE: major adverse cardiac events; PCI: percutaneous coronary intervention; PMI: periprocedural myocardial injury.

Consistent with the results of other functional studies, this study demonstrated that older patients have a higher rate of MACE occurrence. This may be related to the higher prevalence of comorbidities, such as hypertension, stroke, peripheral vascular disease, and poorer kidney function, in elderly patients. The advantages of coronary functional guidance in PCI treatment strategies have also been confirmed across different age groups. The FAME study showed that the 1-year rates of death, myocardial infarction, and repeat revascularization with the angio-guided strategy tended to be higher than those with the FFR-guided strategy, regardless of age group. This indicates that PCI guided by the FFR is beneficial regardless of age. We not only compared the age groups of ≤ 65 years and > 65 years as but also two other special age groups (extremely young, < 55 years, and extremely elderly, ≥ 75 years) to further analyse whether age affects the value of functional selection. The results consistently demonstrated the advantages of QFR-guided strategies over angio-guided strategies across all age groups.

The complexity of coronary lesions in elderly patients may be an important reason for worse PCI prognoses. In this sub-study, the SYNTAX score of patients aged ≥ 65 years was significantly greater than that of patients aged < 65 years, and the functional SYNTAX score calculated by the QFR was also greater in patients aged ≥ 65 years. This shows that patients aged ≥ 65 years have more complex coronary lesions. Whether the patients were ≥ 65 or < 65 years, the average number of stents implanted per patient in the QFR-guided group was significantly lower than that in the angio-guided group, and the average operation time was also lower. Less contrast was used in QFR-guided PCI only in patients younger than 65 years, possibly due to the greater complexity of le-

**Table 6 3-year clinical outcomes stratified by age among patients with PCI deferred.**

| | < 65 yrs (*n* = 102) | ≥ 65 yrs (*n* = 97) | Hazard Ratio (95% CI) | *P*-value |
|---|---|---|---|---|
| MACE | 3 (3.0%) | 8 (8.3%) | 2.91 (0.77, 11.0) | 0.10 |
| All cause death | 0 (0%) | 2 (2.1%) | - | 0.15 |
| Myocardial infarction | 1 (1%) | 1 (1.1%) | 1.09 (0.07, 17.5) | 0.95 |
| Ischemia-driven revascularization | 2 (2%) | 6 (6.4%) | 3.29 (0.67, 16.3) | 0.12 |
| MACE without PMI | 3 (3%) | 8 (8.3%) | 2.91 (0.77, 11.0) | 0.10 |
| Cardiovascular death | 0 (0%) | 2 (2.1%) | - | 0.15 |
| Non-cardiovascular death | 0 | 0 | - | - |
| Periprocedural myocardial infarction | 0 | 0 | - | - |
| Spontaneous myocardial infarction | 1 (1%) | 1 (1.1%) | 1.09 (0.07, 17.5) | 0.95 |
| Revascularization | 5 (4.9%) | 9 (9.6%) | 2.00 (0.67, 5.97) | 0.21 |
| Target vessel revascularization | 1 (1%) | 0 | - | 0.34 |
| Ischemia-driven target vessel revascularization | 1 (1%) | 0 | - | 0.34 |
| Target lesion revascularization | 1 (1%) | 0 | - | 0.34 |
| Ischemia-driven target lesion revascularization | 1 (1%) | 0 | - | 0.34 |
| Target vessel non-target lesion revascularization | 0 | 0 | - | - |
| Ischemia-driven target vessel non-target lesion revascularization | 0 | 0 | - | - |
| Non-target vessel revascularization | 4 (4%) | 9 (9.6%) | 2.49 (0.77, 8.10) | 0.12 |
| Ischemia-driven non-target vessel revascularization | 1 (1%) | 6 (6.4%) | 6.54 (0.79, 54.4) | 0.045 |
| Definite/probable stent thrombosis | 0 | 0 | - | - |
| Definite stent thrombosis | 0 | 0 | - | - |
| Probable stent thrombosis | 0 | 0 | - | - |

Values are *n* (%) unless other indicated. MACE: major adverse cardiac events; PMI: periprocedural myocardial injury.

sions in the ≥ 65 years group, and the amount of contrast used between the QFR-guided and angio-guided groups in patients ≥ 65 years was similar. Therefore, the benefits of the process may still come from the reduction in the number of QFR-guided PCI treatments.

The factors affecting the clinical outcome of PCI in elderly patients include not only the complexity of coronary lesions but also many other factors. In this study, the patients aged ≥ 65 year had significantly more current smokers, hypertension, prior stroke and PCI. The glomerular filtration rate was significantly lower in patients aged ≥ 65 years than in patients aged < 65 years. For patients aged < 65 years, there are also corresponding factors that are associated with the early onset of coronary lesions, such as greater incidences of familial history of coronary heart disease, hyperlipidaemia and diabetes. These characteristics are consistent with the characteristics of that population in other studies. According to the subgroup analysis of age in the FAME study, the rate of MACEs in patients aged ≥ 65 years was greater than that in patients aged < 65 years, but the improvement in MACEs according to FFR guidance was similar in both age groups.[11] In this study, the QFR-guided PCI strategy had similar benefits in different age groups, which is consistent with the trend found by the FAME study and again shows that physiological guidance of PCI can benefit patients of different ages. Even with functional guidance, the mortality rate of PCI in the elderly remains higher than that of younger patients, which is down to other factors. Interestingly, no significant increase in overall event rates was observed in the elderly patients in this study, which may be related to more optimized drug therapies.

A controversial topic in the use of the FFR to assess coronary artery lesions in elderly patients is that long-term hypertension, diabetes, and related ventricular hypertrophy may cause more severe microvascular dysfunction.[17,18] For FFR tests that rely on the maximum hyperaemic state, a higher microvascular resistance may lead to an overestimation of the FFR values.[18,19] This may be more apparent in lesions with mild to moderate stenosis.[11,20,21] In the FAME study, elderly patients had great-

er FFRs at stenoses of 50%-70% and 71%-90%, and their proportion of functionally significant lesions (FFRs ≤ 0.80) was significantly lower than that of younger patients. This suggests that despite similar angiographic appearances, elderly patients have fewer functionally significant lesions, a characteristic not demonstrated in this study. According to the QCA across different levels of stenosis, there was no significant difference in QFR between patients younger than 65 years and those 65 years or older. Similarly, for highly stenotic lesions (diameter stenosis: 71%-90%), there was no difference in the proportion of lesions with a QFR < 0.80 between younger (< 65 years) and older (≥ 65 years) patients (Supplementary Table 2). Another study, which conducted a *post hoc* analysis of 690 coronary pressure wire recordings from 591 patients, showed that the younger group (aged 33–58 years) was more likely to have a positive FFR and negative iFR at a given stenosis level, while the opposite was true for the elderly group (aged 59–69 years or older 70 years). As age increased, the tendency for positive iFR cases under negative FFR conditions also increased. The high vascular response to adenosine was significantly dampened with patient age, suggesting that the microvascular response to adenosine-induced vasodilation diminishes with age, leading to an increase in FFR, while iFR appears to be unaffected.[22] Since the QFR is independent of the maximum hyperaemic state, the results of this study not only show that the QFR has a beneficial role in guiding the PCI strategy in elderly patients but also suggest that for elderly patients, the QFR may be a better choice. From another perspective, in the elderly population, due to a higher incidence of comorbidities and more complex coronary anatomy, there is an increased risk of intolerance to adenosine or complications related to wire manipulation, which confers additional theoretical advantages to QFR.

The present study has several limitations. First, the results of this subgroup analysis should not be generalized to patients with complex multi-vascular or left main disease or to those with acute or subacute (< 72 h) MI. Second, the basic information used did not include features related to age, which may have led us to underestimate the efficacy of the overall model. Therefore, the evaluation power was relatively low for patients < 55 years or ≥ 75 years. Third, the overall SYNTAX score of these patients was not high, indicating that no particularly complex lesions were included, and the inclusion of patients with complex lesions needs to be increased. The microcirculation parameters were not included in the discussion of this study and can be considered in future research to assess the diagnostic efficacy of the QFR in different microcirculation states. Finally, current studies have shown that postoperative FFR can guide the optimal treatment and prognosis of complex lesions, while the accuracy and application scenarios of postoperative QFR still need more research.

## Conclusions

Although the benefits of coronary artery functional guidance for PCI have been widely recognized, its clinical application is not optimal. Compared with coronary angiography-guided treatment, QFR-guided PCI can significantly reduce the incidence of adverse events, streamline the procedures, and reduce costs. In addition, due to their convenience and safety, more extensive application scenarios can greatly improve the proportion of functional assessment methods and optimize the majority of PCI treatments. This study further showed that although the basic clinical information and severity of lesions may differ between age groups, the clinical benefits of QFR-guided PCI treatment are similar. This finding again highlights the importance of functional assessment for optimizing the PCI and increases trust in the use of non-invasive and safe QFR technology in elderly patients.

## CONFLICT OF INTERESTS

None.

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