Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial

Bo Xu, Shengxian Tu*, Lei Song*, Zening Jin, Bo Yu, Guosheng Fu, Yujie Zhou, Jian'an Wang, Yundai Chen, Jun Pu, Lianglong Chen, Xinkai Qu, Junqing Yang, Xuebo Liu, Lijun Guo, Chengxing Shen, Yaojun Zhang, Qi Zhang, Hongwei Pan, Xiaogang Fu, Jian Liu, Yanyan Zhao, Javier Escaned, Yang Wang, William F Fearon, Kefei Dou, Ajay J Kirtane, Yongjian Wu, Patrick W Serruys, Weixian Yang, William Wijns, Changdong Guan, Martin B Leon†, Shubin Qiao*†, Gregg W Stone†, and the FAVOR III China study group‡*

Summary

Background Compared with visual angiographic assessment, pressure wire-based physiological measurement more accurately identifies flow-limiting lesions in patients with coronary artery disease. Nonetheless, angiography remains the most widely used method to guide percutaneous coronary intervention (PCI). In FAVOR III China, we aimed to establish whether clinical outcomes might be improved by lesion selection for PCI using the quantitative flow ratio (QFR), a novel angiography-based approach to estimate the fractional flow reserve.

Methods FAVOR III China is a multicentre, blinded, randomised, sham-controlled trial done at 26 hospitals in China. Patients aged 18 years or older, with stable or unstable angina pectoris or patients who had a myocardial infarction at least 72 h before screening, who had at least one lesion with a diameter stenosis of 50–90% in a coronary artery with a reference vessel of at least 2·5 mm diameter by visual assessment were eligible. Patients were randomly assigned to a QFR-guided strategy (PCI performed only if QFR ≤0·80) or an angiography-guided strategy (PCI based on standard visual angiographic assessment). Participants and clinical assessors were masked to treatment allocation. The primary endpoint was the 1-year rate of major adverse cardiac events, a composite of death from any cause, myocardial infarction, or ischaemia-driven revascularisation. The primary analysis was done in the intention-to-treat population. The trial was registered with ClinicalTrials.gov (NCT03656848).

Findings Between Dec 25, 2018, and Jan 19, 2020, 3847 patients were enrolled. After exclusion of 22 patients who elected not to undergo PCI or who were withdrawn by their physicians, 3825 participants were included in the intention-to-treat population (1913 in the QFR-guided group and 1912 in the angiography-guided group). The mean age was 62·7 years (SD 10·1), 2699 (70·6%) were men and 1126 (29·4%) were women, 1295 (33·9%) had diabetes, and 2428 (63·5%) presented with an acute coronary syndrome. The 1-year primary endpoint occurred in 110 (Kaplan-Meier estimated rate 5·8%) participants in the QFR-guided group and in 167 (8·8%) participants in the angiography-guided group (difference, –3·0% [95% CI –4·7 to –1·4]; hazard ratio 0·65 [95% CI 0·51 to 0·83]; p=0·0004), driven by fewer myocardial infarctions and ischaemia-driven revascularisations in the QFR-guided group than in the angiography-guided group.

Interpretation In FAVOR III China, among patients undergoing PCI, a QFR-guided strategy of lesion selection improved 1-year clinical outcomes compared with standard angiography guidance.

Funding Beijing Municipal Science and Technology Commission, Chinese Academy of Medical Sciences, and the National Clinical Research Centre for Cardiovascular Diseases, Fuwai Hospital.

Introduction

In patients with obstructive coronary artery disease, angiography-based visual assessment remains the most widely used method to guide percutaneous coronary intervention (PCI).[1] Compared with visual assessment, pressure wire-based physiological measurement with or without the administration of hyperaemia-inducing agents more accurately identifies flow-limiting lesions than angiography alone.[2–6] Randomised trials have demonstrated that pressure wire-based physiology-guided lesion selection for PCI improves clinical outcomes.[4,6–10] Despite the strong recommendation in the 2018 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularisation to use pressure wire-based physiology to assess the haemodynamic relevance of intermediate-grade stenoses if evidence of ischaemia is not otherwise available,[5] this method is largely underused in practice because of long procedural time, potential complications from pressure wire instrumentation, side-effects from hyperaemic agents, and costs.[11–13]

Published **Online** November 4, 2021 https://doi.org/10.1016/S0140-6736(21)02248-0

See **Online/Comment** https://doi.org/10.1016/S0140-6736(21)02397-7

*Contributed equally

†Joint senior authors

‡All investigators are listed in the appendix (pp 2–4)

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 (B Xu MBBS, L Song MD, Prof K Dou MD, Prof Y Wu MD, Prof W Yang MD, C Guan MSc, Prof S Qiao MD); **Biomedical Instrument Institute, School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China** (Prof S Tu PhD); **Department of Cardiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China** (Prof Z Jin MD); **Department of Cardiology, the Second Affiliated Hospital of Harbin Medical University, Harbin, China** (Prof B Yu MD); **Department of Cardiology, Sir Run Run Shaw Hospital** (Prof G Fu MD) **and Department of Cardiology, Second Affiliated Hospital** (Prof J Wang MD), **Zhejiang University School of Medicine, Hangzhou, China; Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China** (Prof Y Zhou MD); **Department of Cardiology, the Sixth Medical Centre, Chinese PLA General Hospital, Beijing, China** (Prof Y Chen MD); **Department of Cardiology, Renji Hospital, School of Medicine, Shanghai**

Jiao Tong University, Shanghai, China (Prof J Pu MD); Department of Cardiology, Fujian Medical University Union Hospital, Fuzhou, China (Prof L Chen MD); Department of Cardiology, Huadong Hospital Affiliated to Fudan University, Shanghai, China (Prof X Qu MD); Department of Cardiology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China (J Yang MD); Department of Cardiology, Tongji Hospital (Prof X Liu MD) and Department of Cardiology, Shanghai East Hospital (Prof Q Zhang MD), Tongji University School of Medicine, Shanghai, China; Department of Cardiology, Peking University Third Hospital, Beijing, China (Prof L Guo MD); Department of Cardiology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China (Prof C Shen MD); Department of Cardiology, Xuzhou Third People's Hospital, Xuzhou Medical University, Xuzhou, China (Y Zhang MD); Department of Cardiology, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China (Prof H Pan MD); Shanghai Jiao Tong University-Pulse Medical Imaging Technology Joint Laboratory, Shanghai, China (X Fu MSc); Department of Cardiology, Peking University People's Hospital, Beijing, China (Prof J Liu MD); Medical Research and Biometrics Centre, National Centre for Cardiovascular Diseases, Beijing, China (Y Zhao MSc, Y Wang MSc); Hospital Clínico San Carlos IDISSC, Complutense University of Madrid, Madrid, Spain (J Escaned MD); Division of Cardiovascular Medicine and Stanford Cardiovascular Institute, Stanford University School of Medicine and VA Palo Alto Health Care System, Palo Alto, CA, USA (Prof W F Fearon MD); NewYork-Presbyterian Hospital/Columbia University Medical Centre, New York, NY, USA (Prof A J Kirtane MD, Prof M B Leon MD); The Cardiovascular Research Foundation, New York, NY, USA (Prof A J Kirtane, Prof M B Leon,

Research in context

Evidence before this study

We searched PubMed for reports published in English up to Aug 28, 2021, to identify relevant published clinical studies using the search terms "randomised trial", "meta-analysis", AND "angiography-derived FFR" OR "quantitative flow ratio" OR "FFRangio". This search demonstrated that, to date, no randomised clinical trial comparing an angiography-derived fractional flow reserve guided strategy with a standard angiography-guided strategy for lesion selection in patients undergoing percutaneous coronary intervention (PCI) has been performed. Pressure wire-based physiological assessment with fractional flow reserve and the instantaneous wave-free ratio more accurately identify flow-limiting lesions than angiographic assessment alone. In previous randomised trials, clinical outcomes after PCI were improved when lesions were identified for treatment (or deferral) on the basis of fractional flow reserve rather than angiography. Nevertheless, PCI guided by physiological lesion assessment is underused in practice because of prolonged procedural time, potential complications from pressure wire instrumentation, side-effects from hyperaemic agents, and higher costs. The quantitative flow ratio (QFR) is a novel computational approach in which fractional flow reserve is estimated in real time using three dimensional coronary artery reconstruction and computational fluid dynamics from the standard angiogram. Previous studies have demonstrated a strong correlation between QFR and fractional flow reserve.

Added value of this study

FAVOR III China is the first randomised trial to compare the clinical outcomes of PCI guided by angiography-derived physiological lesion selection and standard angiography-guided lesion selection. QFR guidance resulted in a 35% risk reduction in the 1-year rate of major adverse cardiac events, a composite of death from any cause, myocardial infarction, or ischaemia-driven revascularisation, compared with standard angiography guidance. The benefit was driven mainly by fewer myocardial infarctions (including both periprocedural and non-procedural myocardial infarctions) and fewer ischaemia-driven revascularisations, with similar mortality between groups. Additionally, QFR guidance led to use of fewer stents and less contrast and patient radiation exposure, as well as shorter procedural time.

Implications of all the available evidence

In patients undergoing PCI, a QFR-guided strategy improved 1-year clinical outcomes compared with standard angiography guidance while reducing resource consumption. QFR is simpler to implement than wire-based physiological measurements, which should facilitate the adoption of physiological lesion assessment into routine clinical practice.

The quantitative flow ratio (QFR), derived from three dimensional (3D) coronary artery reconstruction and fluid dynamics computations from the angiogram, enables online estimation of the fractional flow reserve without the use of a pressure wire or pharmacological agents to induce hyperaemia.[14] Previous studies in China,[15] Europe, and Japan[16] have demonstrated the feasibility and accuracy of online QFR assessment in assessing the haemodynamic significance of coronary stenoses compared with pressure wire-based fractional flow reserve measurement. Whether lesion selection for PCI using a QFR-guided strategy might improve outcomes compared with a standard angiography-guided strategy is unknown. We therefore performed the Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease (FAVOR III China) randomised trial to assess the use of QFR guidance in patients who have PCI.

Methods

Study design

The trial design and rationale have been described previously.[17] FAVOR III China was an investigator-initiated, multicentre, blinded, randomised, sham-controlled trial done at 26 hospitals in China (appendix pp 2–4). The trial was designed by the principal investigators, steering committee, and an international advisory board. An independent data safety and monitoring board approved the trial protocol and monitored patient safety at regular intervals (appendix pp 4–6). The trial was approved by the ethics committee at each participating site, and all patients provided written informed consent.

Participants

Adults (≥18 years) in whom PCI was planned on the basis of angiographic assessment were eligible. Further eligibility criteria were stable or unstable angina pectoris; or a myocardial infarction at least 72 h before screening, with at least one lesion with a percentage diameter stenosis of 50–90% in a coronary artery with at least a 2·5 mm reference vessel diameter by visual assessment. Principal exclusion criteria were moderate or severe chronic kidney disease (defined as creatinine >150 μmol/L or estimated glomerular filtration rate <45 mL/kg per 1·73 m²) and severe vessel tortuosity, vessel overlap, or suboptimal angiography likely to preclude QFR determination. Complete inclusion and exclusion criteria are in the appendix (p 7).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio to QFR-guided PCI (intervention group) or angiography-guided PCI (control group) via an internet-enabled web-based response system in block sizes of 6. Randomisation was stratified by diabetes, multivessel disease, the presence of any vessel with diameter stenosis

greater than 90% with Thrombolysis in Myocardial Infarction (TIMI) flow less than 3, and study centre.

The patients and all post-catheterisation laboratory physicians and research personnel were masked to randomisation allocation. To ensure participant masking, patients in both groups wore music-playing headphones during the procedure and had a preset 10-min delay for real or sham QFR calculation before PCI. A masking questionnaire was administered to each patient at discharge and at 6 months and 1 year after the procedure to assess the success of randomisation concealment and the perception of treatment allocation. Complete details of the masking methods are in the appendix (p 9).

Procedures

The target vessels intended to be treated with standard angiography guidance were declared by the operator and recorded before randomisation. In the QFR-guided group, QFR was measured in all coronary arteries containing any lesion with visually assessed diameter stenosis of at least 50% up to 90% and reference vessel diameter of at least 2·5 mm. Following a standard operating procedure as described in the appendix (pp 10–11), two angiographic imaging runs with minimum 25° separation in projection angle were taken and the data was transmitted to the AngioPlus system (Pulse Medical Imaging Technology, Shanghai, China) by a local network of sites for real-time QFR calculation. A pullback curve displays the QFR value at each position of the target vessel. PCI treatment was performed in all lesions with QFR of 0·80 or less and was deferred in lesions with QFR greater than 0·80. PCI was also performed in all lesions with angiographic diameter stenosis greater than 90%. If no lesions had a diameter of stenosis greater than 90% and all interrogated vessels had QFR greater than 0·80, the patient was treated with medical therapy alone.

In the angiography-guided group, PCI was performed on the basis of visual angiographic assessment according to local standard practice. Per protocol, pressure wire-based physiological assessment was not allowed in either treatment group. In both groups, a planned staged PCI procedure was allowed in patients with multivessel disease within 60 days after the index procedure. Patients were followed up by telephone or clinic visits at 1 and 6 months and 1, 2, and 3 years after randomisation. Optimal medical therapy was required in both groups during follow-up based on physician decision and local standard practice (appendix p 12).

Clinical outcomes were adjudicated by an independent clinical events committee masked to randomisation. An angiographic core laboratory performed offline QFR measurements in both groups, in addition to standard quantitative coronary angiographic analyses.

Outcomes

The primary endpoint was the 1-year rate of major adverse cardiac events, defined as the composite of death from any cause, myocardial infarction, or ischaemia-driven revascularisation. The major secondary endpoint was the 1-year rate of major adverse cardiac events excluding periprocedural myocardial infarction arising from the index or planned staged procedures (appendix pp 7–9). Other secondary endpoints were lesion success (residual stenosis <30% for patients treated with stents or 50% for patients treated with drug-coated balloon by visual estimation, with TIMI flow grade 3, in the treated vessel) and procedural success; major adverse cardiac events at 1 and 6 months and 2 and 3 years; death, myocardial infarction, target vessel revascularisation, any revascularisation, and stent thrombosis at 1 and 6 months and 1, 2, and 3 years; PCI strategy changes; and cost-effectiveness at 1 and 6 months and 1 year.

Statistical analysis

The trial was powered for the primary and major secondary endpoints. We assumed a 1-year rate of major adverse cardiac events in the angiography-guided group of 8·7% from two large multicentre clinical trials in which physiology was not used,[18,19] and an event rate of 6·1% in the QFR-guided group from clinical trials using physiological assessment.[9,10] Accounting for a 5% loss to follow-up, 3830 patients provided 85% power to demonstrate that the QFR-guided strategy was superior to the angiography-guided strategy at a one-sided 0·025 significance level. For the major secondary endpoint, assuming 1-year rates of major adverse cardiac events excluding periprocedural myocardial infarction of 6·0% in the angiography-guided group[18,19] and 4·0% in the QFR-guided group,[9,10] 3830 patients provided 80% power to demonstrate superiority at a one-sided α level of 0·025.

Data were collected and analysed according to the predefined statistical analysis plan. The primary and major secondary endpoints were analysed in the intention-to-treat population for the principal analysis and in the per-protocol population as a sensitivity analysis. Protocol deviations included violations in key inclusion or exclusion criteria, any inconsistency between actual treatment and preprocedural intended treatment plan in the angiography-guided group, the QFR measurement not performed per protocol in the QFR-guided group, and treatment not performed based on QFR measurements in the QFR-guided group. Categorical variables were compared between the two groups using the likelihood ratio χ^2 test or Fisher's exact test. Continuous variables with normal distributions were compared using two sample *t* tests, and non-normal continuous data were compared with the Wilcoxon rank-sum test. The time-to-first event rates for each group were estimated using Kaplan-Meier methods and were compared by the log-rank test. Between-group differences were estimated by hazard ratios (HRs) with 95% CIs using a Cox proportional hazards model. Sensitivity analyses of the primary and major secondary endpoints were done by

Prof G W Stone MD); **The Zena and Michael A Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof G W Stone); **Department of Cardiology, National University of Ireland, Galway, Ireland** (Prof P W Serruys MD); **NHLI, Imperial College London, London, UK** (Prof P W Serruys); **The Lambe Institute for Translational Medicine and Curam, National University of Ireland, Galway, Ireland** (Prof W Wijns MD)

Correspondence to:
Dr Bo Xu, 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 100037, China
bxu@citmd.com

See **Online** for appendix

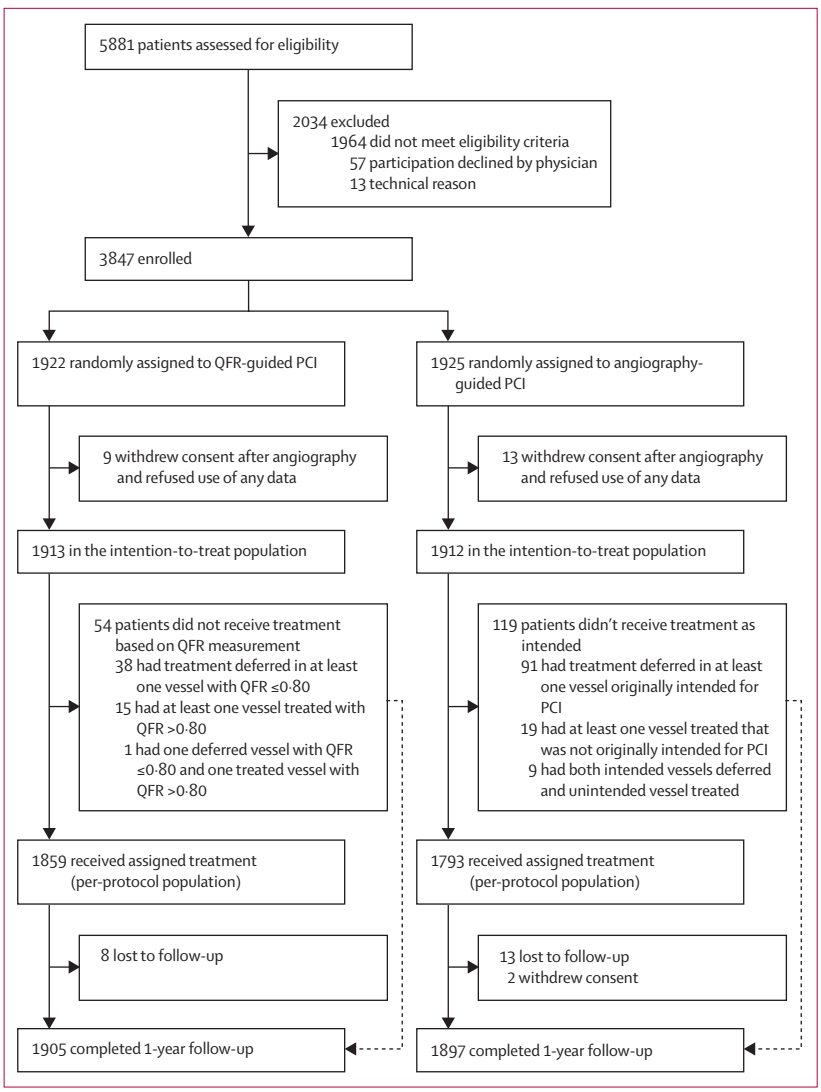

Figure 1: **Trial profile**
PCI=percutaneous coronary intervention. QFR=quantitative flow ratio.

multivariable Cox regression: model 1 included study centre as a random effect; model 2 included the three stratification factors (diabetes, multivessel disease, and the presence of any vessel with diameter stenosis >90% with TIMI flow <3) as fixed effects and study centre as a random effect; and model 3 included the three stratification factors (diabetes, multivessel disease, and the presence of any vessel with diameter stenosis >90% with TIMI flow <3) and additional baseline covariates (age, sex, hypertension, hypercholesterolaemia, previous myocardial infarction, clinical presentation, and anatomic Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery [SYNTAX] score) as fixed effects and study centre as a random effect. All analyses were performed with SAS software, version 9.4. The trial was registered with ClinicalTrials.gov (NCT03656848).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Dec 25, 2018, and Jan 19, 2020, 5881 patients were screened for enrolment, 3847 (65·4%) of whom were enrolled. The most common reasons for screening failure were inappropriate anatomy for PCI (n=526) and absence of at least one lesion with diameter stenosis 50–90% and reference vessel diameter of at least 2·5 mm (n=860; appendix p 27). After randomisation, 22 participants withdrew consent and refused use of any data, 17 of whom elected not to undergo PCI and five of whom were withdrawn by their physicians. Thus, 3825 patients were included in the intention-to-treat population (1913 in the QFR-guided group and 1912 in the angiography-guided group; figure 1; appendix pp 25–26). Baseline clinical characteristics were well balanced between the groups (table 1). The mean age was 62·7 years (SD 10·1), 2699 (70·6%) were men and 1126 (29·4%) were women, 1295 (33·9%) had diabetes, and 2428 (63·5%) presented with an acute coronary syndrome (unstable angina or post myocardial infarction). Patients were effectively masked to their assignment at 1-year follow-up (appendix pp 28–29). Medication use between groups was similar other than antiplatelet therapy (appendix pp 30–31).

Angiographic characteristics were balanced between the groups (table 1). The mean QFR calculation time was 3·9 min (SD 1·4) per patient. Notwithstanding 2–3 min for data transmission, the overall duration for establishing QFR was less than the preset 10-min delay for both groups to preserve masking. The pre-randomisation vessel revascularisation plan was changed in 445 (23·3%) of 1913 patients in the QFR-guided group compared with 119 (6·2%) of 1912 in the angiography-guided group, mainly due to treatment deferral (non-treatment) of at least one vessel originally intended for PCI (375 [19·6%] in the QFR group *vs* 100 [5·2%] in the angiography group) but also unplanned treatment of at least one vessel not originally intended for PCI (85 [4·4%] *vs* 28 [1·5%]; table 2). As a result of the greater rate of treatment deferral in the QFR group than the angiography group, PCI was performed in a smaller proportion of patients in the QFR-guided group (1731 [90·5%]) than in the angiography-guided group (1895 [99·1%]). Fewer stents and less contrast were also used in the QFR-guided group, with shorter fluoroscopy and procedure times.

Angiographic and QFR measurements are in the appendix (p 32–33). From offline QFR analysis by the core laboratory, a greater proportion of lesions with QFR 0·80 or less were treated in the QFR-guided group than in the angiography-guided group (1990 [96·7%] of 2058 lesions *vs* 1843 [91·1%] of 2023 lesions), and the proportion of patients achieving complete functional revascularisation (no residual ischaemia according to

	QFR-guided group (n=1913)	Angiography-guided group (n=1912)
Age, years	62·7 (10·1)	62·7 (10·2)
Gender		
Men	1349 (70·5%)	1350 (70·6%)
Women	564 (29·5%)	562 (29·4%)
Body-mass index, kg/m²	25·1 (22·9–27·0)	24·7 (22·7–27·0)
Diabetes	648 (33·9%)	647 (33·8%)
Use of insulin	166 (8·7%)	181 (9·5%)
Hypertension	1270 (66·4%)	1252 (65·5%)
Hypercholesterolaemia	729 (38·1%)	728 (38·1%)
Cigarette smoking		
Current smoker	574 (30·0%)	568 (29·7%)
Former smoker	284 (14·8%)	282 (14·7%)
Never smoked	1055 (55·1%)	1062 (55·5%)
Family history of coronary artery disease	147 (7·7%)	149 (7·8%)
Previous myocardial infarction	179 (9·4%)	179 (9·4%)
Previous percutaneous coronary intervention	485 (25·4%)	466 (24·4%)
Previous coronary artery bypass grafting	5 (0·3%)	4 (0·2%)
Previous stroke	184 (9·6%)	175 (9·2%)
Peripheral artery disease	55 (2·9%)	71 (3·7%)
Clinical presentation*		
Asymptomatic ischaemia	207 (10·8%)	204 (10·7%)
Stable angina	493 (25·8%)	493 (25·8%)
Unstable angina	1111 (58·1%)	1110 (58·1%)
Post myocardial infarction (within 30 days)	102 (5·3%)	105 (5·5%)
Stable angina (Canadian Cardiovascular Society functional classification)		
I	176/493 (35·7%)	191/493 (38·7%)
II	164/493 (33·3%)	146/493 (29·6%)
III	103/493 (20·9%)	93/493 (18·9%)
IV	50/493 (10·1%)	63/493 (12·8%)
Unstable angina (Braunwald class)		
I	511/1111 (46·0%)	511/1110 (46·0%)
II	510/1111 (45·9%)	503/1110 (45·3%)
III	90/1111 (8·1%)	96/1110 (8·6%)
Estimated glomerular filtration rate (Cockcroft-Gault formula), mL/min per 1·73m²	70·3 (58·4–83·4)	70·0 (58·0–83·9)
Left ventricular ejection fraction, %	63·0 (61·0–66·0)	63·0 (60·0–66·0)
Number of diseased vessels reported		
One-vessel disease	890 (46·5%)	869 (45·4%)
Two-vessel disease	674 (35·2%)	684 (35·8%)
Three-vessel disease	306 (16·0%)	316 (16·5%)
Left main disease	43 (2·2%)	43 (2·2%)
Any vessel with one or more lesions with diameter stenosis >90% and TIMI flow <3	170 (8·9%)	182 (9·5%)
Anatomic SYNTAX score†	9·3 (6·0)	9·6 (6·3)
Functional SYNTAX score‡	8·1 (6·3)	8·0 (6·6)

Data are mean (SD), n (%), median (IQR), or n/N (%). Data on race were not collected. QFR=quantitative flow ratio. SYNTAX=Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. TIMI=Thrombolysis in Myocardial Infarction. *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 centres. †The anatomic SYNTAX score is a scoring system that quantifies angiographic lesion extent and complexity; it was calculated by the angiographic core laboratory. ‡The functional SYNTAX score was calculated by summing the segmental anatomic SYNTAX scores only in vessels with functional ischaemia as defined by offline QFR ≤0·80 as established by the angiographic core laboratory.

Table 1: **Baseline clinical and angiographic characteristics**

post-PCI QFR assessment) was higher in the QFR-guided group (1669 [88·1%] of 1894 *vs* 1552 [82·2%] of 1887 patients with functional SYNTAX score available; table 2).

The composite primary endpoint occurred within 1 year in 110 (Kaplan-Meier estimated rate 5·8%) of 1913 patients in the QFR-guided group and in 167 (8·8%) of 1912 patients

	QFR-guided group (n=1913)	Angiography-guided group (n=1912)	p value
Radial artery approach	1885 (98·5%)	1869 (97·8%)	0·071
PCI performed	1731 (90·5%)	1895 (99·1%)	<0·0001
Drug-eluting stents placed	1667 (87·1%)	1812 (94·8%)	<0·0001
Drug-coated balloon angioplasty	55 (2·9%)	58 (3·0%)	0·77
Non-drug-coated balloon angioplasty	9 (0·5%)	25 (1·3%)	0·0049
Number of stents placed per patient	1·45 (1·02)	1·58 (0·97)	<0·0001
Stent length, mm	42·7 (26·3)	41·9 (26·3)	0·36
Stent diameter, mm	3·03 (0·41)	3·01 (0·41)	0·34
Use of pressure wire-based physiology	2 (0·1%)	1 (0·1%)	0·56
Use of intravascular imaging*	119 (6·2%)	121 (6·3%)	0·89
Contrast medium used per patient, mL	163·0 (75·6)	169·7 (74·2)	0·0060
Fluoroscopy time, min	14·1 (8·0)	14·9 (7·4)	0·0013
Procedure time, min†	53·7 (30·4)	59·4 (30·4)	<0·0001
Adjusted procedure time, min†	44·6 (28·8)	49·5 (30·2)	<0·0001
PCI lesion success‡	2245/2267 (99·0%)	2561/2580 (99·3%)	0·38
PCI procedure success§	1657/1731 (95·7%)	1796/1895 (94·8%)	0·18
Vessels intended to be treated pre randomisation			
Left main	33/2503 (1·3%)	40/2559 (1·6%)	0·46
Left anterior descending	1317/2503 (52·6%)	1281/2559 (50·1%)	0·069
Left circumflex	522/2503 (20·9%)	585/2559 (22·9%)	0·084
Right coronary artery	631/2503 (25·2%)	653/2559 (25·5%)	0·80
Vessels actually treated of those originally intended	2112/2503 (84·4%)	2449/2559 (95·7%)	<0·0001
Left main	29/2112 (1·4%)	38/2449 (1·6%)	0·62
Left anterior descending	1174/2112 (55·6%)	1239/2449 (50·6%)	0·0007
Left circumflex	418/2112 (19·8%)	557/2449 (22·7%)	0·015
Right coronary artery	491/2112 (23·2%)	615/2449 (25·1%)	0·14
Patients with intended vessel deferral or unintended vessel treatment	445 (23·3%)	119 (6·2%)	<0·0001
Deferral (non-treatment) of at least one vessel originally intended for PCI	375 (19·6%)	100 (5·2%)	<0·0001
Treatment of at least one vessel not originally intended for PCI	85 (4·4%)	28 (1·5%)	<0·0001
Residual anatomic SYNTAX score	2·4 (3·6)	2·4 (4·0)	0·49
Residual functional SYNTAX score	0·7 (2·3)	1·0 (2·8)	<0·0001
Residual functional SYNTAX score of 0	1669/1894 (88·1%)	1552/1887 (82·2%)	<0·0001

Data are n (%), mean (SD), or n/N (%). PCI=percutaneous coronary intervention. QFR=quantitative flow ratio. SYNTAX=Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. *Intravascular ultrasound or optical coherence tomography. †Procedure time was defined as the time between the first and last angiogram, including diagnostic coronary angiography, the randomisation process, QFR calculation time or 10-min sham control time, and PCI time; in the adjusted procedure time, the mandated 10-min delay for the real or sham QFR calculation was subtracted. ‡Defined as residual stenosis less than 30% for patients treated with stents or less than 50% for patients treated with balloon angioplasty by visual estimation, with Thrombolysis in Myocardial Infarction flow grade 3 in the treated vessel. §Defined as lesion success in all treated lesions without in-hospital major adverse cardiac events (up to a maximum of 7 days).

Table 2: **Procedural characteristics**

in the angiography-guided group (difference –3·0% [95% CI –4·7 to –1·4; HR 0·65 [95% CI 0·51 to 0·83]; p=0·0004; figure 2, table 3). The composite major secondary endpoint occurred within 1 year in 59 (3·1%) patients in the QFR-guided group and in 91 (4·8%) patients in the angiography-guided group (difference –1·7% [–2·9 to –0·5]; HR 0·64 [0·46 to 0·89]; p=0·0078). Results were similar in the per-protocol population (primary endpoint HR 0·70 [0·55 to 0·90]; major secondary endpoint HR 0·68 [0·48 to 0·96]; appendix pp 14–19) and after multivariable adjustment (appendix p 34). The relative treatment effects for the primary and major secondary endpoints were consistent across subgroups, except for the major secondary endpoint, which favoured the QFR-guided strategy more so in women than men (figure 3; appendix p 20).

The between-group differences in the primary and secondary composite outcomes were driven by lower rates of myocardial infarction (65 [3·4%] of 1913 in the QFR group *vs* 109 [5·7%] of 1912 in the angiography group) and ischaemia-driven revascularisation (38 [2·0%] *vs* 59 [3·1%]) in the QFR group than in the angiography group, with similar mortality rates (appendix pp 21–24). The rates of both periprocedural myocardial infarction (56 [2·9%] *vs* 81 [4·2%]) and non-procedural myocardial infarction (10 [0·5%] *vs* 30 [1·6%]) were lower in the QFR group than in the angiography group (table 3). In a

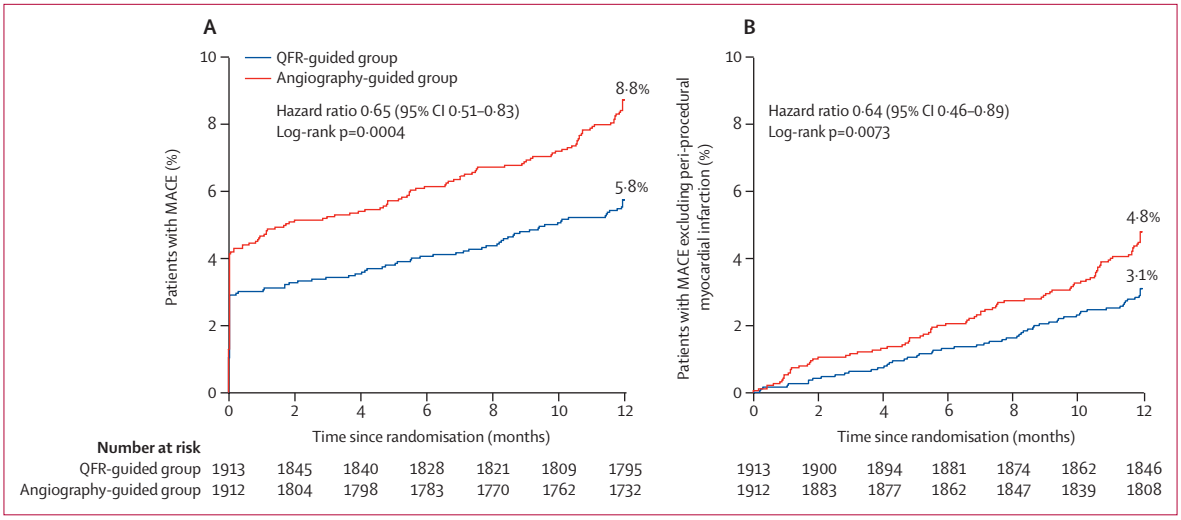

Figure 2: **Kaplan-Meier curves for the primary (A) and major secondary (B) endpoints in the intention-to-treat population**
MACE=major adverse cardiac events. QFR=quantitative flow ratio.

	QFR-guided group (n=1913)	Angiography-guided group (n=1912)	Hazard ratio (95% CI)	p value
Primary endpoint				
MACE	110 (5·8%)	167 (8·8%)	0·65 (0·51–0·83)	0·0004
Death from any cause	13 (0·7%)	9 (0·5%)	1·44 (0·62–3·37)	0·40
Myocardial infarction	65 (3·4%)	109 (5·7%)	0·59 (0·44–0·81)	0·0008
Ischaemia-driven revascularisation	38 (2·0%)	59 (3·1%)	0·64 (0·43–0·96)	0·031
Major secondary endpoint				
MACE excluding periprocedural myocardial infarction	59 (3·1%)	91 (4·8%)	0·64 (0·46–0·89)	0·0078
Other secondary endpoints				
Cardiovascular death	9 (0·5%)	7 (0·4%)	1·28 (0·48–3·44)	0·62
Non-cardiovascular death	4 (0·2%)	2 (0·1%)	1·99 (0·37–10·9)	0·43
Periprocedural myocardial infarction	56 (2·9%)	81 (4·2%)	0·69 (0·49–0·97)	0·033
Non-procedural myocardial infarction	10 (0·5%)	30 (1·6%)	0·33 (0·16–0·68)	0·0025
Any revascularisation	49 (2·6%)	67 (3·5%)	0·73 (0·50–1·05)	0·089
Target vessel revascularisation*	22 (1·2%)	25 (1·3%)	0·88 (0·50–1·56)	0·66
Ischaemia-driven	18 (1·0%)	21 (1·1%)	0·86 (0·46–1·61)	0·63
Target lesion revascularisation	17 (0·9%)	23 (1·2%)	0·74 (0·39–1·38)	0·34
Ischaemia-driven	16 (0·8%)	19 (1·0%)	0·84 (0·43–1·64)	0·61
Non-target lesion revascularisation	5 (0·3%)	4 (0·2%)	1·25 (0·34–4·65)	0·74
Ischaemia-driven	2 (0·1%)	4 (0·2%)	0·50 (0·09–2·73)	0·42
Non-target vessel revascularisation†	32 (1·7%)	45 (2·4%)	0·71 (0·45–1·11)	0·13
Ischaemia-driven	22 (1·2%)	40 (2·1%)	0·55 (0·32–0·92)	0·022
Stent thrombosis, definite or probable	3 (0·2%)	6 (0·3%)	0·50 (0·12–1·99)	0·33
Definite	1 (0·1%)	3 (0·2%)	0·33 (0·03–3·20)	0·34
Probable	2 (0·1%)	3 (0·2%)	0·66 (0·11–3·98)	0·65

Data are n (Kaplan-Meier estimated %) unless otherwise stated. The primary endpoint was the 1-year rate of MACE, defined as the composite of death from any cause, myocardial infarction, or ischaemia-driven revascularisation. MACE=major adverse cardiac events. PCI=percutaneous coronary intervention. QFR=quantitative flow ratio.
*Revascularisation of vessels that were actually treated with PCI after randomisation. †Revascularisation of vessels in which PCI was not previously performed.

Table 3: **1-year clinical outcomes**

sensitivity analysis, the rates of periprocedural myocardial infarction using alternative definitions were lower in the QFR group than the angiography group (appendix p 35). In a post-hoc analysis, the lower rate of events in the QFR group was attributable to fewer events arising both from treated and deferred vessels (appendix pp 36–37).

	QFR-guided group (n=1913)	Angiography-guided group (n=1912)	Hazard ratio (95% CI)	$p_{interaction}$
	n/N (%)	n/N (%)		
Age, years				0·99
<65	58/1050 (5·5%)	89/1058 (8·4%)	0·65 (0·47–0·91)	
≥65	52/863 (6·0%)	78/854 (9·2%)	0·65 (0·46–0·92)	
Gender				0·37
Men	77/1349 (5·7%)	109/1350 (8·1%)	0·70 (0·52–0·93)	
Women	33/564 (5·9%)	58/562 (10·4%)	0·56 (0·36–0·86)	
Diabetes				0·88
Yes	40/648 (6·2%)	62/647 (9·6%)	0·64 (0·43–0·95)	
No	70/1265 (5·6%)	105/1265 (8·3%)	0·66 (0·49–0·89)	
Acute coronary syndrome*				0·27
Yes	70/1213 (5·8%)	96/1215 (7·9%)	0·72 (0·53–0·98)	
No	40/700 (5·7%)	71/697 (10·2%)	0·55 (0·37–0·81)	
Smoking history				0·34
Current	28/574 (4·9%)	45/568 (7·9%)	0·60 (0·38–0·97)	
Former	15/284 (5·3%)	32/282 (11·4%)	0·45 (0·24–0·83)	
Never	67/1055 (6·4%)	90/1062 (8·5%)	0·74 (0·54–1·02)	
Body-mass index, kg/m²				0·32
<30	100/1772 (5·7%)	150/1780 (8·5%)	0·66 (0·51–0·85)	
≥30	8/126 (6·4%)	17/119 (14·3%)	0·43 (0·18–0·99)	
Left ventricular ejection fraction				0·16
≤45%	7/43 (17·0%)	8/66 (12·2%)	1·38 (0·50–3·80)	
>45%	99/1758 (5·6%)	152/1738 (8·8%)	0·63 (0·49–0·82)	
Lesion location†				0·81
Only left main or left anterior descending artery	45/905 (5·0%)	60/843 (7·1%)	0·69 (0·47–1·02)	
Only left circumflex or right coronary artery	30/567 (5·3%)	45/595 (7·6%)	0·69 (0·43–1·09)	
Others	35/441 (8·0%)	62/474 (13·1%)	0·59 (0·39–0·89)	
Lesion length†, mm				0·41
<20	36/974 (3·7%)	61/951 (6·5%)	0·57 (0·38–0·86)	
≥20	74/931 (8·0%)	104/946 (11·0%)	0·71 (0·53–0·96)	
Reference vessel diameter†, mm				0·45
<2·5	47/704 (6·7%)	79/715 (11·1%)	0·59 (0·41–0·85)	
≥2·5	63/1204 (5·3%)	87/1189 (7·3%)	0·71 (0·51–0·98)	
Stenosis severity†				0·60
Percentage diameter stenosis <70%	73/1407 (5·2%)	102/1367 (7·5%)	0·69 (0·51–0·93)	
Percentage diameter stenosis ≥70%	37/501 (7·4%)	64/537 (12·0%)	0·61 (0·41–0·91)	
Multivessel disease‡				0·19
Yes	72/1023 (7·1%)	122/1043 (11·7%)	0·59 (0·44–0·79)	
No	38/890 (4·3%)	45/869 (5·2%)	0·82 (0·53–1·27)	
Calcified lesion†				0·52
Moderate or severe calcification	30/335 (9·0%)	39/330 (11·9%)	0·75 (0·47–1·21)	
No moderate or severe calcification	80/1574 (5·1%)	128/1579 (8·1%)	0·62 (0·47–0·82)	
Bifurcation lesion†				0·52
Yes	57/845 (6·8%)	81/858 (9·5%)	0·71 (0·50–0·99)	
No	53/1064 (5·0%)	86/1051 (8·2%)	0·60 (0·42–0·84)	
Tandem lesion†				0·69
Yes	12/210 (5·7%)	19/192 (9·9%)	0·56 (0·27–1·16)	
No	98/1699 (5·8%)	148/1717 (8·7%)	0·66 (0·51–0·85)	
Angulated or tortuous lesion†				0·32
Yes	32/574 (5·6%)	59/589 (10·0%)	0·54 (0·35–0·84)	
No	78/1335 (5·9%)	108/1320 (8·2%)	0·71 (0·53–0·95)	
QFR grey zone§†				0·06
<0·75	79/1204 (6·6%)	123/1179 (10·5%)	0·62 (0·47–0·82)	
0·75–0·85	21/448 (4·7%)	16/425 (3·8%)	1·25 (0·65–2·40)	
>0·85	10/256 (3·9%)	27/294 (9·3%)	0·41 (0·20–0·85)	
QFR-based functional SYNTAX score†				0·62
<5·0	21/523 (4·0%)	32/571 (5·7%)	0·71 (0·41–1·22)	
5·0–9·0	30/741 (4·1%)	52/693 (7·5%)	0·53 (0·34–0·84)	
>9·0	59/616 (9·6%)	82/603 (13·6%)	0·69 (0·49–0·96)	
Pre-PCI simulated residual QFR†				0·81
≤0·88	34/421 (8·1%)	54/429 (12·6%)	0·63 (0·41–0·96)	
>0·88	76/1486 (5·1%)	112/1468 (7·7%)	0·66 (0·50–0·89)	
QFR-based residual functional SYNTAX score†				0·20
0	68/1669 (4·1%)	97/1552 (6·3%)	0·65 (0·47–0·88)	
≥1	42/225 (18·7%)	68/335 (20·4%)	0·90 (0·61–1·32)	
Centre experience with invasive physiology¶				0·40
Experienced centres	54/937 (5·8%)	89/923 (9·7%)	0·59 (0·42–0·82)	
Less experienced centres	56/976 (5·8%)	78/989 (7·9%)	0·72 (0·51–1·02)	
Learning experience with QFR				0·45
First half of enrolled cases in each centre	47/960 (4·9%)	79/959 (8·3%)	0·58 (0·41–0·84)	
Second half of enrolled cases in each centre	63/953 (6·6%)	88/953 (9·3%)	0·71 (0·51–0·98)	

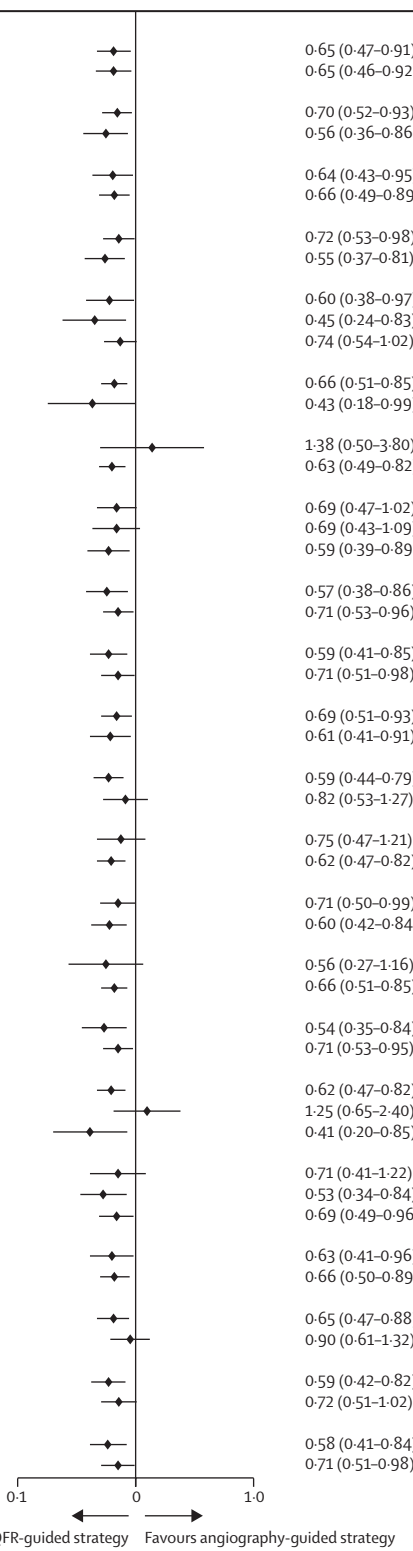

Figure 3: **Subgroup analyses for the primary endpoint**
PCI=percutaneous coronary intervention. QFR=quantitative flow ratio. SYNTAX=Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery. *Includes unstable angina or myocardial infarction within 30 days of procedure. †Assessed by the angiographic core laboratory. ‡Reported by site investigators. §Participants were categorised as part of the QFR 0·75–0·85 subgroup if QFR was 0·75–0·85 for all assessed vessels; otherwise, if participants had at least one vessel with QFR <0·75 they were categorised as part of the QFR <0·75 subgroup. ¶Experienced centre was defined as more than 100 annual invasive pressure wire cases.

Discussion

QFR is a novel method by which the fractional flow reserve, reflecting the ratio of coronary pressure distal to a stenosis and aortic pressure under conditions of maximum myocardial hyperaemia, is estimated in real time using 3D coronary artery reconstruction and computational fluid dynamics from the standard angiogram. Previous studies have shown a strong correlation between QFR and pressure wire-based fractional flow reserve measurements.[15,16] In this large-scale, sham-controlled, blinded, randomised trial, lesion selection for PCI using QFR guidance improved clinical outcomes at 1 year by reducing procedural complications and improving long-term results compared with standard angiography-guided PCI. These results were robust in both the intention-to-treat and per-protocol populations and were consistent across numerous prespecified subgroups.

A novel aspect of the present study was the pre-randomisation declaration by the investigators of the revascularisation plan should the patient be assigned to standard angiography guidance. QFR assessment in all vessels with one or more lesions with diameter stenosis of 50–90% led to changes in the treatment plan for 445 (23·3%) of 1913 patients. Specifically, in 375 (19·6%) cases, at least one vessel containing one or more severe angiographic stenoses intended for PCI was not treated because the QFR result indicated the absence of any haemodynamically obstructive lesion. This led to fewer vessels and lesions being treated in the QFR guidance group than in the angiography guidance group, with fewer stents and less contrast used. Less intervention translated into fewer periprocedural myocardial infarctions with QFR guidance, a finding that was consistent across the numerous definitions of myocardial infarction that are in contemporary use. Avoiding PCI of non-obstructive lesions might also obviate the risk of re-stenosis from their treatment. Indeed, in 182 (9·5%) of 1913 patients, the absence of any physiologically significant vessels led to the PCI procedure being deferred entirely in preference for long-term medical therapy alone, explaining why dual antiplatelet therapy use during follow-up was lower in the QFR-guided group. Conversely, in 85 (4·4%) patients, QFR identified vessels that did contain haemodynamically obstructive lesions (most frequently in the left anterior descending artery) that would not have been treated otherwise on the basis of their benign angiographic appearance. As shown in previous studies, medical therapy only of such lesions results in an increased risk of non-procedural myocardial infarctions and recurrent angina requiring unplanned revascularisation procedures.[20,21]

The net effect was that QFR enabled identification of lesions and vessels that required intervention and those for which PCI could be safely deferred, resulting in lower rates of early and late myocardial infarction, as well as fewer unplanned ischaemia-driven revascularisation procedures during 1-year follow-up than angiography-guided lesion selection. In addition, resource consumption was lower with the QFR-guided approach, with shorter procedure times, fewer stents, and less contrast used, and with less patient radiation exposure, similar to that observed with fractional flow reserve in the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trials with pressure wire-based lesion selection.[7,8] However, compared with invasive physiological assessment, QFR might be more readily adopted into the workflow of angiography-based diagnostic and interventional procedures, does not require use of specialised guide wires, and is easily repeatable multiple times during the procedure. A simple-to-implement technique such as QFR might thus facilitate the routine use of physiological assessment in clinical practice.

Major strengths of our study include its large size, providing adequate power to demonstrate meaningful improvements in clinical outcomes (including fewer myocardial infarctions and fewer revascularisations) despite the excellent results with contemporary drug-eluting stents; incorporation of a sham control that effectively masked the study participants and health-care providers to the randomisation allocation; and the predeclaration of the intended revascularisation plan with angiography guidance. In addition, the FAVOR III China study population was representative of patients undergoing PCI in daily practice (eg, 1295 [34%] with diabetes and 2066 [54%] with multivessel disease). Nonetheless, several limitations of this trial should be noted. First, the accuracy and reproducibility of QFR measurements depend on technique and quality of the angiography acquisition, which currently requires two projections for each vessel. The next-generation QFR system will require only a single projection and incorporates more automated processes that should further reduce analysis variability and time.[22] Second, FAVOR III China used angiography guidance for PCI lesion assessment in the control group, which, notwithstanding current guideline recommendations,[5] remains the current de facto standard of care in most catheterisation laboratories. Although the point estimate for reduction in major adverse cardiac events with QFR guidance in the present trial was similar in magnitude to that observed with invasive pressure wire-based fractional flow reserve guidance in the FAME I and II trials, the relative clinical use of the two approaches is uncertain.[7,8] The ongoing FAVOR III European-Japan randomised trial (NCT03729739) is directly comparing the outcomes of QFR-guided and pressure wire-based fractional flow reserve-guided PCI in 2000 patients. Third, the PCI operators were aware of the group assignments, potentially introducing procedural bias. However, operators declared treatment strategies before randomisation, and the sham-controlled design enabled robust post-procedural masking procedures for patients and clinical assessors. Fourth, patients with

moderate and severe chronic kidney disease, acute ST-segment elevation myocardial infarction, and some complex lesions were excluded. Therefore, patients enrolled in the present study might reflect a lower-risk population than encountered in routine practice. The use of QFR-guided lesion selection for patients with PCI excluded from the present study is unknown. Fifth, although trial enrolment concluded before the COVID-19 pandemic was widespread in China, follow-up procedures might have been affected. We therefore instituted an unscheduled telephone interview to mitigate this effect (appendix p 13). Because patients and post-procedure health-care assessors remained masked, potential ascertainment bias should have affected both groups equally. Sixth, to date, only 1-year follow-up has been completed. Follow-up is planned up to 3 years to assess long-term outcomes. Seventh, health economics and quality-of-life outcomes, representing different dimensions of treatment effectiveness, have not yet been analysed and will be reported separately.

In this multicentre, randomised, sham-controlled trial in patients with coronary artery disease undergoing PCI, a QFR-guided vessel and lesion selection strategy improved 1-year clinical outcomes compared with standard angiography guidance.

Contributors

BX, ST, LS, JE, YWang, WFF, AJK, PWS, WW, MBL, SQ, and GWS contributed to the trial design. BX, ST, LS, ZJ, BY, GF, YZhou, JW, YC, JP, LC, XQ, JY, XL, LG, CS, YZhang, QZ, HP, XF, JL, KD, YWu, WY, CG, and SQ contributed to data collection. BX, ST, LS, YZhao, YWang, CG, MBL, SQ, and GWS analysed and interpreted the data. BX, LS, CG, and GWS drafted the manuscript, which was critically reviewed and revised by MBL, ST, SQ, JE, WFF, AJK, PWS, and WW. All authors reviewed and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. BX and LS have accessed and verified the underlying data.

Declaration of interests

ST is the co-founder of Pulse Medical Imaging Technology and reports grants from Pulse medical imaging technology. XF is an employee of Shanghai Jiao Tong University-Pulse Medical Imaging Technology Joint Laboratory. JE reports consulting or speaker fees from Abbott, Philips, and Boston Scientific, outside the submitted work. WFF reports grants from Abbott Vascular, Boston Scientific, and Medtronic; consulting fees from CathWorks; and minor stock options from HeartFlow, outside the submitted work. AJK reports grants and travel or meal reimbursements from Medtronic, Abbott Vascular/St Jude, Boston Scientific, Abiomed, Siemens/Corindus, Philips/Spectranetics, ReCor Medical, and Cardiovascular Systems; grants from CathWorks; travel or meal reimbursements from Chiesi, Opsens, Zoll, and Regeneron; and consulting fees from IMDS, outside the submitted work. WW reports grants and consulting fees from MicroPort, outside the submitted work; is a medical advisor for Rede Optimus; and is a co-founder of Argonauts, an innovation facilitator. MBL is on an advisory board of a coronary physiology start-up of Cathworks; and reports grants from Abbott, BSC, and Medtronic. GWS reports consulting or speaker fees from Cook, TherOx, Reva, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-wave, Abiomed, Shockwave, MAIA Pharmaceuticals, Vectorious, Cardiomech, Elucid Bio, Occlutech, Infraredx, CorFlow, and Apollo Therapeutics; equity or options from Applied Therapeutics, Biostar family of funds, MedFocus family of funds, Aria, Cardiac Success, Cagent, SpectraWave, and Orchestra Biomed; and consulting or speaker fees and equity or options from Valfix and Ancora, outside the submitted work. All other authors declare no competing interests.

Data sharing

Individual patient data collected in the FAVOR III China trial will not be available to others. The informed consent did not include consent for data sharing with researchers other than the study investigators. Requests for data sharing would require approval by the study sites and their local ethics committees or institutional review boards. In addition, according to the current national general data protection regulations, additional consent would have to be provided from all the patients. These procedures unfortunately preclude the possibility for data sharing. However, the study investigators are committed to working collaboratively with other investigators on projects involving summary-level analyses. All such requests should be submitted to the corresponding author.

Acknowledgments

This was an investigator-initiated study, without any external funding at the time of study design. After the first patient enrolment on Dec 25, 2018, the study group received grant support by the Beijing Municipal Science and Technology Commission (Z191100006619107; effective since August, 2019), Chinese Academy of Medical Sciences (2019XK320056; effective since November, 2019), and the National Clinical Research Centre for Cardiovascular Diseases, Fuwai Hospital (NCRC2020001; effective since July, 2020). Pulse Medical Imaging Technology (Shanghai, China) provided the QFR system and software at no charge for the study. The principal investigators vouch for the accuracy and completeness of the data and adherence of the trial to the protocol. The authors thank all the participating patients for their contributions to the trial. We also thank all the physicians and nurses who cared for the patients, and all the clinical and research staff who assisted with the trial processes.

References

1 Toth GG, Toth B, Johnson NP, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv* 2014; **7:** 751–59.

2 Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv* 2012; **5:** 1029–36.

3 Toth G, Hamilos M, Pyxaras S, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. *Eur Heart J* 2014; **35:** 2831–38.

4 van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet* 2015; **386:** 1853–60.

5 Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019; **40:** 87–165.

6 Parikh RV, Liu G, Plomondon ME, et al. Utilization and outcomes of measuring fractional flow reserve in patients with stable ischemic heart disease. *J Am Coll Cardiol* 2020; **75:** 409–19.

7 Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360:** 213–24.

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

9 Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017; **376:** 1813–23.

10 Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017; **376:** 1824–34.

11 Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. *JACC Cardiovasc Interv* 2020; **13:** 1617–38.

12 De Maria GL, Garcia-Garcia HM, Scarsini R, et al. Novel indices of coronary physiology: do we need alternatives to fractional flow reserve? *Circ Cardiovasc Interv* 2020; **13:** e008487.

13 Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. *Lancet* 2015; **386:** 702–13.

14 Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. *JACC Cardiovasc Interv* 2016; **9:** 2024–35.

15 Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. *J Am Coll Cardiol* 2017; **70:** 3077–87.

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

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

18 Han Y, Xu B, Jing Q, et al. A randomized comparison of novel biodegradable polymer- and durable polymer-coated cobalt-chromium sirolimus-eluting stents. *JACC Cardiovasc Interv* 2014; **7:** 1352–60.

19 Xu B, Gao R, Yang Y, et al. Biodegradable polymer-based sirolimus-eluting stents with differing elution and absorption kinetics: the PANDA III trial. *J Am Coll Cardiol* 2016; **67:** 2249–58.

20 Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med* 2018; **379:** 250–59.

21 Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020; **382:** 1395–407.

22 Tu S, Ding D, Chang Y, Li C, Wijns W, Xu B. Diagnostic accuracy of quantitative flow ratio for assessment of coronary stenosis significance from a single angiographic view: a novel method based on bifurcation fractal law. *Catheter Cardiovasc Interv* 2021; **97** (suppl 2)**:** 1040–47.