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ORIGINAL INVESTIGATIONS

Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis

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ABSTRACT

BACKGROUND Quantitative flow ratio (QFR) is a novel angiography-based method for deriving fractional flow reserve (FFR) without pressure wire or induction of hyperemia. The accuracy of QFR when assessed online in the catheterization laboratory has not been adequately examined to date.

OBJECTIVES The goal of this study was to assess the diagnostic performance of QFR for the diagnosis of hemodynamically significant coronary stenosis defined by FFR ≤0.80.

METHODS This prospective, multicenter trial enrolled patients who had at least 1 lesion with a diameter stenosis of 30% to 90% and a reference diameter ≥2 mm according to visual estimation. QFR, quantitative coronary angiography (QCA), and wire-based FFR were assessed online in blinded fashion during coronary angiography and re-analyzed offline at an independent core laboratory. The primary endpoint was that QFR would improve the diagnostic accuracy of coronary angiography such that the lower boundary of the 2-sided 95% confidence interval (CI) of this estimate exceeded 75%.

RESULTS Between June and July 2017, a total of 308 patients were consecutively enrolled at 5 centers. Online QFR and FFR results were both obtained in 328 of 332 interrogated vessels. Patient- and vessel-level diagnostic accuracy of QFR was 92.4% (95% CI: 88.9% to 95.1%) and 92.7% (95% CI: 89.3% to 95.3%), respectively, both of which were significantly higher than the pre-specified target value ($p < 0.001$). Sensitivity and specificity in identifying hemodynamically significant stenosis were significantly higher for QFR than for QCA (sensitivity: 94.6% vs. 62.5%; difference: 32.0% [$p < 0.001$]; specificity: 91.7% vs. 58.1%; difference: 36.1% [$p < 0.001$]). Positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for QFR were 85.5%, 97.1%, 11.4, and 0.06. Offline analysis also revealed that vessel-level QFR had a high diagnostic accuracy of 93.3% (95% CI: 90.0% to 95.7%).

CONCLUSIONS The study met its prespecified primary performance goal for the level of diagnostic accuracy of QFR in identifying hemodynamically significant coronary stenosis. (The FAVOR [Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis] II China study]; NCT03191708) (J Am Coll Cardiol 2017;70:3077–87)

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ABBREVIATIONS AND ACRONYMS

+LR = positive likelihood ratio

–LR = negative likelihood ratio

ATP = adenosine-5'-triphosphate

CAD = coronary artery disease

CI = confidence interval

FFR = fractional flow reserve

NPV = negative predictive value

PPV = positive predictive value

QCA = quantitative coronary angiography

QFR = quantitative flow ratio

Patients at high risk of having coronary stenosis are evaluated routinely by using invasive coronary angiography. Lesion severity is often assessed anatomically by the relative reduction in coronary artery lumen, which can be quantified by using quantitative coronary angiography (QCA). Fractional flow reserve (FFR) is a method increasingly used for lesion functional evaluation (1). FFR is assessed during coronary angiography by advancing a wire with a pressure transducer toward the stenosis and measuring the ratio in pressure between the 2 sides of the stenosis during medically induced maximum blood flow (hyperemia). Studies have shown that routine use of FFR allows reclassification of individual management in a large proportion of patients (2–4). Implementing a strategy of FFR-guided coronary interventions allowed for both a reduction in the number of implanted stents and an improvement in clinical outcomes (5–8).

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The solid evidence for FFR evaluation of coronary stenosis has supported adoption of an FFR-based management strategy at many centers; however, the need for interrogating the stenosis with a pressure wire, the cost of the wire, and the limitations associated with induction of hyperemia have restricted its widespread adoption. Quantitative flow ratio (QFR) is a novel method for evaluating the functional significance of coronary stenosis by computation of FFR in the vessel based on 3-dimensional angiographic reconstruction and fluid dynamics algorithms (9,10). The FAVOR (Functional Assessment by Various Flow Reconstructions) pilot study showed promising results for core laboratory-based QFR computation in identifying the presence of functionally significant stenosis in selected patients (9). Similar results were observed in subsequent studies that included only intermediate coronary stenoses (11) or used myocardial perfusion imaging as the reference standard to define ischemia (12). However, the diagnostic accuracy of QFR in consecutive patients when assessed online in the diagnostic catheterization laboratory has not been adequately examined to date and is therefore the subject of the present study.

METHODS

STUDY DESIGN. The FAVOR (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis) II China study is a prospective, multicenter trial designed to evaluate the diagnostic accuracy of online QFR in identifying hemodynamically significant coronary artery disease (CAD) by using pressure wire-based FFR as the reference standard. QFR and QCA analyses were performed online before FFR measurement in a blinded fashion.

The study was performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines of the China Food and Drug Administration. The study was conducted at 5 hospitals in 3 major cities in China. The Online Appendix lists the hospitals and investigators. The study protocol was approved by the institutional review board at each site. All patients provided written informed consent.

STUDY POPULATION. Adults with suspected or known CAD, who were admitted for coronary angiography between June 13, 2017, and July 20, 2017, due to high risk of significant coronary stenosis, were consecutively enrolled. Patients were not eligible if they had myocardial infarction within 72 h of coronary angiography, severe heart failure, allergy to the contrast agent or adenosine, a serum creatinine level >150 μmol/l, or a glomerular filtration rate <45 ml/kg/1.73 m^2; were ineligible for diagnostic intervention or FFR examination; or had factors that might substantially affect the angiographic image quality (e.g., frequent atrial premature beat or atrial fibrillation). Angiographic inclusion criteria were as follows: ≥1 stenosis with percent diameter stenosis between 30% and 90% in a vessel ≥2 mm by visual

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estimation. Angiographic exclusion criteria were as follows: ostial lesions <3 mm from the aorta; severe vessel overlap or tortuosity at the stenotic segments; the luminal reduction was caused by myocardial bridge; poor angiographic image quality precluding contour detection; and main vessels with stenotic side branches downstream of the interrogated lesion.

CORONARY ANGIOGRAPHY AND QCA ANALYSIS. Angiographic images were recorded at 15 frames/s by monoplane or biplane radiographic systems (AXIOM Artis, Siemens Healthcare, Erlangen, Germany; Innova, GE, Wauwatosa, Wisconsin; AlluraXper, Philips, Amsterdam, the Netherlands; INTEGRIS Allura, Philips). A table with recommended projection views (Online Table 1) was provided to the sites for angiographic image acquisition. The contrast medium was injected manually with a forceful and stable injection or by the pump at a rate of approximately 4 ml/s. QCA was performed by using angiogram vendor-integrated QCA software or by a QCA workstation (Beijing Crealife Technology Co., Ltd., Beijing, China). Either isocenter calibration or catheter calibration was applied based on site preference.

ONLINE QFR ASSESSMENT. Two angiographic image runs acquired at different angles ≥25° were transferred by local network to the QFR system (AngioPlus, Pulse Medical Imaging Technology, Shanghai Co., Ltd., Shanghai, China) that used the same algorithms for QFR computation as previously described (9). Analysis required a few steps with observer interaction (Online Figure 1). The lumen contour was automatically delineated by extensively validated algorithms. Manual correction was allowed in case of suboptimal angiographic image quality, following a standard operation procedure (13). The contrast flow model, which uses a frame count method to derive contrast flow velocity from coronary angiography (9), was used in this study for QFR computation. QFR was analyzed by well-trained technicians who had performed QFR in at least 30 patients. The QFR system was placed in the control room so that the operators inside the catheterization laboratory were blinded to the QFR results. Before QFR analysis, the technicians were informed about the location where the operators intended to measure FFR so that QFR could be compared with FFR at the same vessel site. The time for QFR analysis from loading the 2 angiographic image runs in the QFR system to the generation of the QFR report was recorded.

FFR MEASUREMENT. After QFR analysis completion, the operators inside the catheterization laboratory started to measure FFR. The RadiAnalyzer Xpress instrument and Certus pressure wire (St. Jude Medical, St. Paul, Minnesota) were used in all cases. Hyperemia was induced in all cases by intravenous administration of adenosine-5'-triphosphate (ATP) via the antecubital vein at ≥160 μg/l/min. Pressure data were recorded for at least 3 s of stable value before ATP administration and at least 10 s of stable value during hyperemia. In all cases, the pressure sensor was returned to the guiding catheter tip to exclude pressure drift. A limited drift with a mean coronary pressure distal to a coronary stenosis/mean aortic pressure ranging from 0.95 to 1.05 during hyperemia was accepted; otherwise, the procedure had to be repeated. Notably, for FFR values between 0.75 and 0.85, an even smaller drift was accepted, defined as resting distal coronary pressure/aortic pressure values at the guiding tip between 0.98 and 1.02.

CORE LABORATORY ANALYSIS. All angiographic imaging data and FFR traces were sent to an independent core laboratory (CCRF, Beijing, China) for offline analysis. QCA analysis, QFR analysis, and FFR reading were performed in blinded fashion by using QAngio XA (Medis, Leiden, the Netherlands), AngioPlus (Pulse, Shanghai, China), and RadiView (St. Jude Medical), retrospectively.

DATA MANAGEMENT. Data were managed by an independent contract research organization (CCRF). Source data including QCA report, QFR report, and FFR values were collected online by local investigators. Detailed case-report forms were completed, with supplemental data for each patient, and subsequently transferred into an electronic data capture system for statistical analysis.

ENDPOINTS AND STATISTICAL ANALYSIS. The primary endpoint was the diagnostic accuracy of online QFR (≤0.8 or >0.8) to identify hemodynamically significant coronary stenosis with FFR (≤0.8 or >0.8) as the reference standard. Major secondary endpoints were the sensitivity and specificity for online QFR and QCA in identifying hemodynamically significant coronary stenosis with FFR as the reference standard.

The trial was powered for testing significance of both the primary endpoint and the major secondary endpoint. For the primary endpoint, the diagnostic accuracy of QFR was hypothesized to be greater than the target goal of 75% at a 2-sided significance level of 0.05. The target goal was chosen to be higher than the upper boundary of the diagnostic accuracy of QCA, which was 74% in the FAVOR pilot study (9). A total of 277 patients with 1 lesion each would yield 90% power to demonstrate significance of the primary endpoint. Assuming anticipated loss to analysis of 10% due to failed QCA, QFR, or FFR assessment, at

TABLE 1 Baseline Characteristics of the Study Population (N = 308)

Age, yrs	61.3 ± 10.4
Female	26.3 (81)
Body mass index, kg/m^2	25.2 ± 3.3 (N = 304*)
Diabetes mellitus	27.9 (86)
Hypertension	60.1 (185)
Hyperlipidemia	45.1 (139)
Current smoker	28.2 (87)
Family history of coronary artery disease	16.6 (51)
Previous myocardial infarction	15.6 (48)
Previous PCI	21.1 (65)
Previous CABG	0.3 (1)
Clinical presentation	
Silent ischemia	11.0 (34)
Stable angina pectoris	23.4 (72)
Unstable angina pectoris	61.0 (188)
Acute myocardial infarction within 1 month	4.5 (14)
Left ventricular ejection fraction, %	63.4 ± 6.3 (N = 295*)

Values are mean ± SD or % (n). *Number of patients for whom continuous variables were calculated.
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

most, enrollment of 308 patients was required. For the major secondary endpoint, assuming sensitivity and specificity was 0.74 and 0.91, respectively, for QFR, and 0.48 and 0.76 for QCA (9), 308 patients would yield >80% power to demonstrate superiority of QFR over QCA with a 2-sided type I error of 0.05. Detailed sample size calculations with assumptions are described in the Online Appendix.

TABLE 2 Vessel Characteristics According to Coronary Angiography, QFR, and FFR (N = 308, 332 Vessels)

Interrogated vessels	
Left anterior descending artery	55.7 (185)
Diagonal branch	0.6 (2)
Left circumflex artery	14.8 (49)
Obtuse marginal branch	1.5 (5)
Ramus intermediate	0.3 (1)
Right coronary artery	26.2 (87)
Posterior descending artery	0.3 (1)
Posterolateral branch	0.6 (2)
Reference vessel diameter, mm	2.82 ± 0.56
Minimal lumen diameter, mm	1.51 ± 0.44
Diameter stenosis, %	46.5 ± 11.3
Lesion length, mm	13.1 ± 6.4
Bifurcation lesions	24.7 (82)
Tortuous vessels	14.2 (47)
Moderate or severe calcified lesions	18.4 (61)
Thrombotic lesions	0.3 (1)
Tandem lesions	46.3 (152)
Online FFR analysis	
FFR (per vessel)	0.82 ± 0.12 (n = 330*)
Vessels with FFR ≤0.80	34.2 (113/330*)
Vessels with 0.75 ≤ FFR ≤0.85	32.4 (107/330*)
Patients with FFR measurement in >1 vessel	7.2 (22/306*)

Values are % (n), mean ± SD, or % (n/N), unless otherwise indicated. *There are 2 patients (2 vessels) missing FFR measurements.
FFR = fractional flow reserve; QCA = quantitative coronary angiography; QFR = quantitative flow ratio.

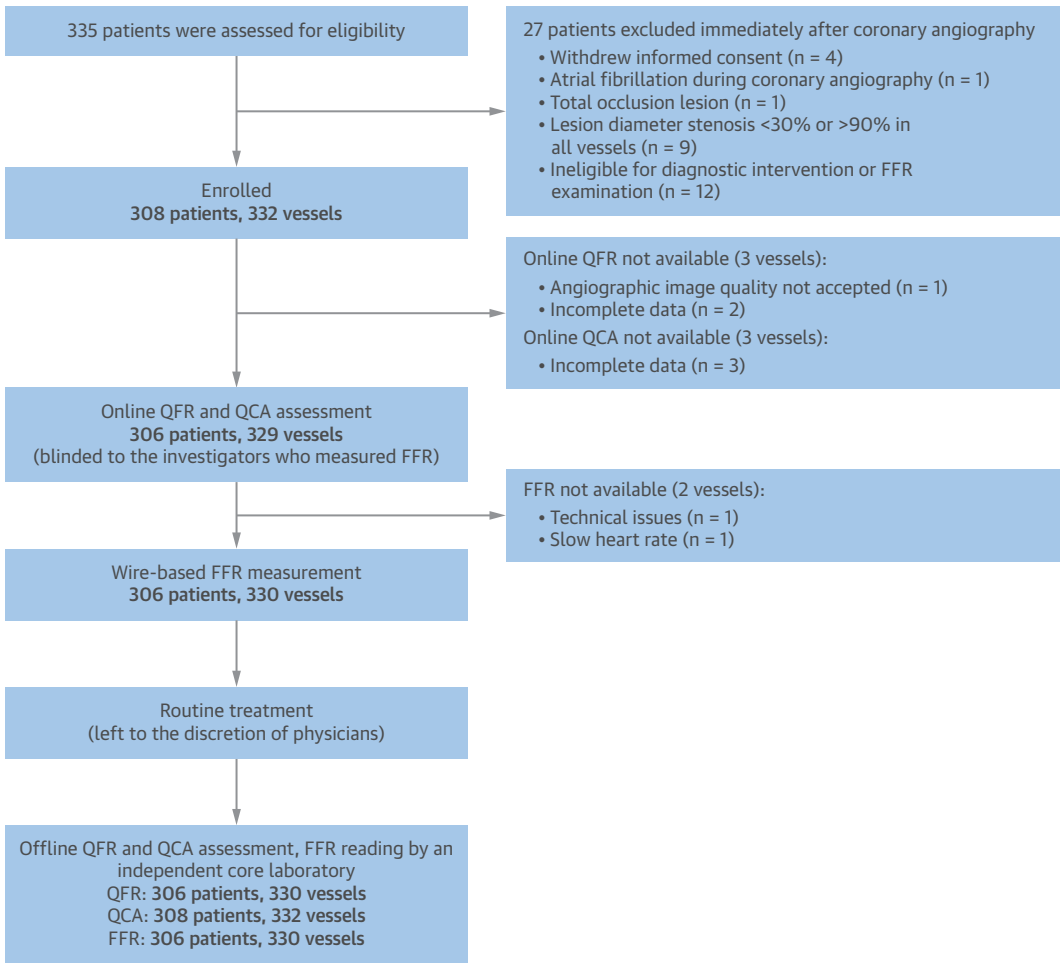
Baseline demographic and vessel characteristics were collected for all the patients in the intention-to-treat population. The assessment of the primary and secondary study endpoints were analyzed based on the as-diagnostic set, which included patients/vessels with both QFR and FFR assessed; thus, there was no data complement for the missing value. Continuous variables are presented as mean ± SD, and categorical variables are presented as counts and percentages. The 2-sided 95% confidence intervals (CIs) of the primary endpoint (i.e., diagnostic accuracy of online QFR) were estimated at both vessel and patient levels by using the Clopper-Pearson exact method. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), and negative likelihood ratio (-LR) of QFR and QCA, with the FFR as the reference standard, were calculated, and the 95% CIs were added, as appropriate.

For considering the effect of paired observations, the generalized estimating equations were used for vessel-level analysis of sensitivity, specificity, NPV, and PPV. The PROC GENMOD in SAS (SAS Institute, Inc., Cary, North Carolina) with the repeated statement was used. The center effect was also adjusted in the same model. The related p value and 2-sided 95% CIs of the difference on sensitivity, specificity, NPV, and PPV between QFR and QCA were estimated, using FFR as the reference standard. The receiver-operating curves of online QFR and QCA, with the FFR as gold standard, were estimated by using a logistic regression model at the vessel level. Correlation between QFR and FFR was determined by Pearson's correlation coefficient (r). Pairwise comparisons between QFR and FFR were made by using paired Student's *t*-tests. All statistical analyses were performed with a test significance level of 0.05 using SAS version 9.4 (SAS Institute, Inc.).

RESULTS

BASELINE PATIENT AND LESION CHARACTERISTICS. Figure 1 presents the study flowchart. Between June 2017 and July 2017, a total of 308 patients with 332 interrogated vessels were enrolled. Table 1 summarizes the baseline clinical characteristics of the enrolled patients. Mean age of the patients was 61.3 ± 10.4 years, 81 (26.3%) were women, 86 (27.9%) had diabetes, and 48 (15.6%) had a previous myocardial infarction.

FIGURE 1 Study Flowchart



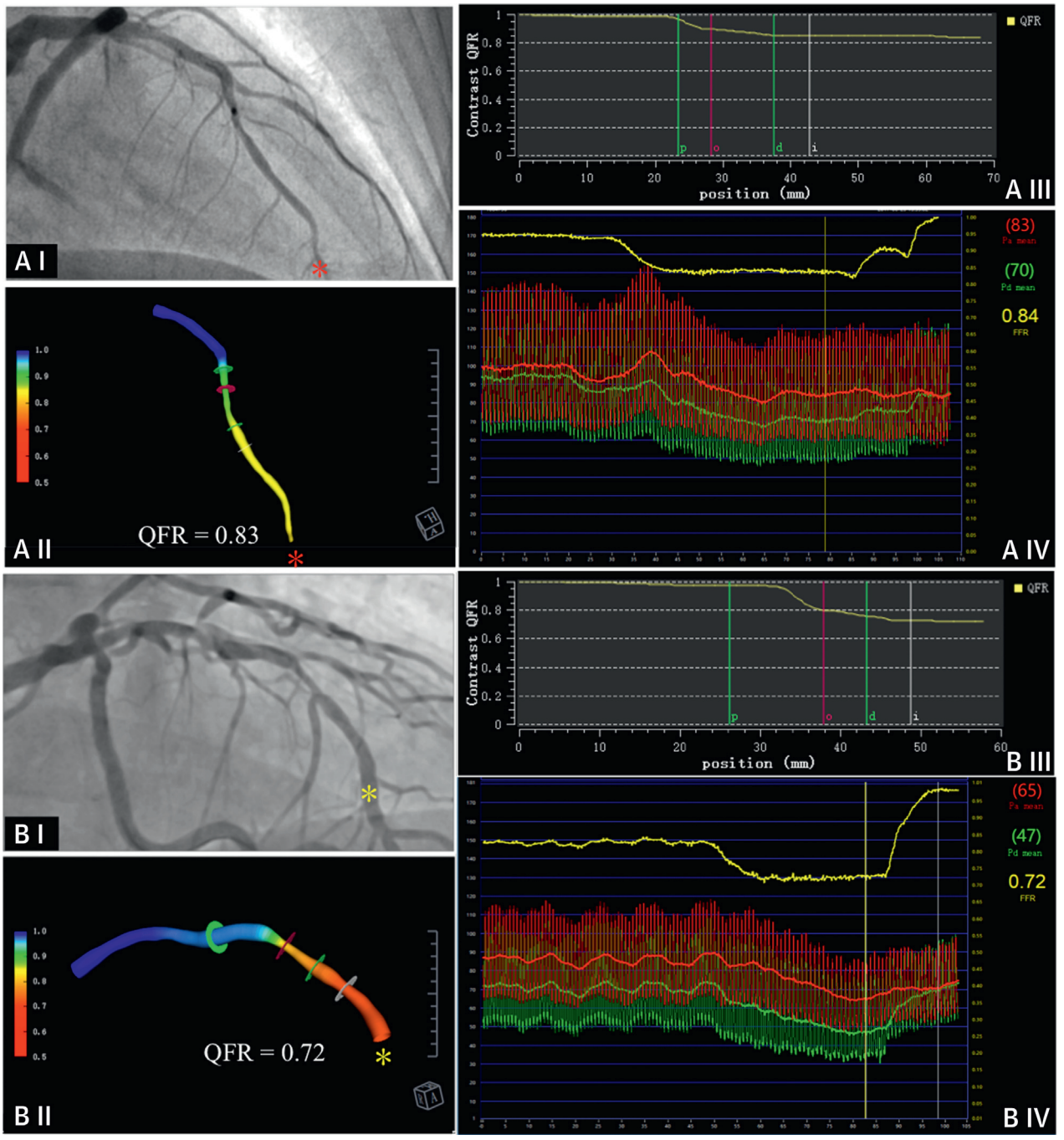
The analyses of this study were based on the as-diagnostic set: in 328 vessels from 304 patients in whom online quantitative flow ratio (QFR) and fractional flow reserve (FFR) were both assessed. There was 1 patient (1 vessel) in the as-diagnostic set without online quantitative coronary angiography (QCA) analysis, which resulted in the online QCA diagnostic performance evaluation left to 327 vessels from 303 patients. Offline QFR and FFR were both assessed in 304 patients (328 vessels), with completed analysis of offline QCA.

Procedural and vessel characteristics are shown in Table 2. A total of 185 (55.7%) interrogated vessels were left anterior descending arteries, 24.7% had bifurcation lesions, 14.2% had tortuous vessels, and 18.4% had moderate or severe calcified lesions.

Among 332 interrogated vessels, QFR and QCA were successfully assessed in 329 vessels (99.1%), whereas FFR measurement was obtained in 330 vessels (99.4%). The interrogated vessels had an FFR of 0.82 ± 0.12. FFR ≤0.80 was noted in 113 vessels (34.2%). QFR and FFR were both assessed in 328 vessels from 304 patients, constituting the as-diagnostic set for assessment of the primary and secondary study endpoints.

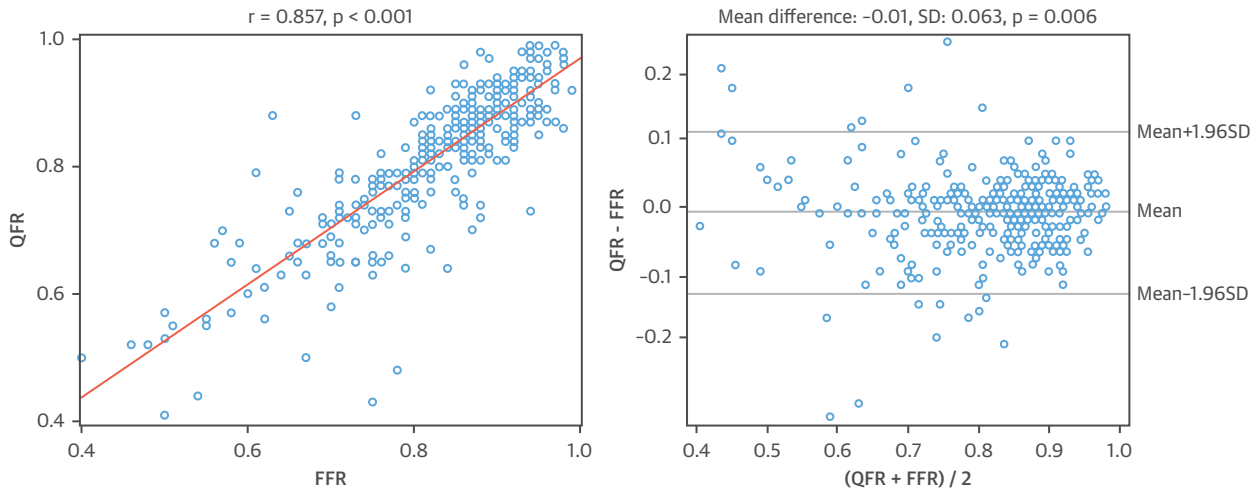
CORRELATION AND AGREEMENT BETWEEN QFR AND FFR. Figure 2 displays 2 representative examples of QFR and FFR assessments in this study. Good correlation between FFR and QFR was observed for both online ($r = 0.86$; $p < 0.001$) and offline ($r = 0.88$; $p < 0.001$) assessments. There was good agreement between QFR and FFR for both online (mean difference: −0.01 ± 0.06; $p = 0.006$) and offline (mean difference: 0.002 ± 0.06; $p = 0.61$) assessments (Figure 3, Online Figure 2). The absolute numerical difference between QFR and FFR was >0.10 in 28 (8.5%) vessels and >0.05 in 103 (31.4%) vessels. In 10.3%, 5.5%, and 6.7% of the interrogated left anterior descending artery, left circumflex artery, and right

FIGURE 2 Representative Cases From the FAVOR II China Study



(A I) Coronary angiography shows left anterior descending artery (LAD) with intermediate stenosis. **(A II)** QFR was computed as 0.83 at the **red asterisk**. **(A III)** QFR pull-back (p: proximal lesion marker; o: lesion core; d: distal lesion marker; corresponding to disks in **B II**). **(A IV)** FFR measured by pressure wire at the **red asterisk** was 0.84. **(B I)** Coronary angiography shows LAD with intermediate stenosis, which is hemodynamically significant as indicated by QFR and FFR. **(B II)** QFR was 0.72 at the **yellow asterisk**. **(B III)** QFR pull-back. **(B IV)** FFR was 0.72 at the **yellow asterisk**. FAVOR II = Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis II; other abbreviations as in Figure 1.

FIGURE 3 Correlation and Agreement Between FFR and QFR



QFR demonstrated good correlation and agreements with FFR. Abbreviations as in **Figure 1**.

coronary artery, the numerical difference exceed 0.10 (Online Table 2). Tandem lesions were present in 152 (46.3%) vessels. The difference between QFR and FFR was not statistically different between the subgroups with and without tandem lesions (−0.016 ± 0.068 vs. −0.004 ± 0.058; p = 0.10).

DIAGNOSTIC PERFORMANCE OF QFR AND QCA FOR IDENTIFYING SIGNIFICANT STENOSIS. The primary endpoint, per-vessel diagnostic accuracy of QFR, was 92.7% (95% CI: 89.3% to 95.3%), which was significantly higher than the protocol-specified target value (p < 0.001) (**Central Illustration**). The accuracy was similar in different vessels (Online Table 3). Clinical discordance occurred in 24 (7.3%) vessels: FFR >0.80 but QFR ≤0.80 in 18 vessels, whereas FFR ≤0.80 but QFR >0.80 in 6 vessels (Online Table 2). Patient-level analysis showed similar diagnostic accuracy of QFR: 92.4% (95% CI: 88.9% to 95.1%) (Online Figure 3). By comparison, online QCA showed a lower diagnostic accuracy (59.6%; difference, 34.9%; p < 0.001).

The major secondary endpoints, sensitivity and specificity in the diagnosis of hemodynamically significant stenosis, were significantly higher with QFR than with QCA (sensitivity: 94.6% vs. 62.5%; difference: 32.0% [p < 0.001]; specificity: 91.7% vs. 58.1%; difference: 36.1% [p < 0.001]). PPV, NPV, +LR, and -LR were 85.5%, 97.1%, 11.4, and 0.06 for online QFR, respectively, and 43.8%, 74.9%, 1.49, and 0.65 for online QCA, respectively (**Table 3**).

Offline analysis by the core laboratory also showed a high diagnostic accuracy of 93.3% (95% CI: 90.0% to 95.7%) for QFR, with an improved diagnostic performance compared with dedicated QCA analysis (sensitivity: 94.1% [95% CI: 88.3% to 97.6%] vs. 49.6% [95% CI: 41.1% to 59.7%]; specificity: 92.8% [95% CI: 88.4% to 95.9%] vs. 72.2% [95% CI: 65.7% to 78.2%]; p < 0.001 for all) (Online Table 4).

As shown in **Figure 4**, the area under the receiver-operating characteristic curve was significantly larger for QFR than for QCA (0.96 vs. 0.66; difference: 0.31; p < 0.001). Similar results were revealed by the offline analysis (Online Figure 4).

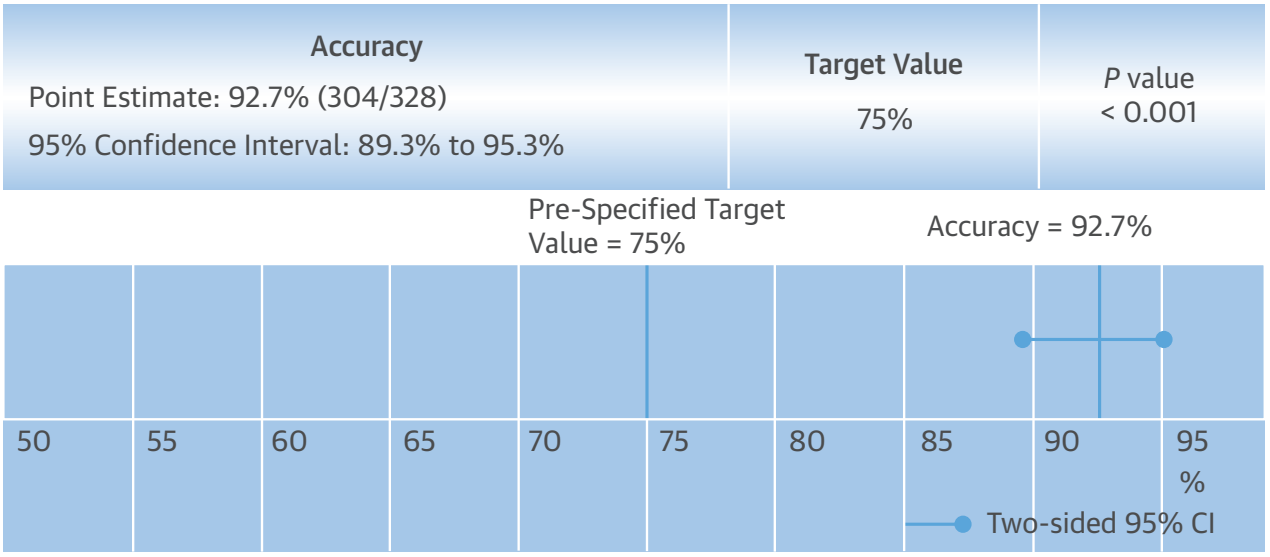
DIAGNOSTIC PERFORMANCE OF QFR IN INTERMEDIATE LESIONS. In a subgroup analysis of intermediate lesions with diameter stenosis between 40% and 80% by visual estimation, which comprised 82.8% of all interrogated vessels, the diagnostic accuracy, sensitivity, specificity, PPV, NPV, +LR, and -LR of online QFR in identifying physiologically significant stenosis was 92.3%, 92.2%, 92.3%, 82.6%, 96.8%, 12.0, and 0.08, respectively. Diagnostic performance of QFR was also superior to QCA in this subgroup (Online Table 5).

COMPUTATIONAL PERFORMANCE OF ONLINE QFR. Mean time for QFR assessment (including 3-dimensional angiographic reconstruction and frame count analysis) was 4.36 ± 2.55 min.

DISCUSSION

In this adequately powered multicenter study, we observed that QFR, an angiography-based approach for fast computation of FFR, demonstrated high

CENTRAL ILLUSTRATION **QFR for Coronary Stenosis: Per-Vessel Diagnostic Accuracy of QFR**



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Diagnostic accuracy was defined as the consistency ratio of quantitative flow ratio (QFR)-evaluated outcomes (≤0.8 or >0.8) with the reference standard fractional flow reserve (FFR)-evaluated outcomes (≤0.8 or >0.8). CI = confidence interval.

feasibility and accuracy in identifying hemodynamically significant coronary stenosis when performed by clinical staff during standard invasive coronary angiography. Patient- and vessel-level diagnostic accuracy of QFR were 92.4% (95% CI: 88.9% to 95.1%) and 92.7% (95% CI: 89.3% to 95.3%), respectively, which were both significantly higher than the prespecified target value ($p < 0.001$). Compared with anatomical assessment of coronary obstruction using QCA, QFR substantially improved the diagnostic performance of coronary angiography in identifying the stenosis that actually caused myocardial ischemia. Thus, the study met both the prespecified primary performance goal and the major secondary performance goal.

The results of this study expand on findings and reported clinical potentials from the previous FAVOR pilot study (9), in which QFR was assessed by core laboratories and compared with wire-based FFR in 84 vessels from 73 patients. The pilot study showed that QFR computed by using the contrast flow model, derived from coronary angiography without induction of hyperemia, had a high accuracy of 86% for the diagnosis of ischemia defined according to FFR ≤0.80.

The present study was the first trial with adequate power to assess the diagnostic accuracy of in-procedure QFR, and it documented excellent diagnostic accuracy of 92.7% (with strong +LR of 11.4 and -LR of 0.06) for QFR in a consecutively enrolled patient population when QFR was assessed online in the catheterization laboratory. The improvement in the diagnostic accuracy of QFR compared with that in the FAVOR pilot study was likely secondary to the following advantages when assessing QFR online: 1) the acquisition guide for obtaining 2 good angiographic runs with minimal foreshortening and overlap was implemented to ensure optimal image quality, resulting in more accurate 3-dimensional angiographic reconstruction and QFR computation; and 2) consensus on the position to compare QFR and FFR was obtained by the operators and the QFR analysts before the QFR and FFR assessments. This process is identical to the clinical scenario and allows comparison of QFR and FFR at exactly the same position. This approach is of particular importance for validation of QFR in vessels with tandem lesions or diffused disease where pressure may drop gradually or in multiple steps throughout the vessel.

Coronary angiography has been used routinely for evaluation of stenosis severity for decades, and a diameter stenosis of 50% according to QCA is generally taken as the cutoff value to identify physiologically significant coronary stenosis. Nevertheless, substantial discrepancy between anatomical obstruction and physiological significance was

TABLE 3 Diagnostic Performance of QFR ≤0.8 and QCA Diameter Stenosis ≥50% Versus FFR ≤0.8

	QFR ≤0.8		Diameter Stenosis by QCA ≥50%			
	Estimate, % (95% CI)	No. of Patients in Group	Estimate, % (95% CI)	No. of Patients in Group	Difference 95% (CI)	p Value
Accuracy	92.7 (89.3–95.3)	328	59.6 (54.1–65.0)	327	34.9 (28.3–41.5)	<0.001
Sensitivity	94.6 (88.7–98.0)	112	62.5 (52.9–71.5)	112	32.0 (21.0–43.1)	<0.001
Specificity	91.7 (87.1–95.0)	216	58.1 (51.2–64.8)	215	36.1 (27.9–44.3)	<0.001
PPV	85.5 (78.0–91.2)	124	43.8 (35.9–51.8)	160	42.0 (31.4–52.7)	<0.001
NPV	97.1 (93.7–98.9)	204	74.9 (67.6–81.2)	167	24.4 (15.6–33.2)	<0.001
+LR	11.4 (7.1–17.0)	328	1.49 (1.21–1.85)	327	-	-
-LR	0.06 (0.03–0.13)	328	0.65 (0.50–0.84)	327	-	-

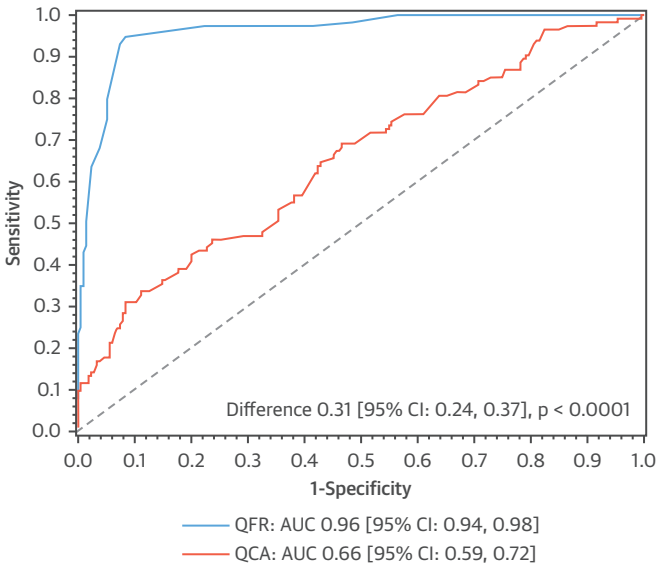
Diagnostic accuracy was defined as the consistency ratio of QFR-evaluated outcomes (≤0.8 or >0.8) to the reference standard FFR-evaluated outcomes (≤0.8 or >0.8). Sensitivity was defined as the proportion of QFR ≤0.8 or diameter stenosis ≥50% by QCA in vessels with hemodynamically significant stenosis; specificity was defined as the proportion of QFR >0.8 or diameter stenosis <50% by QCA in vessels without hemodynamically significant stenosis.

+LR = positive likelihood ratio; -LR = negative likelihood ratio; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; other abbreviations as in Table 2.

reported in a study including 4,000 stenoses (14). The present study also found a limited accuracy of 59.6% according to online QCA analysis and 64.0% according to offline QCA analysis in predicting FFR <0.80. In contrast, applying QFR computation to the angiographic analysis without using extra pressure wire and inducing hyperemia substantially improved the diagnostic accuracy to 92.7%. The accuracy was similar (92.3%) when QFR was applied to the patient cohort with only intermediate stenoses (percent diameter stenosis of 40% to 80% by visual estimation). These findings may indicate that QFR bears the potential for a wider adoption of physiological assessment in patients undergoing coronary angiography, especially at diagnostic catheterization laboratories without percutaneous coronary intervention (PCI) facilities.

Studies (2,3) have shown that management of patients with CAD is significantly altered when using FFR at the diagnostic stage by avoiding unnecessary revascularization of a large portion of interrogated vessels at the time of coronary angiography. For patients already selected for PCI, use of FFR is useful for optimization of PCI strategies, allowing a reduction in the number of implanted stents and improvement in clinical outcomes (15,16). A meta-analysis (7) showed that use of an FFR-assisted strategy in patients with stable CAD with intermediate stenosis reduced revascularization by one-half, with 20% fewer adverse events and 10% better angina relief. In China, the number of coronary catheterizations and PCI procedures has significantly increased in the past 2 decades. Nevertheless, a relatively lower portion of patients had undergone functional assessment before PCI, although FFR had been available for clinical use for several years (17). The cost of the pressure wire, the prolonged procedure time secondary to hyperemia induction, and technical issues are the main reasons for the limited adoption of an FFR-assisted strategy. In the present study, excessive pressure drift was often encountered, warranting repeated pressure calibration and wire manipulation to achieve a reliable FFR measurement. In contrast, QFR can be computed in-procedure from 2 conventional angiographic images without extra wire manipulation and vasodilator-induced hyperemia. Patients allergic to vasodilators (i.e., adenosine, ATP) and those ineligible for interventional FFR examination (i.e., severe tortuous and

FIGURE 4 Comparison of Receiver-Operating Curves for the Discrimination of Functionally Significant Stenosis



FFR was used as the reference standard. An FFR ≤0.8, QFR ≤0.8, and QCA identified stenosis >50% as diagnostic of ischemia. AUC = area under the receiver-operating characteristic curve; CI = confidence interval; other abbreviations as in Figure 1.

heavily calcified lesion) can also be assessed by using QFR, thereby increasing the overall clinical feasibility of functional lesion evaluation.

In the past years, several angiography-based solutions (9,18-20) for deriving FFR without using pressure wire have been developed, and promising results were reported. However, in all of these studies, FFR computation was performed offline in the core laboratory. The accuracy remains unknown when these solutions are accessed in the catheterization laboratory by medical and technical staff. To the best of our knowledge, this study is the first that applied QFR computation online during the diagnostic angiography procedure. We reported high feasibility of online QFR computation, and QFR can be readily available during the diagnostic angiography procedure. The high diagnostic accuracy found in this study warrants further investigation into the clinical benefit of a QFR-assisted management strategy for patients with stable CAD and intermediate stenosis.

STUDY LIMITATIONS. Not all the vessels were interrogated for the enrolled patients. The vessels with diameter stenosis <30% or >90% were not assessed because performing physiological assessments in such lesions was left unnecessary. Side branches of bifurcation lesions with Medina type 1,1,1 or 1,0,1 were not assessed. Generalizability of QFR to the side branches of coronary bifurcation lesions requires further investigation (21). Although the accuracy of QFR was high in the present study, there were still numerical differences between QFR and FFR. Nevertheless, for the subgroup with FFR between 0.75 and 0.85, in which a small numerical difference between QFR and FFR can lead to clinical discordance, QFR had high diagnostic accuracy (86.0% [95% CI: 77.9% to 91.9%]) (Online Table 6). In addition, 15.6% of patients had previous myocardial infarction, which might have increased the possibility of inaccurate physiology measurements but also reflects a standard clinical population. Because clinical decisions in the study population were based on FFR measurements, it was not possible to directly evaluate clinical outcome by using a QFR-based diagnostic strategy. Randomized trials comparing clinical outcomes after the use of QFR-based diagnostic strategies and standard diagnostic strategies are warranted.

CONCLUSIONS

The FAVOR II China study met its prespecified primary performance goal for the level of diagnostic accuracy of QFR in identifying hemodynamically significant coronary stenosis. It demonstrated the clinical utility of QFR for use in diagnostic catheterization laboratories, and QFR bears the potential of improving angiography-based identification of functionally significant stenosis during coronary angiography.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Measurement of the QFR during coronary angiography accurately identifies hemodynamically significant coronary stenosis compared with FFR.

TRANSLATIONAL OUTLOOK: Adequately powered randomized trials comparing clinical outcomes of patients undergoing revascularization guided by QFR, FFR, and other diagnostic strategies are warranted.

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KEY WORDS fractional flow reserve, ischemia, quantitative coronary angiography, quantitative flow ratio

APPENDIX For a list of participating hospitals and investigators and supplemental statistical analyses, as well as tables and figures, please see the online version of this article.