Disclosure Statement of Financial Interest

- Funding for the study was provided by the Pulse medical imaging technology (Shanghai) Co., Ltd; the National Key Research and Development Program of China (Grant No. 2016YFC0100500); and the Natural Science Foundation of China (Grant No. 31500797 and 81570456)

- I, (Bo Xu) have no relevant conflicts of interest to disclose

Background

- Patients at high risk of having coronary stenosis are evaluated routinely by invasive coronary angiography
- Fractional flow reserve (FFR) is an increasingly often used method for lesion functional evaluation
- Studies demonstrated that routine use of FFR allowed reclassification of individual management in a large proportion of patients
- 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

Curzen N et al. *Circ Cardiovasc Interv*. 2014;7:248-55; Van Belle E et al. *Circulation*. 2014;129:173-85; Park SJ et al. *Eur Heart J*. 2013;34:3353-61

Quantitative Flow Ratio (QFR)

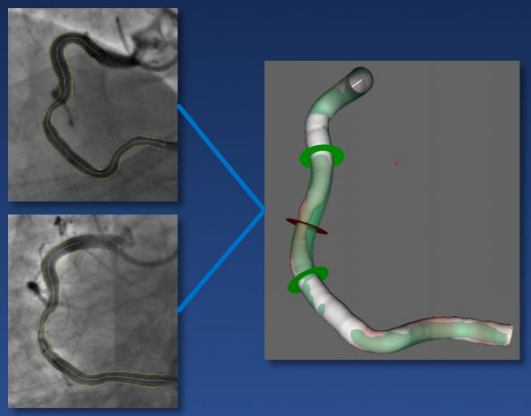
Standard Angiogram

Data Transmission System

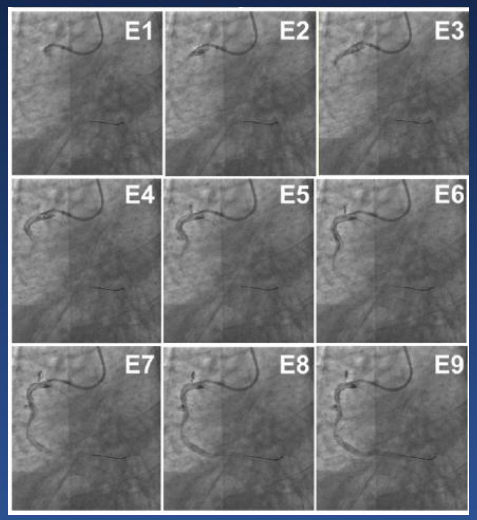
Two image runs with angle difference ≥25°

AngioPlus System

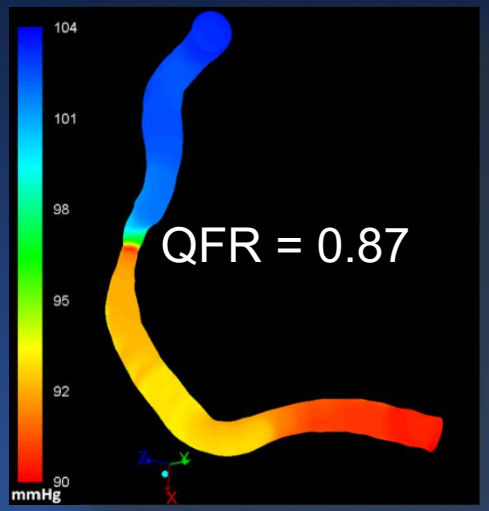
3D Reconstruction



Modified Frame Count



QFR



Without Inducing Hyperemia

Tu S et al. *JACC Cardiovasc Interv*. 2014;7:768-77; Tu S et al. *JACC Cardiovasc Interv*. 2016;9:2024-35

QFR Validation: FAVOR Pilot Study

	fQFR ≤ 0.8	cQFR ≤ 0.8	aQFR ≤ 0.8	DS% ≥ 50%
Accuracy	80 (71-89)	86 (78-93)	87 (80-94)	65 (55-76)
Sensitivity	67 (46-84)	74 (54-89)	78 (58-91)	44 (26-65)
Specificity	86 (74-94)	91 (81-97)	91 (81-97)	79 (66-89)
PPV	69 (48-86)	80 (59-93)	81 (61-93)	50 (29-71)
NPV	85 (73-93)	88 (77-95)	90 (79-96)	75 (62-85)
LR+	4.8 (2.4-9.5)	8.4 (3.6-20.1)	8.9 (3.7-21.0)	2.1(1.1-4.1)
LR-	0.4 (0.2-0.7)	0.3 (0.1-0.5)	0.2 (0.1-0.5)	0.7 (0.5-1.0)
AUC	0.88 (0.79-0.94)	0.92 (0.85-0.97)	0.91 (0.83-0.96)	0.72 (0.62-0.82)

- Good diagnostic accuracy for contrast-flow QFR (without inducing hyperemia);
- However, QFR analysis was performed in the core lab; QFR accuracy when performed **online** in the cath lab had not been properly examined to date.

Tu S et al. *JACC Cardiovasc Interv*. 2016;9:2024-35

Objectives

- To evaluate the diagnostic accuracy of online angiography-based QFR in identifying hemodynamically-significant coronary stenosis by using pressure wire-based FFR as the reference standard

FAVOR II China (N=308)

Prospective, multicenter clinical study (in a blinded fashion)

Major Inclusion: Age ≥ 18 years; stable, unstable angina; diameter stenosis between 30% and 90% in a vessel ≥ 2 mm by visual estimation

Major Exclusion: Myocardial infarction within 72 hours; severe heart failure (NYHA ≥ III); ostial lesions, or main vessels with stenotic side branches downstream the interrogated lesion

↓

Online QFR and QCA assessment
(blinded to the investigators who measured FFR)

↓

Wire-based FFR measurement

Primary Endpoint: Diagnostic accuracy* of online QFR as compared with FFR.

Major Secondary Endpoint: Sensitivity^ and specificity‖ of online QFR as compared with online QCA, when using FFR as a reference standard.

*Diagnostic accuracy: defined as consistency ratio of QFR evaluated outcomes (≤0.8 or >0.8) with the reference standard FFR evaluated outcomes (≤0.8 or >0.8); ^Sensitivity: proportion of QFR≤0.8 or QCA≥50% in vessels with hemodynamically-significant stenosis as measured by FFR (FFR≤0.8); ‖Specificity: proportion of QFR>0.8 or QCA<50% in vessels without hemodynamically-significant stenosis as measured by FFR (FFR≤0.8).

ClinicalTrials.gov NCT0319170

Statistical Assumptions

The study was powered for testing both primary and major secondary endpoint

For the primary endpoint:

- Target value = 75%
- Estimated accuracy = 83%
- Two-sided type I error = 0.05

277 patients with paired QFR and FFR would yield at least 90% power to achieve target goal

Assuming anticipated loss to analysis of 10% due to failed QCA, QFR or FFR assessment, enrollment of 308 patients were required

For the major secondary endpoint:

- Assuming sensitivity and specificity was 0.74 and 0.91 for QFR, while 0.48 and 0.76 for QCA
- Two-sided type I error = 0.05

308 patients would yield >80% power to demonstrate superiority of QFR over QCA

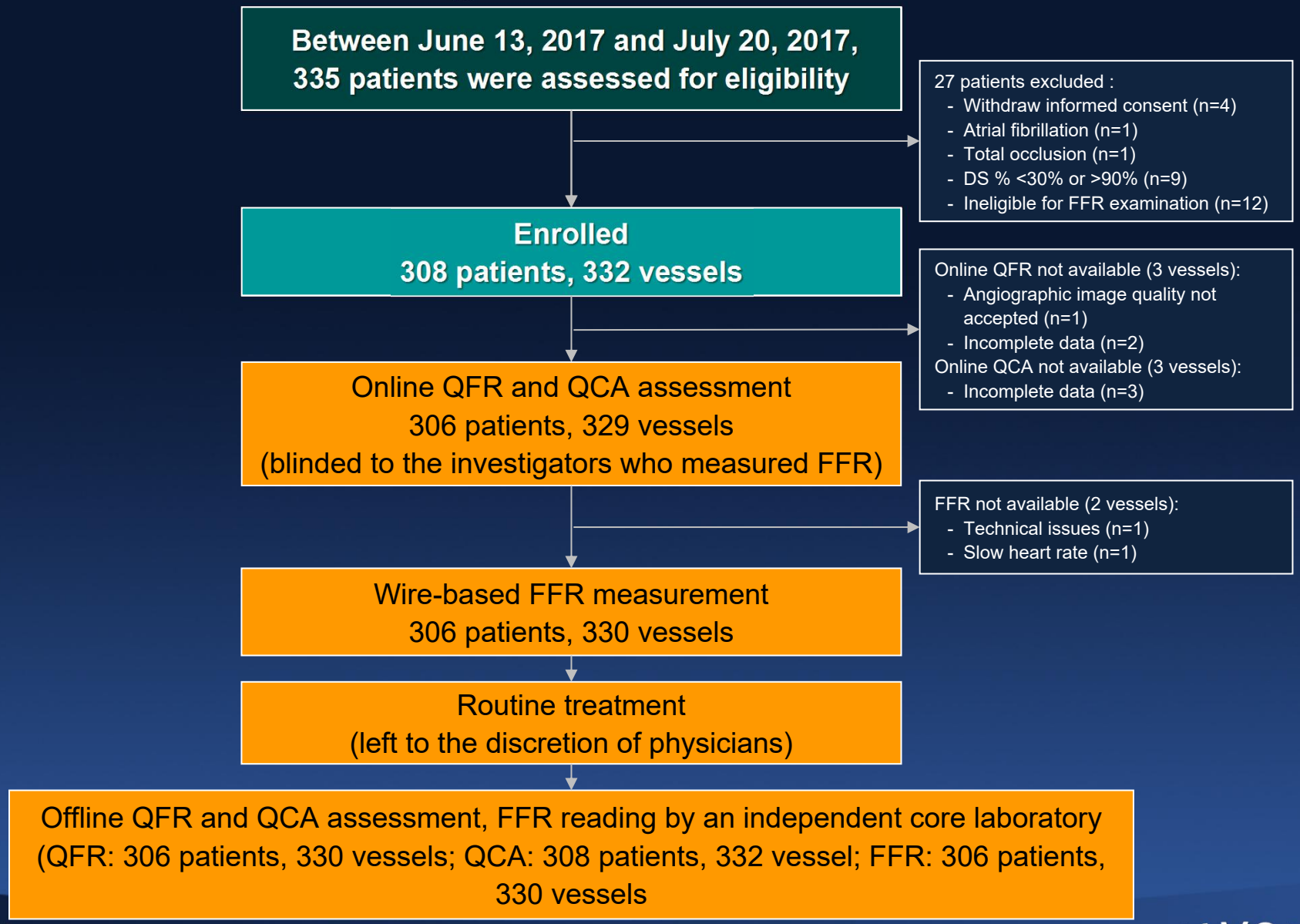
Study Organization

Principal Investigator	Shengshou Hu, MD
Co-Principal Investigator	Bo Xu, MBBS and Shubin Qiao, MD
Data Management and Data Monitoring	CCRF, Beijing, China
Angiographic Core Lab	
Statistical Analysis	Medical Research and Biometrics Center, National Center for Cardiovascular Diseases, Beijing, China
Sponsor	Pulse Medical Imaging Technology (Shanghai) Co., Ltd

Sites and Investigators

Investigators	Hospital, City	Patients Enrolled
Shengshou Hu, Shubin Qiao, and Bo Xu	Fu Wai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China	140
Xinkai Qu and Weiyi Fang	Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China	53
Yundai Chen and Feng Tian	Chinese PLA General Hospital, Beijing, China	50
Junqing Yang and Jiyan Chen	Guangdong General Hospital, Guangzhou, China	45
Lijun Guo	Peking University Third Hospital, Beijing, China	20

Study Flow Chart



Baseline Patient Demographics

	Patients (N=308)
Age, years	61.3 ± 10.4
Women	26.3%
Diabetes Mellitus	27.9%
Hypertension	60.1%
Hyperlipidemia	45.1%
Current Smoker	28.2%
Family History of CAD	16.6%
Previous MI	15.6%
Previous PCI	21.1%
AMI within 1 Month	4.5%
Stable Angina	23.4%
Unstable Angina	61.0%
Left Ventricular Ejection Fraction, %	63.4 ± 6.3

Vessel Characteristics

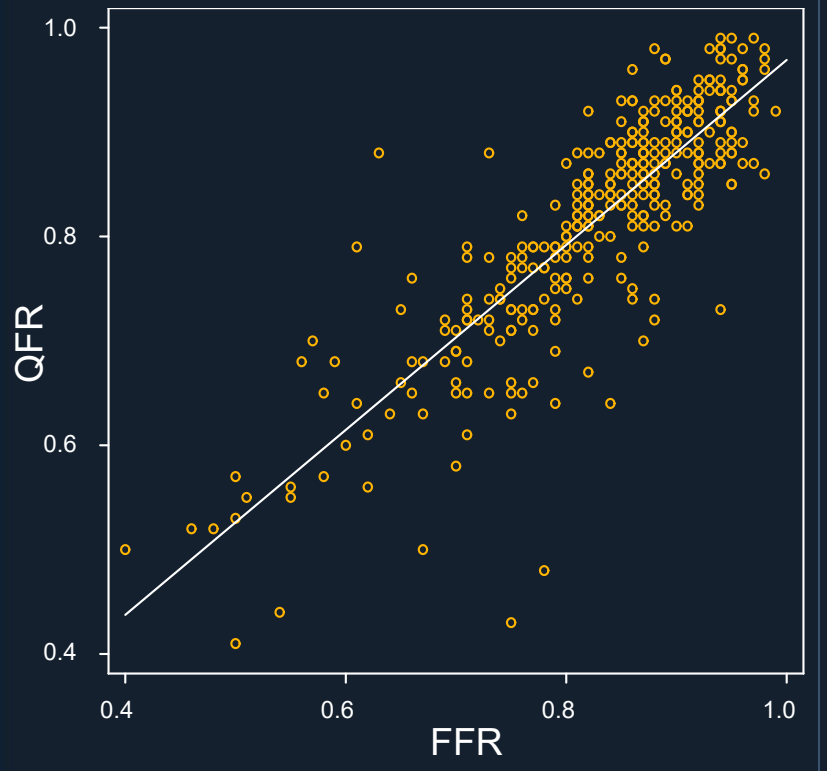
	Patients (N=308) Vessels (N=332)
Interrogated Vessels	
Left Anterior Descending Artery	55.7%
Diagonal Branch	0.6%
Left Circumflex Artery	14.8%
Obtuse Marginal Branch	1.5%
Ramus Intermediate	0.3%
Right Coronary Artery	26.2%
Posterior Descending Artery	0.3%
Posterolateral Branch	0.6%
Reference Vessel Diameter, 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

Lesion/Procedural Characteristics

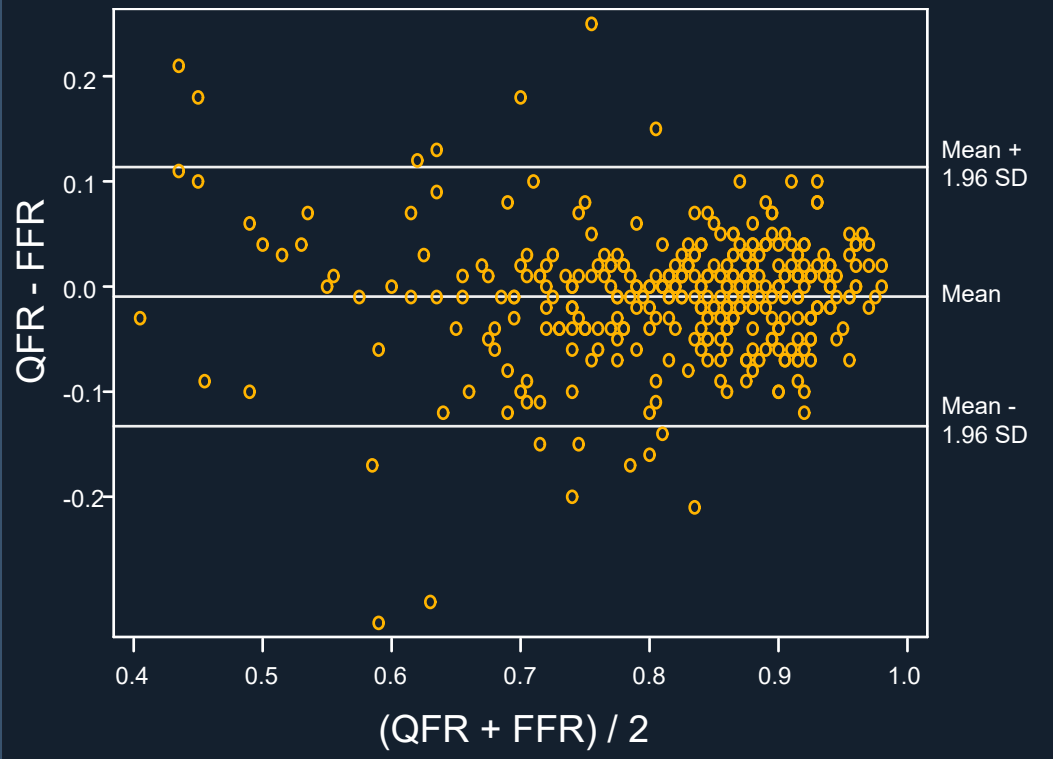
	Patients (N=308) Vessels (N=332)
Bifurcation Lesions	24.7%
Tortuous Vessels	14.2%
Moderate or Severe Calcified Lesions	18.4%
Thrombotic Lesions	0.3%
Tandem Lesions	46.3%
Online FFR Analysis	
FFR (Per Vessel)	0.82 ± 0.12
Vessels with FFR ≤ 0.80	34.2%
Vessels with 0.75 ≤ FFR ≤ 0.85	32.4%
Patients with FFR Measurement in > 1 Vessel	7.2%
Mean Time for QFR Assessment, mins	4.36 ± 2.55

Correlation and Agreement of QFR and FFR (Online Analysis)

r = 0.857, p < 0.001

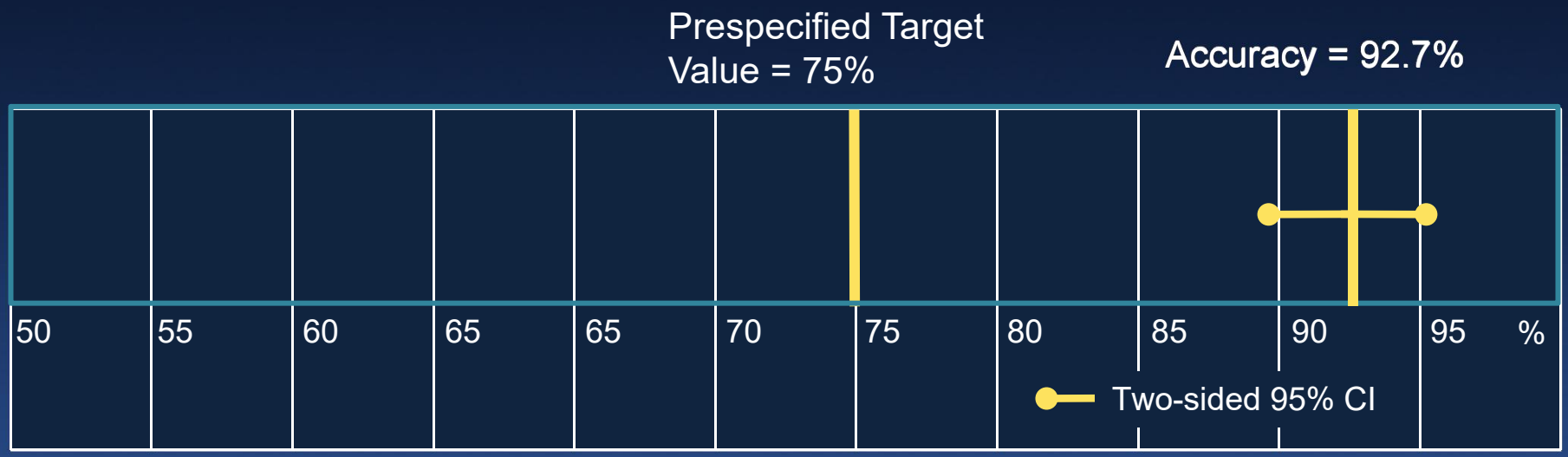


Mean difference: -0.01, SD: 0.063, p = 0.006



Primary Endpoint: Online Per-Vessel QFR Diagnostic Accuracy

Accuracy	Target Value	p Value
Point Estimate: 92.7% (304/328) 95% Confidence Interval: 89.3% to 95.3%	75%	< 0.0001



Prespecified Performance Goal Met

Diagnostic Accuracy of QFR in Different Interrogated Vessels

Interrogated Vessels	Accuracy	
	Estimate, % (95% CI)	No. of Patients in Group
LAD	92.4 (87.6, 95.8)	184
LCX	96.4 (87.5, 99.6)	55
RCA	91.0 (83.1, 96.0)	89
	Difference, % (95% CI)	p Value
LAD vs. LCX	-4.0 (-9.9, 2.3)	0.30
LAD vs. RCA	1.4 (-5.5, 8.8)	0.70
LCX vs. RCA	5.4 (-2.3, 13.7)	0.22

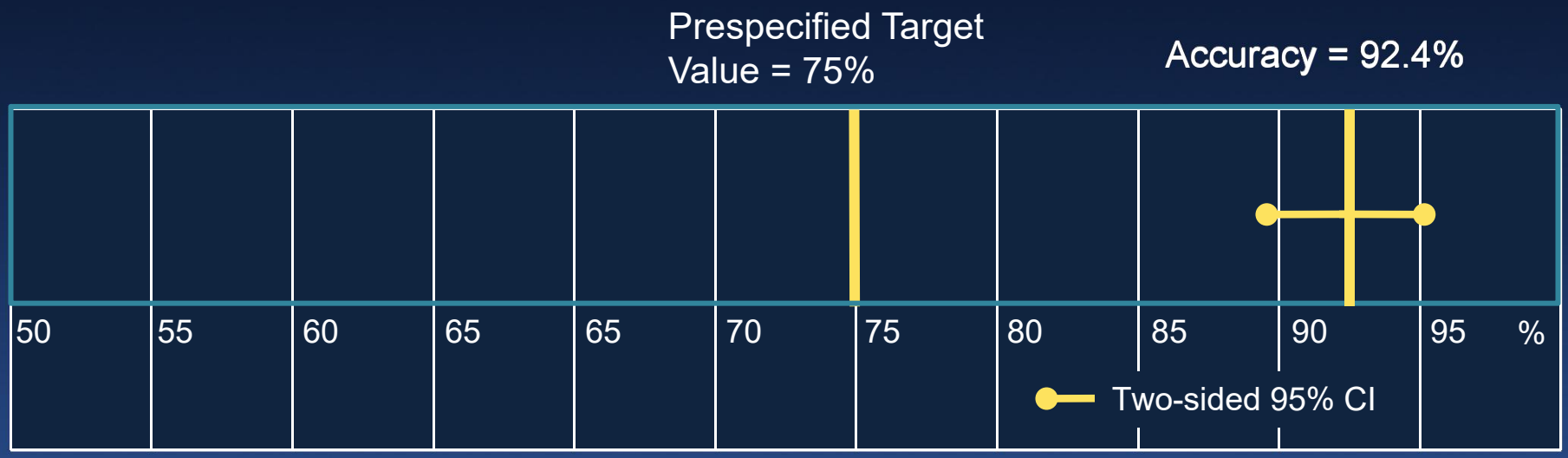
Diagnostic Consistency for Identifying Hemodynamically-Significant Stenosis by QFR and FFR

	FFR > 0.8	FFR ≤ 0.8
QFR > 0.8	198	6
QFR ≤ 0.8	18	106

Difference Between QFR and FFR	
> 0.05	31.4% (103/328)
> 0.1	8.5% (28/328)
LAD	10.3% (19/184)
LCX	5.5% (3/55)
RCA	6.7% (6/89)

Online Per-Patient Diagnostic Accuracy of QFR

Accuracy	Target Value	p Value
Point Estimate: 92.4% (281/304) 95% Confidence Interval: 88.9% to 95.1%	75%	< 0.0001



Prespecified Performance Goal Met

Diagnostic Performance of QFR and QCA (Online Analysis)

	QFR ≤ 0.8	Diameter Stenosis by QCA ≥ 50%	Difference 95% (CI)	p Value
Accuracy, %	92.7 (89.3, 95.3)	59.6 (54.1, 65.0)	34.9 (28.3, 41.5)	< 0.001
Sensitivity, %	94.6 (88.7, 98.0)	62.5 (52.9, 71.5)	32.0 (21.0, 43.1)	< 0.001
Specificity, %	91.7 (87.1, 95.0)	58.1 (51.2, 64.8)	36.1 (27.9, 44.3)	< 0.001
PPV, %	85.5 (78.0, 91.2)	43.8 (35.9, 51.8)	42.0 (31.4, 52.7)	< 0.001
NPV, %	97.1 (93.7, 98.9)	74.9 (67.6, 81.2)	24.4 (15.6, 33.2)	< 0.001
+ LR	11.4 (7.1, 17.0)	1.49 (1.21, 1.85)	-	-
- LR	0.06 (0.03, 0.13)	0.65 (0.50, 0.84)	-	-

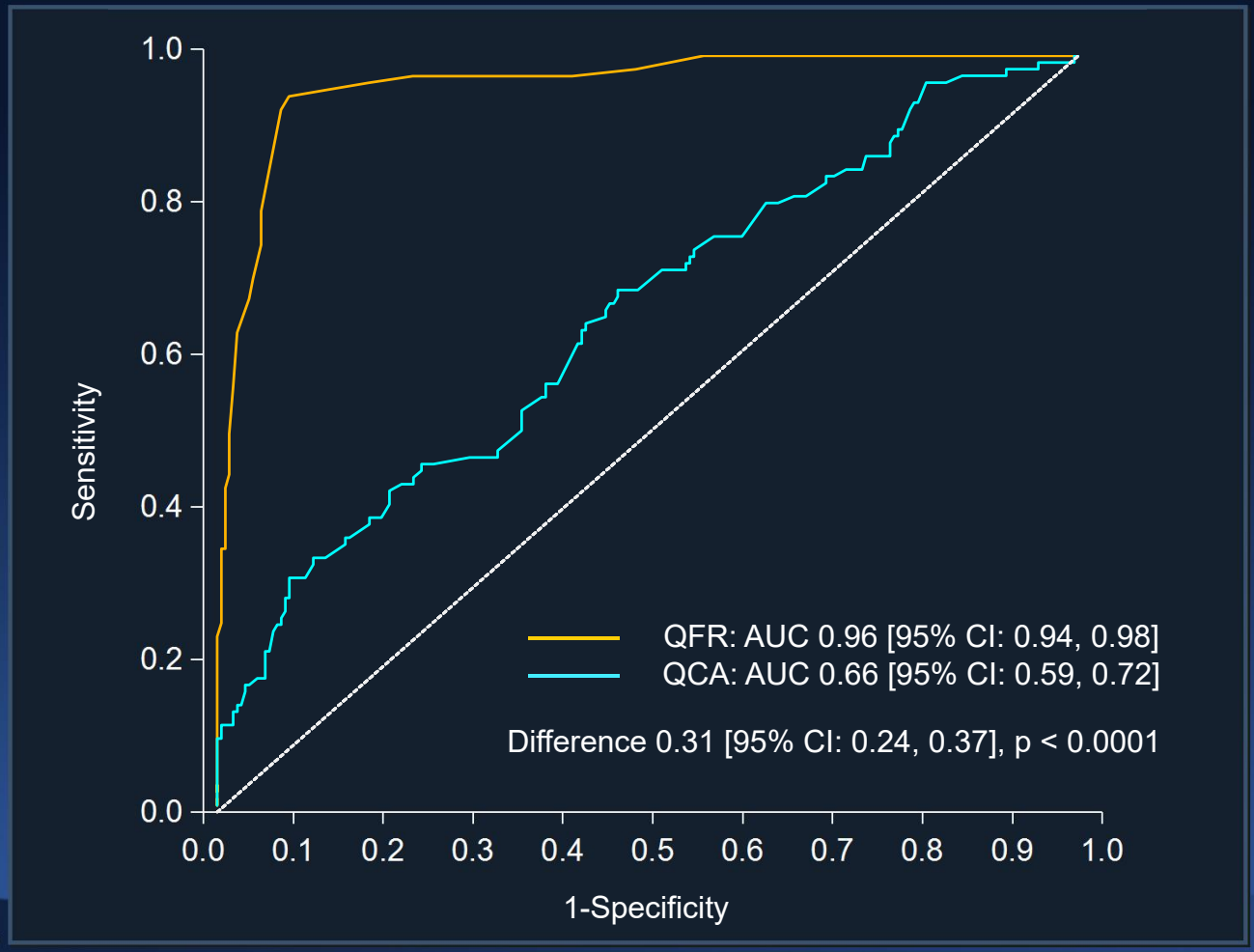
PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio

Diagnostic Performance of QFR and QCA (Offline Analysis)

	QFR ≤ 0.8	Diameter Stenosis by QCA ≥ 50%	Difference 95% (CI)	p Value
Accuracy, %	93.3 (90.0, 95.7)	64.0 (58.6, 69.2)	29.9 (23.2, 36.7)	<0.001
Sensitivity, %	94.1 (88.3, 97.6)	49.6 (41.1, 59.7)	44.4 (33.0, 55.7)	<0.001
Specificity, %	92.8 (88.4, 95.9)	72.2 (65.7, 78.2)	21.3 (13.2, 29.4)	<0.001
PPV, %	88.2 (81.3, 93.2)	50.4 (41.0, 59.8)	37.0 (25.4, 48.6)	<0.001
NPV, %	96.5 (93.0, 98.6)	71.6 (65.0, 77.5)	26.8 (18.5, 35.0)	<0.001
+ LR	13.1 (8.04, 21.0)	1.81 (1.36, 2.40)	-	-
- LR	0.06 (0.03, 0.13)	0.69 (0.57, 0.84)	-	-

PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio

Receiver Operating Curves for the Discrimination of Functionally Significant Stenosis (Online Analysis)



Diagnostic Performance of QFR and QCA in Subgroup of DS% [40% - 80%] by Visual Estimation

	QFR ≤ 0.8	Diameter Stenosis by QCA ≥ 50%	Difference 95% (CI)	p Value
Accuracy, %	92.3 (88.5, 95.2)	58.5 (52.4, 64.4)	36.6 (29.2, 44.1)	< 0.001
Sensitivity, %	92.2 (83.8, 97.1)	54.5 (42.8, 65.9)	44.1 (28.4, 59.9)	< 0.001
Specificity, %	92.3 (87.7, 95.7)	60.0 (52.8, 66.9)	35.1 (26.4, 43.8)	< 0.001
PPV, %	82.6 (72.9, 89.9)	35.0 (26.5, 44.2)	50.5 (37.0, 64.1)	< 0.001
NPV, %	96.8 (93.1, 98.8)	77.0 (69.5, 83.4)	22.9 (13.8, 32.0)	< 0.001
+ LR	12.0 (7.34, 20.0)	1.36 (1.04, 1.78)	-	-
- LR	0.08 (0.04, 0.18)	0.76 (0.58, 0.99)	-	-

PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio

Diagnostic Accuracy of QFR in the FFR "Grey Zone" Subgroup

	0.75 ≤ FFR ≤ 0.85		FFR < 0.75 or FFR > 0.85	
	Estimate, % (95% CI)	No. of Vessels in Group	Estimate, % (95% CI)	No. of Vessels in Group
QFR Accuracy, %	86.0 (77.9, 91.9)	107	95.9 (92.4, 98.1)	221

For the subgroup with FFR between 0.75 and 0.85 where a small numerical difference between QFR and FFR can lead to clinical discordance, QFR still had high diagnostic accuracy (86.0% [95% CI: 77.9% to 91.9%])

Limitations

- Not all the vessels were interrogated for the enrolled patients: the vessels with diameter stenosis below 30% or above 90% were not assessed as performing physiological assessment 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 still requires further investigation.
- Although the accuracy of QFR was high in the present study, there was still numerical difference between QFR and FFR. Nevertheless, for the subgroup with FFR between 0.75 and 0.85 where a small numerical difference between QFR and FFR can lead to clinical discordance, QFR still had high diagnostic accuracy.
- Additionally, there were 15.6% patients with previous myocardial infarction, which might have increased the possibility of inaccurate physiology measurements but also reflects a standard clinical population.
- As clinical decisions in the study population were based on FFR measurements, it was not possible to directly evaluate clinical outcome by a QFR based diagnostic strategy. Randomized trials comparing clinical outcomes after 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 demonstrates 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.