

# WITHDRAWN: Diagnostic Performance of Immediate Angiography Derived Quantitative Flow Ratio In Patients After Second Generation Drug Eluting Stent And Bioresorbable Scaffold Implantation

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## Research Article

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

# Abstract

Quantitative flow ratio (QFR) is a novel angiography derived fractional flow reserve (FFR). However, its diagnostic performance has only been validated in native coronary lesion but not yet in vessels after stent implantation. This study aims to evaluate the diagnostic performance of QFR in coronary vessels immediately after everolimus eluting stent (EES) and bioresorbable scaffold (BRS) implantation. This is a retrospective, two centers, validation cohort study. 73 stable angina patients who received at least one native vessel EES/BRS implantation with immediate FFR assessment were screened. Cases with aorto-ostial stenoses, bridge vessel at the distal of targeted vessel, acute coronary syndrome, previous coronary artery bypass grafting, age < 18 years, lack of  $\geq 2$  final angiographic projections were excluded. Contrast QFR assessment was performed blinded to FFR assessment. A good correlation ( $r = 0.680$ ,  $p < 0.001$ ) was found between QFR and FFR. In the EES implantation cohort, a good correlation ( $r = 0.769$ ,  $p < 0.001$ ) was found between QFR and FFR, while moderate correlation ( $r = 0.446$ ,  $p = 0.038$ ) was found in the BRS cohort. The area under the ROC curve for detecting  $FFR \leq 0.86$  was 0.883 for the total subjects. QFR assessment after immediate EES/BRS implantation is feasible, and remains good correlation and agreement with FFR. QFR might be a promising tool for guiding stent implantation optimizing to improve clinical outcomes.

## Backgrounds

Coronary revascularization driven by evidence of myocardial ischemia is the indication for percutaneous coronary intervention (PCI)[1]. Nowadays, fractional flow reserve (FFR) has been the golden standard invasive method to evaluate the functional significance of coronary artery stenoses, usually induced by adenosine infusion[2].  $FFR \leq 0.80$  indicates functionally significant stenoses, whereas physiological revascularization is associated with superior outcomes[3]. On this ground, recent guidelines recommend the measurement of FFR in defining the functional significance of intermediate coronary stenoses as a class IA recommendation[4]. Quantitative flow ratio (QFR) is a novel method to evaluate the functional significance of coronary stenoses by FFR calculation on 3-dimensional angiographic reconstruction and fluid dynamics algorithms[5]. The FAVOR Pilot study showed promising results of QFR computation in identifying the presence of functionally significant stenoses in interrogated vessels[5]. The favorable results of QFR that does not require pharmacologic hyperemia induction bears the potential of a wider adoption of FFR-based lesion assessment through a reduction in procedure time, risk, and costs. QFR computation is superior to angiographic assessment for coronary artery stenoses using FFR as a reference standard in FAVOR II Europe-Japan Study[6]. The FAVOR II China study showed that QFR demonstrated high feasibility and accuracy in identifying hemodynamically significant coronary stenoses after coronary angiography[7]. The ongoing FAVOR III China study will examine the effectiveness and cost-effectiveness of a QFR-guided versus an angiography-guided PCI strategy in coronary artery disease patients[8].

The aforementioned studies demonstrated the feasibility and accuracy of QFR in functional stenoses severity, potentially enabling broader clinical applications. In fact, diagnostic performance of QFR has not

been thoroughly evaluated in patients after stent implantation using FFR as a reference standard. As alternative methods to evaluate functional significance of remaining coronary stenoses after stent implantation, functional coronary blood flow assessment has recently emerged, allowing wire-free functional assessment of residual stenoses. To further evaluate the effect of physiological-guided PCI, QFR was developed for invasive FFR approximation in patients after stent implantation. Clinically, many patients are based solely on angiographic assessment of coronary artery stenoses after PCI. This may lead to a significant rate of unnecessary operation, expense and patients' pain, because angiography is imprecise in determining the haemodynamic significance of residual coronary artery stenoses. As QFR is able to assess the haemodynamic significance with high diagnostic accuracy (92.7% in FAVOR II China study), this technique might be atraumatically used to guide patient assessment of PCI efficacy.

In addition to the potential application in evaluating strategy of coronary revascularization, QFR can be used to assess the efficacy of stents implantation by evaluating the physiological functionality of coronary artery. Accordingly, the aim of this study is to evaluate the effect of PCI and the relationship between QFR and FFR in a cohort of patients after EES or BRS implantation.

## **Methods**

### **Study population**

Patients were referred for invasive FFR measurement and subsequently PCI if needed, then included in this study. Patients were excluded of aorta-ostial stenoses, bridge vessel at the distal of targeted vessel, acute coronary syndrome (ACS), previous coronary artery bypass grafting (CABG), age < 18 years, lack of  $\geq 2$  final angiographic projections. The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine and all patients provided written informed consent.

### **Invasive coronary angiography and FFR measurement**

Angiographic projections were performed with biplane systems. At least two adequate contrast-filled angiographic projections with  $> 25^\circ$  apart were acquired for QFR calculation. For invasive FFR measurements, the pressure wire was located far from the stent and maximal hyperaemia was induced by continuous intravenous infusion of adenosine (0.14 mg/kg/min). For the invasive FFR and QFR models, all projections were required with 15 frames/s.

### **Quantitative flow ratio calculation**

Details concerning the QFR calculation have been reported previously. The observer calculated the contrast flow QFR values, unaware of the pressure-wire FFR value. The location of the FFR pressure-wire was identified at the angiographic projections and the QFR values were measured at the same location. For each vessel the flow models were applied to a 3D reconstruction of that vessel. QFR uses frame count analysis from regular (non-hyperaemic) angiographic projections to model hyperaemic flow velocity.

## Statistical analysis

Continuous variables were depicted as mean $\pm$ SD, n (%) or median with interquartile range according to their distributions, which were checked by the Kolmogorov-Smirnov test. The one-sample T test was used to test whether the QFR and FFR values differed significantly from zero. Agreement between the QFR and FFR was assessed using Bland-Altman and correlation was determined by Pearson's correlation coefficient. Pair wise comparisons of different QFR analyses were assessed using Bland-Altman plots. Receiver operator characteristic (ROC) curves were compared using the DeLong method. All statistical analyses were performed with the use of SPSS Statistics software (version 20.0). A P value < 0.05 was considered statistically significant.

## Results

### Patients

In total, 73 patients who were referred for FFR were included in the study. The baseline characteristics of all patients are shown in Table 1. 17 patients had previous diabetes mellitus and 40 patients had previous hypertension. 22 patients had been smoking. 55 patients had prior PCI. None patient had prior ACS, CABG or chronic obstructive pulmonary diseases (COPD). 51 patients had been implanted with everolimus-eluting stents (EES) and 22 patients had been implanted with bioresorbable scaffold (BRS).

### Relationship between QFR and FFR

In total, 73 coronary arteries were analysed. The mean of QFR and FFR values was  $0.91\pm 0.06$  and  $0.94\pm 0.06$  ( $p < 0.05$ ), respectively. Hence, no systematic under- or over-estimation of the QFR was observed when compared with FFR values. Pearson's correlation and agreement between QFR and FFR were 0.680,  $p < 0.01$  and  $-0.03\pm 0.09$ , respectively in Figure 1A and 1B. Pearson's correlation between QFR and FFR were 0.74,  $p < 0.01$  in EES group (Figure 1C) and 0.45,  $p = 0.04$  in BRS group (Figure 1E) respectively. The agreement between QFR and FFR were  $-0.03\pm 0.08$  in EES group (Figure 1D) and  $-0.02\pm 0.12$  in BRS group (Figure 1F) respectively. The area under the ROC curve for QFR to detect an invasive FFR of  $\leq 0.86$  was 0.869 (Figure 2).

## Discussion

In this study, QFR showed a good correlation and agreement with invasive FFR for the detection of cutoff 0.86 in patients after stent implantation. In addition, the physiologic QFR indices were evaluated using FFR as a reference standard. Importantly, QFR showed excellent correlation and certifying performance for invasive FFR, regardless of clinical presentation and types of implanted stents. Especially, both EES and BRS groups show excellent agreement and correlation.

As coronary revascularization is beneficial, there have been numerous efforts to detect the presence of myocardial ischemia. Although many non-invasive tests to assess myocardial ischemia are available,

previous studies reported a low diagnostic yield[8]. FFR has been validated in several large-scale randomized controlled trials and considered as a standard invasive method to define the functional significance of coronary stenoses[9]. In fact, the low utilization rate of FFR may be related to the cost of additional coronary artery instruments, drugs and equipment, prolongation of program time, discomfort of adenosine treatment, and limited confidence in results, experience, or personal beliefs[10]. In order to overcome these limitations, these efforts have developed some new techniques to evaluate the functional significance of non-invasive detection of coronary artery stenoses.

QFR is a method derived from angiography, which provides functional assessment of coronary artery stenoses by calculating the number of 3-dimensional quantifying coronary angiography (3D QCA) and TIMI frames without increasing pressure wire or causing congestion. A good correlation and agreement were observed between QFR and FFR in the FAVOR Pilot Study[5]. In that study, QFR and FFR of 84 coronary arteries in 73 patients with moderate coronary artery stenoses were compared. The FAVOR II China Study assessed the diagnostic accuracy of QFR prior to FFR measurement[7]. Compared with diameter stenoses (DS)  $\geq 50\%$  assessed by QCA, the diagnostic accuracy of QFR  $\leq 0.80$  is much higher (92.7% vs. 59.6%,  $P = 0.001$ ) in FAVOR II China Study. The FAVOR II Europe-Japan Study assessed the diagnostic accuracy of QFR in 317 vessels from 272 patients with intermediate coronary stenoses[6]. Using FFR as the reference standard, diagnostic accuracy of QFR was 87%. A good correlation ( $r = 0.70$ ,  $P = 0.001$ ) and agreement (mean difference  $0.01 \pm 0.08$ ) were observed between QFR and FFR in the WIFI II Study[11]. Furthermore, QFR showed a good correlation ( $r = 0.80$ ,  $P < 0.001$ ) and agreement (mean difference  $0.01 \pm 0.05$ ) with FFR in a retrospective study performed in 151 coronary arteries from 142 patients.

Although QFR has not been a gold standard for evaluating myocardial ischemia, QFR is the most studied angiography-derived FFR technologies. Thus, QFR may provide better decisions in PCI. So far, current clinical trials have assessed the coronary artery stenoses in patients before PCI. QFR has not been well validated with FFR in evaluating patients after coronary stent implantation. No research has been reported on whether QFR is comparable to FFR in patients with residual coronary artery stenoses after coronary stenting. In this study, we got a conclusion that QFR showed a good correlation and agreement with FFR in patients after stent implantation both in the EES group and in the BRS group. This study verifies the availability of QFR with FFR in patients after stent implantation. The correlation and agreement between QFR and FFR were 0.63,  $p < 0.01$  and  $-0.03 \pm 0.09$ , respectively. The data was comparable to the results of the previous trials.

We found good correlation and agreement not only in EES group but also in BRS group. The brightest thing is that these stents include BRS in our study, the latest generation of stent. QFR and FFR have good correlation ( $r = 0.45$ ,  $p = 0.04$ ) and agreement ( $-0.02 \pm 0.12$ ) after BRS implantation, which has not been reported in previous studies. This may broaden the scope of application for QFR, especially for post-PCI evaluation of different stent types.

According to the European Society of Cardiology (ESC) guidelines, FFR is recommended to identify hemodynamically significant coronary lesions when evidence of myocardial ischemia is not available[12]. During the Big Data Age, the use of QFR in the catheter laboratory is very feasible. When computed by specialized technicians, the average QFR calculation time is only  $4.36 \pm 2.55$  min[13]. QFR could be important clinic use in hospital that are not capable to perform FFR, especially when you need to assess whether residual coronary stenoses is needed to be treated. In fact, the reproducibility of QFR has been evaluated in a number of studies. Chang et al.'s recent studies have shown that QFR has a good reproducibility in evaluating the hemodynamic significance of coronary heart disease when QFR is performed in two independent core laboratories (mean difference in QFR  $0.004 \pm 0.03$ )[14]. QFR showed a high diagnostic accuracy for the identification of  $FFR \geq 0.86$  in patients after coronary stent implantation. It is convenient to assess coronary artery residual stenoses after PCI. This is a good situation that QFR can be applied in simple lesions PCI, perhaps in complex lesions.

Nowadays, visual assessment alone is known to be inaccurate in determining the haemodynamic significance of residual coronary stenoses. More then, additional functional testing, FFR for example, is lost-time and may lead to increased X-ray exposure. The use of QFR could significantly extend the possibility to perform functional assessment of residual coronary stenoses to a wide range of hospitals. According to this study, QFR enables the usability in a large subset of patients and primary hospitals. Our study showed that QFR was similar in accuracy to FFR in estimating residual coronary stenoses after stent implanting, which saved operating time and needed less radiation.

## Limitation

This study was limited by its retrospective character. The acquisition guide enables the selection of optimal angiographic projections with a minimum of vessel overlap and/or foreshortening. The use of this acquisition guide in the catheterization laboratory would probably lead to a smaller amount of included coronary arteries in our study. Moreover, residual coronary stenoses would be more accurate when performed on prospectively selected angiographic projections with high image quality. The selection of angiographic images may result in a superior diagnostic accuracy of QFR and a further increase in the proportion of patients that could be correctly deferred from invasive FFR referral after stent implantation. Our patients cohort is a real-world representation of the patients that are currently referred for invasive FFR according to the guidelines. Finally, selection bias cannot be excluded due to the retrospective design of this study.

## Conclusions

QFR shows a high correlation and good agreement with FFR in stent-treated arteries immediately after PCI.

## Abbreviations

QFR quantitative flow ratio

FFR fractional flow reserve

EES everolimus eluting stent

BRS bioresorbable scaffold

PCI percutaneous coronary intervention

ACS acute coronary syndrome

CABG coronary artery bypass grafting

ROC receiver operator characteristic

COPD obstructive pulmonary diseases

3D QCA 3-dimensional quantifying coronary angiography

DS diameter stenoses

ESC European Society of Cardiology

## **Declarations**

### **Acknowledgments**

None.

### **Authors' Contributions**

Chongying Jin contributed to all aspects of this study, including study concept and design, data acquisition, statistical analysis and revising the report. Zhengwei Li contributed to statistical analysis, study concept and design, data acquisition and manuscript drafting. Jiachen Zhan, Jia Han and Guosheng Fu contributed to study concept and design, data acquisition.

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**Conflict of interest** The authors declare that they have no conflict of interest.

### **Disclosures**

The authors declare no conflict of interest.

## Ethical approval

The study was performed in compliance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine (No. 20200917).

## Consent to participate

Informed consent was obtained from all individual participants included in the study.

## Consent for publication

Patients signed informed consent regarding publishing their data and photographs.

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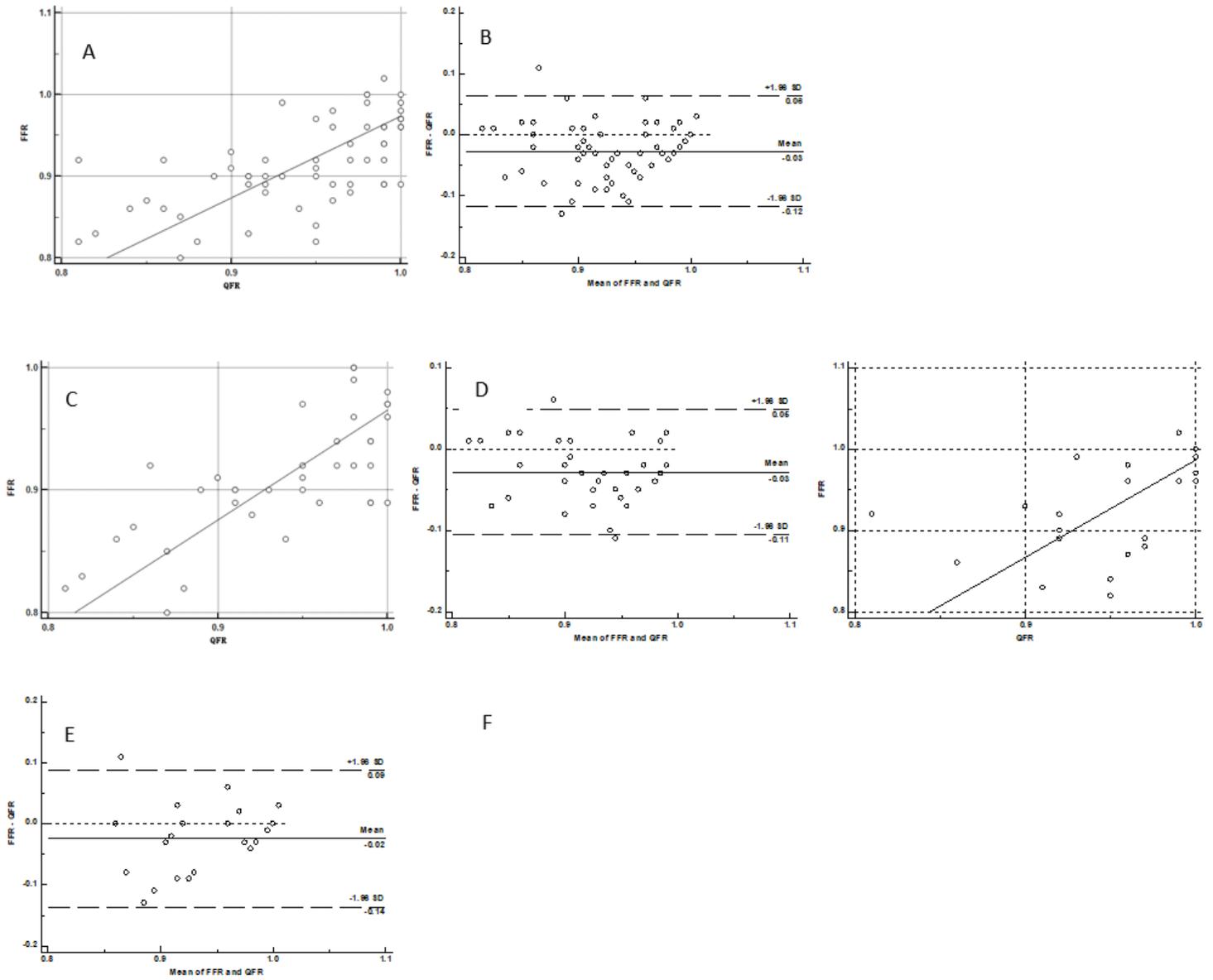
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## Tables

Table 1. Baseline patient characteristics

|                       | Total (75)          |
|-----------------------|---------------------|
| Age(years)            | 65.24±8.98          |
| Male                  | 53(70.7%)           |
| BMI kg/m <sup>2</sup> | 24.64±3.16          |
| Cr                    | 79.76±18.45         |
| eGFR                  | 87.99±21.98         |
| Lp(a)                 | 11.25(5.38,32.50)   |
| LDL-C                 | 1.99±0.78           |
| NT Pro BNP            | 55.00(26.00,129.00) |
| HbA1c %               | 6.22±1.17           |
| LVEF(%)               | 68.49±7.92          |
| Diabetes              | 17 22.7%            |
| Hypertension          | 40 53.3%            |
| Smoking               | 22 29.3%            |
| Prior MI              | 0                   |
| COPD                  | 0                   |
| Prior CABG            | 0                   |
| Prior PCI             | 55 73.3%            |
| EES                   | 53(70.7%)           |
| BRS                   | 22(29.3%)           |

## Figures



**Figure 1**

Pearson's correlation (A) and agreement (B) between QFR and FFR in 60 patients. Pearson's correlation (C) and agreement (D) between QFR and FFR in EES group. Pearson's correlation (E) and agreement (F) between QFR and FFR in BRS group.

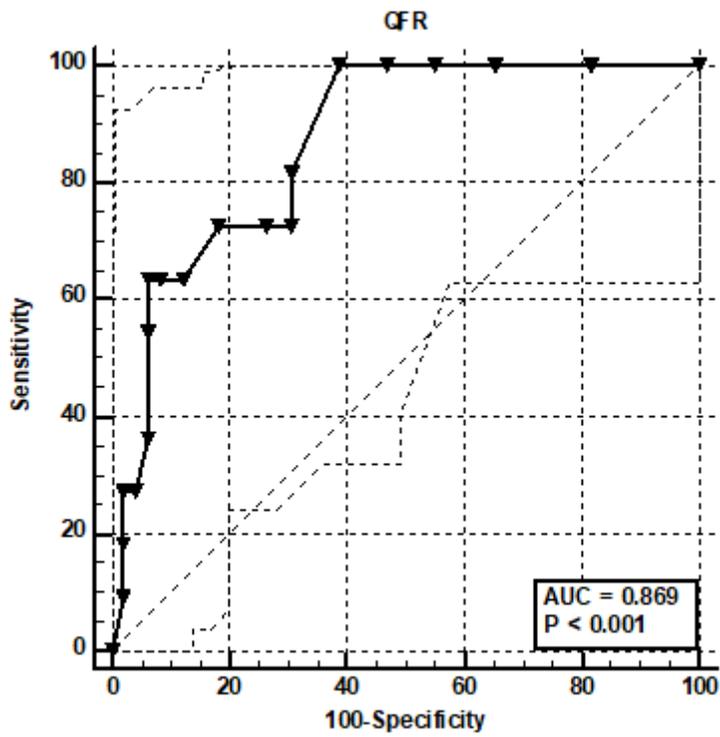


Figure 2

receiver-operating characteristic curve for QFR to detect an invasive FFR of  $\leq 0.86$ .