EuroIntervention 2021;17:e396-e398 published online July 2019 ■ published online e-edition August 2021

# Quantitative flow ratio for functional evaluation of in-stent restenosis

**Catherine Liontou**[1], MD, PhD; Hernán Mejía-Rentería[1], MD; Francesco Lauri[1], MD; Sonoka Goto[1,2], MD; Hyun Jong Lee[3], MD, PhD; Masafumi Nakayama[2,4], MD, PhD; Alicia Quirós[5], PhD; Fernando Macaya[1], MD; Nieves Gonzalo[1], MD, PhD; Iván Núñez-Gil[1], MD, PhD; Pablo Salinas[1], MD, PhD; Maria Del Trigo[1], MD, PhD; Javier Escaned[1]*, MD, PhD

*1. Hospital Clínico San Carlos IDISSC and Universidad Complutense de Madrid, Madrid, Spain; 2. Cardiovascular Center, Toda Chuo General Hospital, Toda, Japan; 3. Division of Cardiology, Department of Internal Medicine, Sejong General Hospital, Bucheon, Republic of Korea; 4. Joint Graduate School of Tokyo Women's Medical University and Waseda University, Tokyo, Japan; 5. Department of Mathematics, Universidad de León, León, Spain*

*This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00955*

## Introduction

Coronary angiography is the most common diagnostic tool to assess in-stent restenosis (ISR) severity, both in clinical practice and in trials[1]. However, given its poor ability to depict the relevance of functional stenosis, fractional flow reserve (FFR) has been proposed as the reference standard to ascertain functional ISR severity[2]. More recently, quantitative flow ratio (QFR) has been validated in *de novo* lesions as an angiography-based approach to functional stenosis characterisation that does not require intracoronary instrumentation[3]. We investigated the diagnostic performance of QFR in ISR lesions, using FFR as the reference standard.

## Methods

This was a multicentre, international, retrospective, blinded study, enrolling patients from three hospitals in three countries (Hospital Clínico San Carlos, Spain; Toda Chuo General Hospital, Japan; and Sejong General Hospital, Republic of Korea). The study population consisted of a group of ISR patients in whom FFR was used to guide coronary revascularisation. Patients with ISR defined as ≥50% diameter stenosis (DS) within the stent, or within 5 mm from the stent edges, luminal narrowing as judged visually were considered for the study. Details regarding data collection and analysis are available in **Supplementary Appendix 1**.

## Results

QFR analysis was performed in 78 vessels (73 patients) with ISR, all investigated with FFR **(Figure 1)**. **Supplementary Appendix 2** and **Supplementary Table 1** show details of patient demographics and clinical characteristics. Angiographic and physiological variables are shown in **Table 1**. Stenosis severity was intermediate both in terms of angiography (mean %DS: 51±9%) and FFR (mean value: 0.79±0.09).

The mean difference between FFR and QFR was only 0.01±0.09 **(Supplementary Figure 1)**. Classification agreement between FFR and QFR (in terms of dichotomous functional significance) was high, i.e., 83%. Functional assessment of ISR

**Corresponding author: Hospital Clínico San Carlos IDISSC and Universidad Complutense de Madrid, Calle Prof. Martin Lagos s/n, 28040 Madrid, Spain. E-mail: escaned@secardiologia.es*



SUBMITTED ON 28/09/2018 - REVISION RECEIVED ON 1st 10/04/2019 / 2nd 26/06/2019 - ACCEPTED ON 26/07/2019

DOI: 10.4244/EIJ-D-18-00955

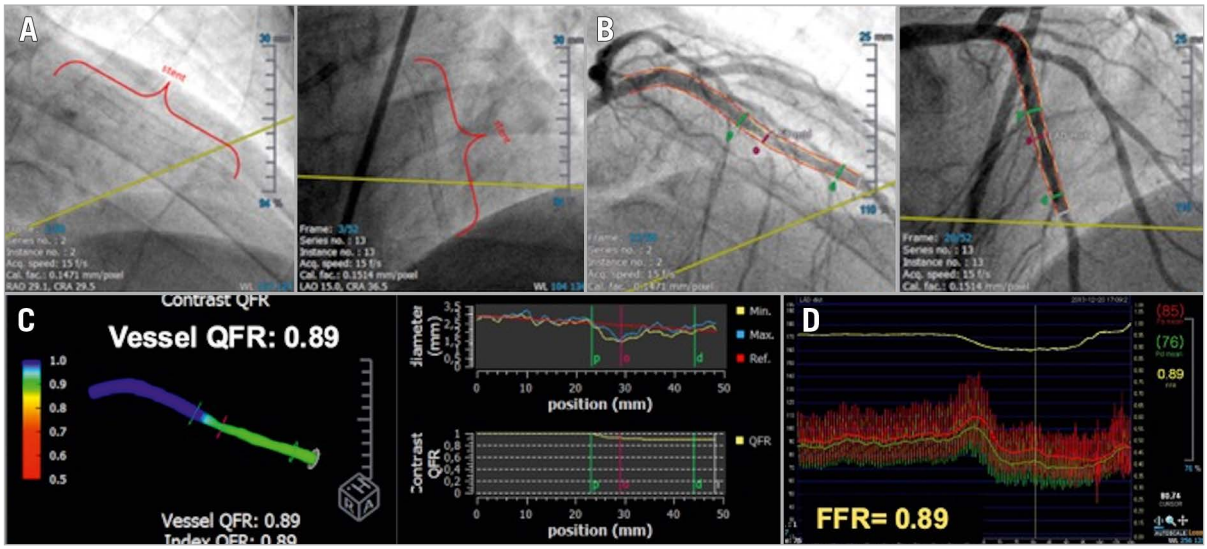



**Figure 1.** *Case example of QFR analysis of intermediate ISR in left anterior descending artery (LAD). A) Long LAD stented segment analysed. B) Two angiographic projections >25° apart allow three-dimensional vessel reconstruction. C) QFR computed based on 3D-QCA and TIMI frame count, resulting in a QFR value of 0.89 (non-significant). Green lines represent the proximal and distal borders of the segment with the most significant lesion and the red line represents the most severe stenosis level. D) FFR value was 0.89.*

lesions with QFR was comparable to that reported in *de novo* lesions in previous studies **(Supplementary Table 2)**. Additionally, the area under the receiver operating characteristic (ROC) curve (AUC) demonstrated high diagnostic performance of QFR regarding its ability to establish ISR relevance, taking FFR as reference (AUC: 0.90 [0.83-0.97]) **(Figure 2)**. Although there was a difference in classification agreement between vessels, this was not of statistical significance **(Supplementary Table 3)**. The study also confirmed the low diagnostic yield of angiography in ISR: in terms of functional severity a 50% DS criterion correctly classified only 68% of ISR cases **(Table 2)**. QFR analysis of ISR cases correctly reclassified (as judged by FFR) 45% of ISR lesions as functionally non-significant.

**Table 1. Vessel characteristics.**

| QFR analysis in ISR N=78 vessels | |
|---|---|
| Lesion location, n (%) | |
| Left anterior descending | 46 (59) |
| Left circumflex artery | 12 (15) |
| Obtuse marginal branch | 4 (5) |
| Right coronary artery | 16 (21) |
| Segment location, n (%) | |
| Proximal | 33 (42.3) |
| Mid | 41 (52.6) |
| Distal | 4 (5) |
| Reference vessel diameter, mm | 2.7 (2.2-3.0) |
| Minimal lumen diameter, mm | 1.3 (1.0-1.5) |
| %DS (mean) | 51±9 |
| Vessels with DS by 3D-QCA ≥50%, n (%) | 38 (49) |
| Area stenosis, % (mean) | 67±10 |
| Lesion length, mm | 19.2 (12.9-31.4) |
| FFR (per vessel) | 0.81 (0.75-0.87) |
| Vessels with FFR ≤0.80 (%) | 33 (42) |
| QFR (per vessel) | 0.80 (0.72-0.87) |
| Vessels with QFR ≤0.80 (%) | 40 (51) |

## Discussion

Our findings support the use of QFR to outline the functional relevance of ISR, with similar diagnostic efficiency to that reported for QFR in major studies in *de novo* lesions. Compared with available series, the classification agreement of QFR and FFR in ISR lesions was similar to that of two major pivotal studies of QFR-FFR in *de*

**Table 2. Diagnostic performance of QFR and 3D-QCA DS in ISR population using FFR as reference.**

| | QFR | DS by 3D-QCA ≥50% |
|---|---|---|
| Classification agreement, n (%) | 65 (83%) | 53 (68%) |
| Spearman/Pearson correlation (rho/r) | 0.731 | 0.433 |
| AUC | 0.90 (0.83-0.97) | 0.74 (0.63-0.85) |
| Sensitivity (%) | 91 (74-97) | 70 (51-83) |
| Specificity (%) | 78 (62-88) | 67 (50-79) |
| PPV | 75 (58-86) | 61 (43-75) |
| NPV | 92 (77-97) | 75 (58-86) |
| + LR | 4.1 (2.3-7.1) | 2.0 (1.3-3.3) |
| – LR | 0.1 (0.0-0.3) | 0.4 (0.2-0.7) |

3D-QCA: three-dimensional quantitative coronary angiography; AUC: area under the curve; DS: diameter stenosis; FFR: fractional flow reserve; ISR: in-stent restenosis; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; QFR: quantitative flow ratio

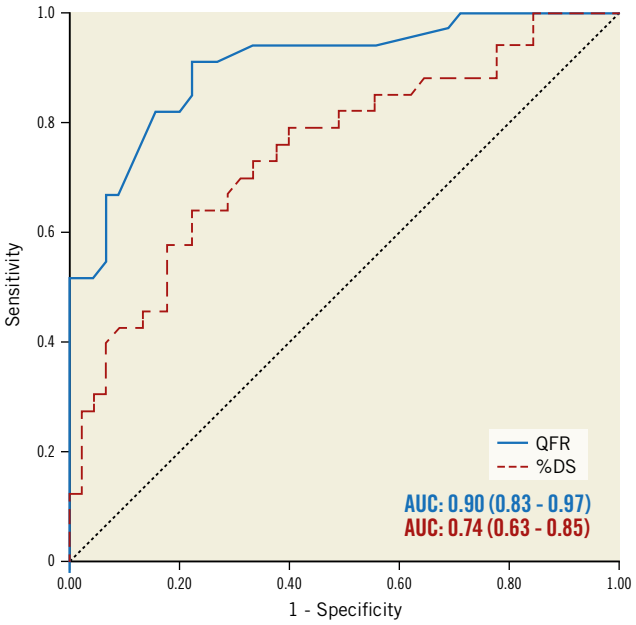



**Figure 2.** *Significant difference in diagnostic performance of QFR and %DS in identifying significant lesions in the ISR population. The area under the curve using FFR as reference standard shows high diagnostic accuracy of QFR but low diagnostic accuracy of %DS for ISR lesions.*

*novo* lesions[4,5]. Importantly, 45% of the ISR cases deemed significant by angiographic criteria were judged as functionally non-significant both by QFR and by FFR, showing that, due to its high negative predictive value, QFR can lead to safe deferral of revascularisation in a significant proportion of ISR lesions. Furthermore, QFR can be useful as a research tool in assessing the long-term results of stenting.

## Limitations

The main limitation of our study was its retrospective character, with exclusion of cases with suboptimal angiography or vessel overlap, something which may have caused selection bias.

## Conclusion

QFR has a high diagnostic performance in assessing ISR lesions, similar to that in *de novo* lesions. It may therefore facilitate adoption of functional assessment in these lesions.

## Impact on daily practice

By not requiring intracoronary instrumentation or drug administration, QFR may facilitate the adoption of functional assessment in ISR. Given its high negative predictive value, QFR will contribute to avoiding unnecessary interventions in patients with ISR.

## Acknowledgements

We are grateful to Pilar Jiménez-Quevedo, MD, PhD, Luis Nombela-Franco, MD, PhD, Carlos Macaya, MD, PhD, and Antonio Fernández-Ortiz, MD, PhD, for their contribution to data acquisition.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

## References

1. Alfonso F, Cequier A, Angel J, Marti V, Zueco J, Bethencourt A, Mantilla R, Lopez-Minguez JR, Gomez-Recio M, Moris C, Perez-Vizcayno MJ, Fernandez C, Macaya C, Seabra-Gomes R; Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) Investigators. Value of the American College of Cardiology/American Heart Association angiographic classification of coronary lesion morphology in patients with in-stent restenosis. Insights from the Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) randomized trial. *Am Heart J.* 2006;151:681.e1-9.

2. Nam CW, Rha SW, Koo BK, Doh JH, Chung WY, Yoon MH, Tahk SJ, Lee BK, Lee JB, Yoo KD, Cho YK, Chung IS, Hur SH, Kim KB, Choi CU, Oh DJ. Usefulness of coronary pressure measurement for functional evaluation of drug-eluting stent restenosis. *Am J Cardiol.* 2011;107:1783-6.

3. Tu S, Barbato E, Köszegi Z, Yang J, Sun Z, Holm NR, Tar B, Li Y, Rusinaru D, Wijns W, Reiber JH. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. *JACC Cardiovasc Interv.* 2014;7:768-77.

4. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, Nef H, Naber C, Barbierato M, Tu S, Neghabat O, Madsen M, Tebaldi M, Tanigaki T, Kochman J, Somi S, Esposito G, Mercone G, Mejia-Renteria H, Ronco F, Botker HE, Wijns W, Christiansen EH, Holm NR. 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.

5. Westra J, Tu S, Winther S, Nissen L, Vestergaard MB, Andersen BK, Holck EN, Fox Maule C, Johansen JK, Andreasen LN, Simonsen JK, Zhang Y, Kristensen SD, Maeng M, Kaltoft A, Terkelsen CJ, Krusell LR, Jakobsen L, Reiber JHC, Lassen JF, Bottcher M, Botker HE, Christiansen EH, Holm NR. Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio During Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II). *Circ Cardiovasc Imaging.* 2018;11:e007107.

## Supplementary data

**Supplementary Appendix 1.** Methods.

**Supplementary Appendix 2.** Results.

**Supplementary Figure 1.** Agreement between QFR and FFR.

**Supplementary Table 1.** Demographic and clinical characteristics of the ISR population.

**Supplementary Table 2.** Classification agreement between QFR and FFR in previous large studies.

**Supplementary Table 3.** Classification agreement between QFR and FFR according to vessel analysis.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00955*

**Supplementary data**

**Supplementary Appendix 1. Methods**

**Study design**

This study enrolled patients from three hospitals in three countries (Hospital Clínico San Carlos, Spain; Toda Chuo General Hospital, Japan; and Sejong General Hospital, Republic of Korea). Patients' demographic and clinical characteristics, procedural reports, angiographic views and raw coronary physiology data were collected from the participating hospitals and sent to the core laboratory (Hospital Clínico San Carlos) where the QFR analysis was performed in a blinded fashion regarding FFR values.

**Study population**

The study group consisted of patients with ISR in whom FFR was used to guide coronary revascularisation. Patients with ISR defined as ≥50% diameter stenosis (DS) within the stent, or within 5 mm from the stent edges, luminal narrowing as judged visually were considered for the study. In cases of acute myocardial infarction, the investigated vessel was not the culprit one.

The initial study population consisted of 202 vessels (190 patients): 56% were derived from Hospital Clinico San Carlos, 12% from Toda Chuo Hospital, and 32% from Sejong Hospital. Out of these, 90 vessels had to be excluded before starting QFR analysis due to the following exclusion criteria: history of coronary artery bypass surgery, ostial left main or ostial right coronary artery lesions, occlusive restenosis, bioresorbable scaffolds, incompatibility of angiographic images with QFR software. Another 34 vessels were excluded after starting QFR analysis due to inherent QFR exclusion criteria: lack of at least two angiographic projections >25$^{o}$ apart, severe vessel tortuosity and/or overlap limiting QFR analysis. The final study population included a total of 73 ISR patients (78 vessels).

**Pressure wire assessment**

FFR values were obtained both from raw physiology studies and from procedural reports. Intracoronary nitrates were administered before physiology measurements

and hyperaemia was induced by intravenous infusion of adenosine (140 mcg/kg/min) through a femoral or antecubital vein during a minimum of two minutes. FFR was calculated as the minimum ratio between intracoronary distal pressure and aortic pressure during steady state hyperaemia. In the majority of cases pressure drift was checked with the wire sensor at the tip of the guiding catheter.

**QFR analysis**

Two angiographic images separated >25$^{o}$ were selected to perform three-dimensional reconstruction of the target vessel using dedicated software (QAngio-XA 3D, research edition, version 1.0; Medis, Leiden, the Netherlands). Calibration was automatically performed. End-diastolic frames properly opacified by contrast were selected. Two anatomical markers, e.g., bifurcations, were identified as reference points in the two angiographic views for automated correction of system distortions. A distal landmark in the target vessel was selected, matching the original position of the pressure-wire sensor. Whenever required, the lumen contour automatically delineated by the software algorithms was manually corrected following standard procedure. The proximal (start) point of QFR analysis was placed in the proximal segment of the vessel ensuring that it could serve as a reference "healthy" segment (i.e., devoid of angiographic stenosis). The proximal reference size was automatically calculated with the "Automatic" function in most cases, unless there was an ostial LAD or LCX lesion. In these cases, in order to deal with the dimensional gap with the LM, the reference size was selected using the "Normal" or the "Fix" reference function, taking into account the sex and BMI of the patient. The detailed methodology has been described previously. The percent diameter stenosis (%DS), percent area stenosis (%AS), lesion length, minimum lumen diameter and reference vessel diameter were automatically derived from three-dimensional reconstruction. The contrast flow model, which uses TIMI frame count to derive contrast flow velocity from coronary angiography without pharmacologically induced hyperaemia, was used for final QFR computation.

**Statistical analysis**

All continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Continuous variables are presented as mean

values±standard deviation or median ($25^{th}$–$75^{th}$ percentile) depending on the normality of their distribution. Categorical variables are presented as count and percentage (%). Differences between two continuous variables were assessed using the Student's t-test or Mann-Whitney U test as appropriate. Associations between categorical variables were evaluated with the Fisher's exact test. Associations between continuous variables were quantified by Pearson's or Spearman's correlation coefficient, as appropriate. Demographic and clinical data were analysed on a per-patient basis, while the remaining calculations were analysed on a per-vessel basis. Diagnostic performance of QFR and 3D-QCA-derived %DS were assessed by the area under the ROC curve (AUC), taking FFR as reference. Classification agreement between QFR and FFR was obtained according to the threshold of ≤0.80 for both techniques. The relationship and agreement between QFR and FFR were assessed by Spearman correlation coefficient and Bland-Altman plot, respectively. A p-value <0.05 was considered statistically significant. SPSS statistics, Version 19 (IBM Corp., Armonk, NY, USA) and the MatchIt package of R software (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

**Supplementary Appendix 2. Results**

**Demographic, clinical and lesion characteristics**

A total of 78 vessels (from 73 patients), which had been treated with stent implantation and developed ISR, were included in the study. Demographic and clinical characteristics are shown in **Supplementary Table 1**.

Overall, the left anterior descending artery was the most frequently studied vessel. The mean length of the implanted stent in ISR was 21±7 mm. The stenoses had intermediate angiographic severity (%DS derived by 3D-QCA 51±9%).

**Coronary physiology characteristics**

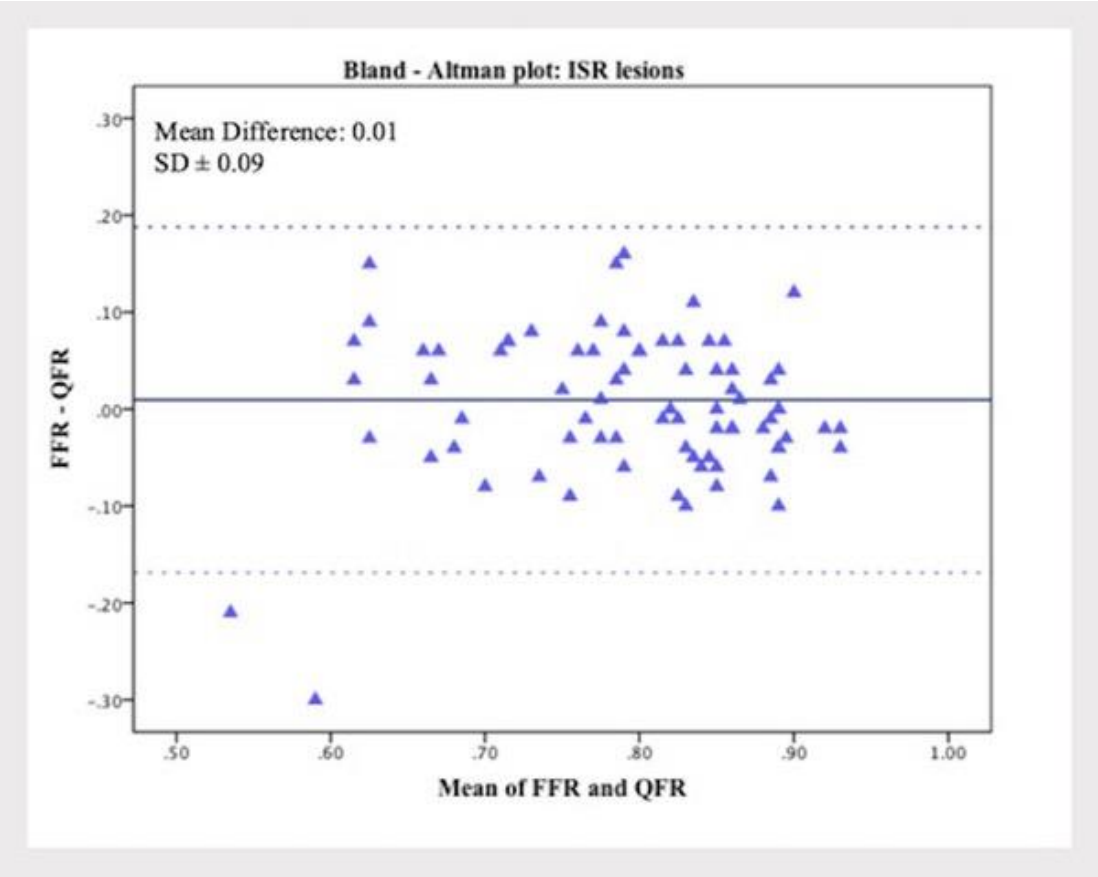
The investigated ISR lesions had intermediate functional severity, as judged both by FFR and QFR (mean FFR value: 0.79±0.09, mean QFR value: 0.78±0.11). The mean difference between FFR and QFR values was not significant **(Supplementary Figure 1)**. ISR lesions were functionally non-significant in 58% and 49% of cases according to FFR and QFR values, respectively.

The classification agreement between FFR and QFR (in terms of dichotomous functional significance) was as high as 83%, similar to that reported in two previous studies **(Supplementary Table 2)**. The mean difference between FFR and QFR was low (0.01±0.09). Additionally, a strong correlation between FFR and QFR values was found (rho=0.73, p<0.001). Although there was a difference in classification agreement according to the investigated vessel, this was not of statistical significance **(Supplementary Table 3)**.

Functional assessment of ISR lesions with QFR showed a high diagnostic performance (AUC 0.90 [95% CI: 0.83–0.97]). Sensitivity, specificity, positive and negative predictive values were 91%, 78%, 75% and 92%, respectively.

**Assessment of stenosis severity with 3D-QCA**

The correlation between %DS and FFR was only moderate (r=-0.43, p<0.001), and its diagnostic performance in assessing functionally significant lesions was notably inferior to QFR **(Table 2, Figure 2)**.




**Supplementary Figure 1.** Agreement between QFR and FFR.

Bland-Altman plot shows good agreement between QFR and FFR in ISR lesions. The lines illustrate the mean difference ±2SD.

**Supplementary Table 1. Demographic and clinical characteristics of the ISR population.**

| | |
|---|---|
| **Age, years** | 67.5±11 |
| **Male, N (%)** | 59 (81) |
| **BMI, kg/m$^2$** | 26.5 (24.3–28.9) |
| **HTN, N (%)** | 52 (71) |
| **Dyslipidaemia, N (%)** | 52 (71) |
| **Smoker, N (%)** | 11 (15) |
| **Diabetes mellitus, N (%)** | 22 (30) |
| **CKD, N (%)** | 9 (12) |
| **Previous MI, N (%)** | 42 (58) |
| **Clinical presentation** | |
| **Stable angina, N (%)** | 50 (69) |
| **Unstable angina, N (%)** | 19 (26) |
| **Acute MI, N (%)** | 4 (6) |

BMI: body mass index; CKD: chronic kidney disease; HTN: hypertension; MI: myocardial infarction

**Supplementary Table 2. Classification agreement between QFR and FFR in previous large studies.**

| Study | Classification agreement |
|---|---|
| FAVOR II Europe – Japan Study | 86.8% |
| FAVOR II China Study | 92.7% |
| WIFI II Study | 83% |
| Current ISR study | 83% |

**Supplementary Table 3. Classification agreement according to vessel analysis.**

| | N=78 | | |
|---|---|---|---|
| **Vessel** | **N** | **Classification agreement** | ***p*-value** |
| LAD | 46 | 76% | |
| LCX-OM | 16 | 94% | 0.120 |
| RCA | 16 | 94% | |