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Functional assessment of coronary stenosis with angiography-based Quantitative Flow Ratio compared with Fractional Flow Reserve in patients with severe aortic stenosis.

Short title: QFR in severe aortic stenosis

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Abstract

Aims: To investigate the diagnostic performance of quantitative flow ratio (QFR) in assessing the physiological relevance of coronary lesions in the presence of severe aortic valve stenosis (SAS).

Methods and Results: 115 SAS patients (138 coronary arteries) were included. Functional assessment of coronary stenoses was performed with fractional flow reserve (FFR) before transcatheter aortic-valve implantation (TAVI). Subsequently, QFR was calculated at a central core laboratory, blinded to FFR results. The diagnostic yield of QFR was assessed using FFR as reference.

Coronary stenoses were intermediate (diameter stenosis $48 \pm 10\%$, FFR 0.84 [0.77-0.89], QFR 0.82 [0.73-0.89]). Per-vessel sensitivity, specificity, area under the ROC curve and accuracy of QFR were 84% (95% CI 71-92%), 80% (95% CI 69-88%), 0.88 (95% CI 0.82-0.93) and 81%, respectively. Diagnostic accuracy of QFR significantly decreased in patients with aortic valve area (AVA) $< 0.60 \text{ cm}^2$. Diagnostic performance of QFR was superior to angiography in assessing the FFR-based functional significance (AUC 0.88 [95% CI 0.82-0.93] vs. 0.74 [95% CI 0.66-0.81], respectively; $p = 0.0002$).

Conclusions: Compared with FFR, QFR has a good diagnostic yield and is superior to angiography in assessing the functional relevance of coronary lesions in SAS patients awaiting TAVI, particularly when AVA is $\geq 0.6 \text{ cm}^2$.

Keywords: aortic stenosis, coronary artery disease, fractional flow reserve, TAVI

Condensed abstract

Diagnostic performance of quantitative flow ratio (QFR), a novel angiography-based functional assessment method of coronary stenosis, was assessed in 115 patients with concomitant severe aortic stenosis (SAS) awaiting TAVI. Using FFR as reference, sensitivity, specificity, area under the ROC curve and accuracy of QFR were 84% (95% CI 71-92%), 80% (95% CI 69-88%), 0.88 (95% CI 0.82-0.93) and 81%, respectively. QFR was superior to angiography (AUC 0.88 [95% CI 0.82-0.93] vs. 0.74 [95% CI 0.66-0.81], respectively; $p = 0.0002$). We conclude that overall, QFR has a good diagnostic yield in determining the functional relevance of coronary stenosis in SAS patients.

Abbreviations and acronyms

- AVA: aortic valve area
- CAD: Coronary artery disease
- FFR: Fractional flow reserve
- QFR: Quantitative flow ratio
- TAVI: Transcatheter aortic-valve implantation
- SAS: Severe aortic stenosis
- 3D-QCA: Three-dimensional quantitative coronary angiography

Introduction

Concomitant coronary artery disease (CAD) is frequently found in patients with symptomatic severe aortic valve stenosis (SAS) undergoing transcatheter aortic valve implantation (TAVI), making their management particularly challenging [1]. In this clinical setting, coronary revascularization is empirically recommended in proximal and angiographically severe coronary stenoses [2]. Although functional stenosis evaluation with fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) that have shown to improve cardiovascular outcomes in patients with stable CAD [2], the use of these indices in patients with SAS is hampered by substantial differences in coronary physiology and patient characteristics. Both indices can be affected by altered left ventricular pressures, microcirculatory function, and the development of left ventricular hypertrophy caused by SAS [3][4][5]. Despite some studies suggest that even in the presence of SAS FFR can be used to assess coronary stenoses [4][6][7], larger studies are required to confirm these findings. However, even if the reliability of FFR in this setting is confirmed with larger series, the hemodynamic frailty of patients undergoing TAVI will likely deter many operators from using vasoactive drugs and performing intracoronary wire assessment.

Recently, wire- and adenosine-free functional assessment of coronary stenoses have become possible due to developments in functional angiography, allowing calculation of virtual FFR based on computation of three-dimensional quantitative coronary angiography (3D-QCA) with mathematical or fluids dynamic-derived equations [8]. One of these methods, quantitative flow ratio (QFR) [9], has shown a high accuracy in determining the physiological relevance of coronary stenoses in different clinical settings [10][11][12]. While the concept of QFR may be very attractive for guiding clinical decisions in SAS patients with concomitant CAD, its potential applicability in patients awaiting TAVI has never been investigated. The objective of this study was to determine the diagnostic yield of QFR in assessing the functional relevance of coronary stenoses in SAS patients before TAVI, using FFR assessment as the reference standard.

Methods

Study design and population

The QASTA study (functional assessment of coronary stenoses by the novel Quantitative flow ratio in patients with severe Aortic Stenosis undergoing Transcatheter Aortic valve implantation) is a multicenter, retrospective study with blind analysis of angiographic data involving seven centers from Spain, Italy, Canada, South Korea and the United States. The study enrolled patients with SAS and concomitant CAD in whom coronary stenoses were interrogated with FFR before TAVI. Coronary stenoses suitable for FFR interrogation were defined at operator criteria, usually involving lesions with diameter stenosis between 40-80% by visual estimation. SAS was diagnosed by transthoracic echocardiogram using the valve area ($< 1.0 \text{ cm}^2$; indexed valve area $< 0.6 \text{ cm}^2/\text{m}^2$ body surface area) or flow-pressure parameters (mean gradient $>40 \text{ mm Hg}$, maximum jet velocity $>4.0 \text{ m/s}$, and velocity ratio <0.25) [13]. DICOM files of coronary angiograms were sent and centrally analyzed in the QFR core-laboratory located at Hospital Clinico San Carlos, Madrid, Spain. QFR assessment was performed by certified analysts, blinded to both FFR values and clinical decisions about coronary revascularization. QFR analysis was performed by using the routine diagnostic angiography acquired before TAVI (supplementary figure 1). The diagnostic performance of QFR in determining the functional stenoses relevance was assessed using FFR before TAVI as reference. Exclusion criteria were ostial disease in the left main or in the right coronary artery, target vessel with collateral circulation or coronary flow from patent surgical grafts, severe diffuse disease, in-stent restenosis, target vessel with myocardial bridging, target vessel with previous myocardial infarction, poor angiography image quality, absence of two angiographic projections separated by more than 25° , angiograms with frame rate <12.5 frames per second, and severe tortuosity or overlapping limiting an optimal 3D reconstruction of the target vessel. Participants gave their written informed consent for the index physiological procedures and the study was conducted according to Helsinki declaration.

Invasive FFR assessment, QFR analysis and statistics: See Supplementary material.

Results

Baseline characteristics of study population

A total of 138 coronary arteries from 115 patients were included in the analysis after fulfilling participation criteria (Figure 1). Median age was 82 years (IQR 75-86) (male, 47%). Mean aortic pressure gradient and aortic valve area (AVA) were 47.5 ± 16.9 mmHg and 0.68 ± 0.22 cm², respectively. The most commonly interrogated vessel was the left anterior descending coronary artery (58%), and the majority of target stenoses were of adequate size for percutaneous angioplasty (reference diameter 2.8 mm [IQR 2.5-3.2]). Supplementary table and table 1 summarize the clinical and anatomical characteristics of the study population.

Coronary stenoses severity and physiological assessment

In per-vessel analysis, overall stenoses severity was angiographically and functionally intermediate as determined by the percent diameter stenosis ($48 \pm 10\%$ derived from 3D-QCA), FFR (median 0.84 [0.77-0.89]) and QFR (median 0.82 [0.73-0.89]) (Figure 2, table 1). The number of ischemia-causing stenoses as judged by $\text{FFR} \leq 0.80$ or $\text{QFR} \leq 0.80$ were similar for both methods (40% vs. 46%, respectively; $p = 0.315$).

Diagnostic performance of QFR

The supplementary figure 2 depicts the correlation and agreement between FFR and QFR. The per-vessel ROC assessment using $\text{FFR} \leq 0.80$ as the reference identified a sensitivity, specificity and AUC of QFR of 84% (95% CI 71-92), 80% (95% CI 69-88) and 0.88 (95% CI 0.82-0.93), respectively (Table 2). Using ≤ 0.80 as cutoff for both techniques, QFR correctly classified the functional significance of coronary stenosis in 112 vessels (81%).

Comparison between QFR and %DS in predicting $\text{FFR} \leq 0.80$

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QFR was superior to angiography (%DS by 3D-QCA) in determining the functional significance of coronary stenoses as assessed by per-vessel ROC analysis: AUC 0.88 vs. 0.74 ($p = 0.0002$ for ROC curve comparison) (Figure 3A), sensitivity 84% vs. 58% ($p < 0.0001$) and specificity 80% vs. 70% ($p = 0.055$) (Table 2).

ROC analysis identified $\geq 49\%$ as the best cutoff for %DS (by 3D-QCA) to predict an FFR ≤ 0.80 (Supplementary Figure 3). Using the cutoff ≤ 0.80 for QFR and $\geq 50\%$ for %DS, QFR was superior to angiography in correctly classifying FFR-based functional stenosis relevance (112 vessels [81%] vs. 90 vessels [65%], respectively; $p = 0.0028$). Per-patient ROC analysis is shown in Supplementary Figure 4.

Effect of aortic stenosis severity on QFR diagnostic performance

The classification agreement between QFR and FFR was significantly different across different ranges of AVA (Figure 4A). In patients with AVA $\geq 0.80 \text{ cm}^2$ the classification agreement between both methods was as high as 91%, decreased to 79% when AVA was $0.60 - 0.80 \text{ cm}^2$, and 66% when AVA was $< 0.60 \text{ cm}^2$ ($p = 0.022$ for comparison between AVA ranges). In addition, the AUC for QFR in patients with AVA $\geq 0.60 \text{ cm}^2$ was as high as 0.97, whereas in patients with AVA $< 0.60 \text{ cm}^2$ decreased to 0.67 ($p = 0.0110$ for comparison between AUC) (Figure 3B). A significant effect of aortic stenosis severity on the agreement between QFR and FFR could not be demonstrated when mean transvalvular pressure gradient was used as an index of reference (Figure 4B).

Discussion

The main findings of this study are: 1) Overall, QFR has a good diagnostic yield in determining the physiological relevance of coronary stenoses in SAS patients scheduled for TAVI, as estimated with FFR. 2) The diagnostic efficiency of QFR is particularly high (AUC 0.97) when patients with very severe aortic stenosis ($AVA \leq 0.60 \text{ cm}^2$) are excluded. 3) Compared with angiography, QFR is superior in determining the FFR-based physiological stenosis relevance.

Up to 50% of patients with symptomatic SAS present concomitant CAD [1][15]. In that subset, current clinical practice guidelines recommend revascularization if coronary stenosis involves vessel proximal segments and in whom surgical valve replacement or TAVI is planned [2]. Of note, this recommendation is based on angiographic assessment of stenosis severity, whereas physiology-guided clinical decision-making is not supported yet by the clinical guidelines. This is due to a number of considerations: 1) There is a paucity data of the prognostic impact of CAD in SAS patients, especially in the elderly patients. 2) The value of PCI before TAVI is questionable in elderly patients with moderate CAD, SAS and absence of angina symptoms. 3) Randomized clinical trials evaluating the clinical value of physiology-guided revascularization in SAS patients have not been ever conducted. 4) Coronary hemodynamics secondary to structural and functional abnormalities caused by SAS may influence intracoronary trans-stenotic pressure gradients.

Notwithstanding this, numerous efforts have been placed in understanding coronary hemodynamics caused by aortic stenosis, and how treatment of aortic stenosis modifies physiological assessment of coronary lesions by pressure gradients. Some observational studies found that FFR values obtained under the challenging physiological conditions of SAS are similar to those obtained after TAVI [4][6][7]. However, despite promising results it remains to be seen whether wide adoption of FFR will occur in this population: many operators may be reluctant to use vasoactive drugs (which are fundamental to perform FFR) in order to avoid potential

hemodynamic adverse effects in the presence of SAS, and considerations that have been put forward to explain the relatively low adoption of FFR outwith the context of SAS, such as associated costs, increase use of contrast, and length of the diagnostic procedure, may also influence its use in patients with SAS.

To circumvent these challenges for functional coronary lesion assessment in SAS, we investigated the diagnostic yield of QFR, a novel technique based on fast computation of coronary angiography using advanced mathematical algorithms. Previous studies reported a high accuracy of QFR in different clinical settings, including stable CAD and non-culprit stenoses in acute coronary syndromes [10][11][12][16], but its diagnostic yield in presence of SAS has not been evaluated. In this study we demonstrated that, overall, QFR has a good diagnostic performance in determining the FFR-based functional relevance of coronary stenoses in patients awaiting TAVI, with an AUC of 0.88 and classification agreement of 81%. The applicability of our findings is supported by the characteristics of the study population, with mean values of physiological indices (FFR, QFR), angiography stenosis severity (%DS) and aortic valve severity similar to those reported in previous registries [10][17][18]. Furthermore, the use of FFR as a reference obtained before TAVI is supported by available studies [4][7].

Our study also provides new insights on the impact of SAS on functional assessment of coronary stenoses with pressure guidewires. Although we found an overall good diagnostic yield of QFR, it was lower compared with previous studies out of the context of aortic valve disease [10][11]. A plausible hypothesis is that this decrease in diagnostic accuracy is due to the presence of microvascular dysfunction, which in the case of SAS may be the result of numerous mechanisms including structural remodelling of microvessels, increased extravascular compression of capillaries due to left ventricular pressure overload, and left ventricular hypertrophy [1][5][19][20]. In theory, a graded increase in these microvascular abnormalities could be expected as the severity of aortic stenosis increases [3], modifying the correlation and agreement between QFR (an angiography-based method that partially ignores the

microcirculatory status) and FFR (an intracoronary technique subjected to modulation by the subtended microcirculation). This could explain also why the QFR diagnostic performance decreased as aortic valve area decreased. Therefore, we hypothesize that the discrepancy between QFR and FFR in SAS should reflect the extent to which the microcirculatory status deviates from the expected reference status (i.e. the boundary conditions assumed in QFR calculation for healthy coronary circulation). In support of this rationale, a previous study from our group found a lower diagnostic performance of QFR compared with FFR in presence of high microvascular resistance [21]. However, because in our study we do not have invasive coronary flow measurements, coronary flow reserve (CFR) or microvascular resistances cannot be derived, and our reasoning can be considered only as hypothesis-generating.

Abnormalities in coronary flow also deserve attention as potential contributors to discrepancies between QFR and FFR. A number of studies demonstrated that resting coronary flow is significantly increased in SAS patients, being the main factor affecting CFR as a consequence of reduced delta between hyperemic and resting flow [5][22]. It is important to note that algorithms for calculation of contrast-QFR model estimates the hyperemic coronary flow by computing the contrast medium transport time under resting conditions, using frame counting, while the fixed-QFR model uses an empiric flow velocity (0.35 m/s) [14]. In our study, a further analysis demonstrated a significantly lower AUC for the fixed-QFR model compared with the contrast-QFR model (AUC 0.84 [0.77-0.91] vs. 0.88 [0.82-0.93], respectively; $p = 0.0027$ for comparison of AUC) (Supplementary figure 5). This finding is consistent with previous reports outwith the context of SAS [14][21], supporting the value of incorporating patient-specific flow characteristics for QFR calculation even in the presence of SAS. However, whether changes in resting flow after removal of aortic stenosis causes a significant change in the diagnostic performance of QFR deserves further investigation.

Finally, interestingly we found that the significant impact of aortic valve area on diagnostic performance of QFR was not found in terms of mean aortic gradient (Figure 4).

Compared to aortic valve area, aortic pressure gradient depends more on left ventricular systolic function. In advanced aortic stenosis, it is expected certain degree of ventricular dysfunction which in some cases can limit the accuracy of mean pressure gradient to accurately reflect the aortic stenosis severity. Low-flow, low-gradient aortic stenosis with reduced ejection fraction can be found in this setting. One can argue that a major degree of microvascular dysfunction could be also expected in this subset. In other words, some patients with mean pressure gradient <50 mmHg may have reduced LVEF as consequence of advanced aortic stenosis (supplementary figure 6), which may involve more profound microvascular abnormalities that affect the diagnostic performance of QFR in this subgroup of patients.

Quantitative flow ratio vs. angiography

In patients with primary indication for TAVI or surgical aortic valve replacement, the most recent ESC guidelines recommend coronary revascularization according to stenosis angiographic severity [2]. However, in the FFR era this recommendation is challenged by the well-documented inaccuracy of angiography in determining the functional relevance of coronary stenoses [17], even in the presence of SAS [23]. In our study, we found a clear superiority of QFR over angiography (AUC 0.88 vs. 0.74, $p = 0.0002$) in identifying functionally significant stenoses. Of note, we compared QFR with %DS derived from 3D-QCA, an angiography method that has demonstrated higher accuracy than conventional visual or two-dimensional parameters used in everyday practice [24].

In summary, we found a good diagnostic yield of QFR in assessing the functional relevance of coronary stenoses in SAS patients awaiting TAVI, particularly a high NPV for the safe deferral of revascularization. These results make QFR a promising technique in this population, since it does not depend on hyperemic drugs or additional coronary instrumentation. However, large-scale prospective studies are needed to confirm the findings of our study, as well as clinical studies evaluating outcomes when physiology is used to guide revascularisation in this population.

Study Limitations

Our study has several limitations: i) Due to the retrospective nature of the study, the index angiography studies were not performed with a view to analyzing QFR. This angiography-based method depends highly on the image quality, precluding QFR calculation or limiting its accuracy if angiography image quality is not suitable. To minimize the effect of angiogram quality on QFR accuracy, we enforced angiographic inclusion criteria following the recommendations of previous QFR studies. It remains plausible that QFR-aware angiograms obtained prospectively would increase, even further, the diagnostic yield of the technique. ii) Given the retrospective nature of the study, and that FFR was performed at operator's discretion in most of the participating centers, the results can be subjected to selection bias. iii) The route of adenosine administration was not homogeneous in all centers (i.e. intravenous vs. intracoronary), mirroring clinical practice across different catheterization laboratories throughout the world when performing invasive physiological assessment. iv) Agreement between QFR and FFR after TAVI was not evaluated. Despite the increased interest in understanding coronary physiological changes caused by relief of aortic stenosis, data on the effect of TAVI or aortic valve replacement on coronary hemodynamics is still scarce. Furthermore, since transcatheter heart valves can hamper invasive functional assessment of coronary stenoses with catheters and pressure-wires, evaluation of the need for coronary revascularization before TAVI is preferable, and in case of surgical replacement may facilitate decision making on the best treatment strategy.

Conclusion

Compared with FFR, QFR has a good diagnostic yield and is superior to angiography in assessing the functional relevance of coronary lesions in SAS patients awaiting TAVI, particularly when AVA is $\geq 0.6 \text{ cm}^2$.

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Impact on daily practice

In our study we found that overall, QFR has a good diagnostic yield in determining the physiological relevance of coronary lesions in patients with concomitant SAS undergoing TAVI. Importantly, unlike FFR, QFR omits the need for vasoactive drugs and pressure-wires, avoiding pharmacological adverse effects and additional procedural-related risks in hemodynamically fragile SAS patients. On this ground, QFR has the potential of improving adoption of physiology into the clinical-decision workflow in SAS patients with concomitant CAD. However, the clinical evidence regarding the benefit of physiology-guided coronary revascularization in this population is still scarce and deserves further investigation.

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Appendix

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Figure Legends

Figure 1

Title: Study Flowchart

FFR = fractional flow reserve; QFR = quantitative flow ratio; SAS = severe aortic stenosis; TAVI = transcatheter aortic valve implantation.

Figure 2

Title: Coronary stenoses severity of the study population

Per-vessel analysis depicts intermediate severity of coronary stenoses as determined by %DS-3DQCA, FFR and QFR. Abbreviations as in figure 1.

Figure 3

Title: Diagnostic yield of QFR in SAS patients

A: Comparison of area under the curve (AUC) between QFR and percent diameter stenosis (%DS) using $\text{FFR} \leq 0.80$ as reference. B: Diagnostic yield of QFR according to aortic valve area (AVA).

* P value for comparison of AUC.

Figure 4

Title: Accuracy of QFR according to aortic stenosis severity

A: Accuracy of QFR (i.e. classification agreement with FFR) decreased as aortic valve area decreased, being significantly lower in patients with aortic valve area $< 0.60 \text{ cm}^2$. B: A trend towards lower accuracy of QFR was observed when mean aortic gradient increased. N = number of patients in each range of aortic valve area or mean aortic gradient.

Tables

Table 1. Anatomic and physiologic characteristics (N = 138 coronary vessels)

<i>Target vessel</i>	
Left anterior descending artery	80 (58)
Left circumflex artery	29 (21)
Right coronary artery	29 (21)
<i>3-dimensional quantitative angiography</i>	
Reference diameter, mm	2.8 (2.5-3.2)
Minimum lumen diameter, mm	1.4 (1.2-1.7)
Diameter stenosis, %	48±10
Lesion length, mm	23 (13-33)
<i>Physiology measurements</i>	
FFR	0.84 (0.77-0.89)
Vessels with FFR ≤0.80	55 (40)
QFR	0.82 (0.73-0.89)
Vessels with QFR≤0.80	63 (46)
Fixed-QFR	0.83 (0.74-0.89)
Vessels with fixed-QFR≤0.80	62 (45)

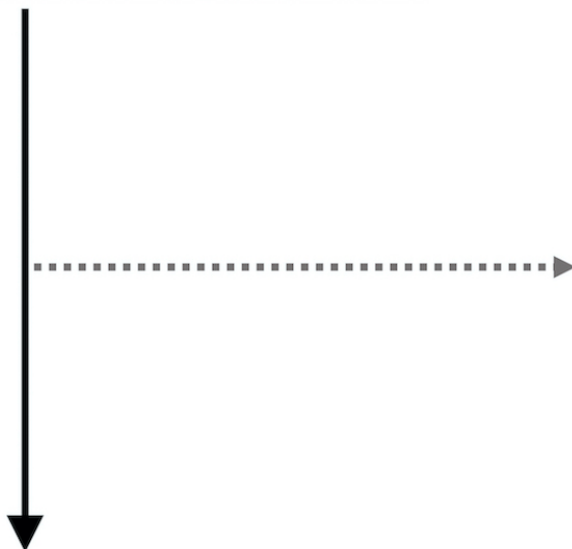
Values are n (%), mean ± SD, or median (IQR). FFR = fractional flow reserve; QFR = quantitative flow ratio.

Table 2. Diagnostic parameters of QFR and %DS

	QFR ≤ 0.80	%DS ≥ 50%	P *
	N = 138	N = 138	
AUC	0.88 (0.82 – 0.93)	0.74 (0.66 – 0.81)	0.0002
Accuracy, %	112 (81)	90 (65)	0.0028
Correlation	0.68 (0.58 – 0.76)	-0.44 (-0.56 to -0.29)	<0.0001
Sensitivity	84 (71 - 92)	58 (44 - 71)	<0.0001
Specificity	80 (69 - 88)	70 (59 - 80)	0.0528
NPV	88 (80 - 93)	72 (64 - 78)	0.0009
PPV	73 (64 - 81)	56 (46 - 66)	0.0032

Values are n (%) for accuracy, n (95% CI) for correlation, and % (95% CI) for all other parameters. * p value for comparison between QFR and %DS. AUC = area under the curve; %DS = percent diameter stenosis. Other abbreviations as in table 2.

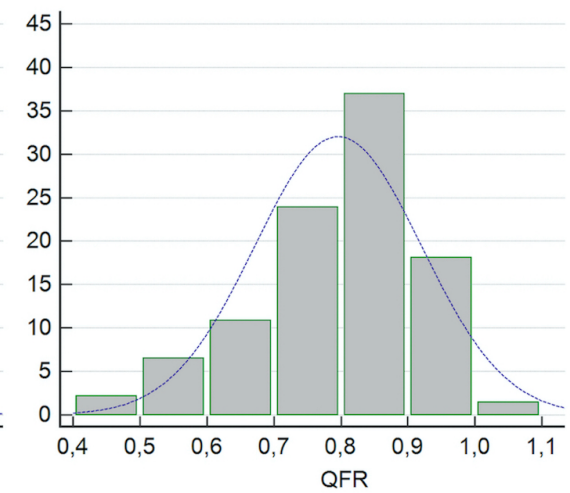
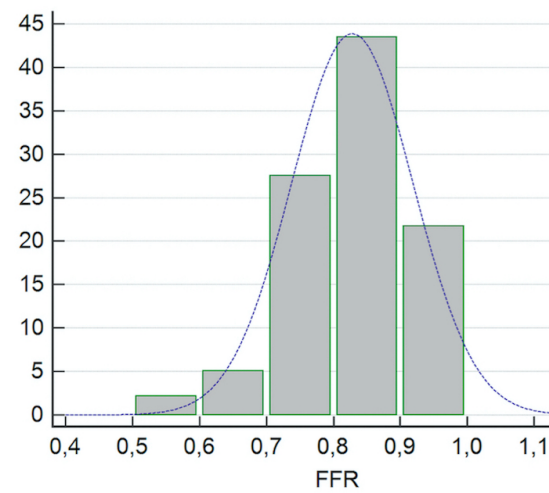
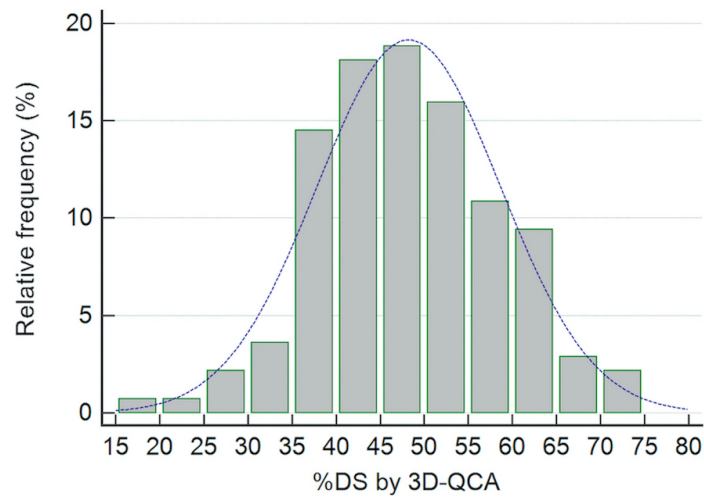
161 patients (196 vessels) with SAS and coronary lesions underwent FFR assessment before TAVI



115 patients (138 vessels) underwent QFR analysis

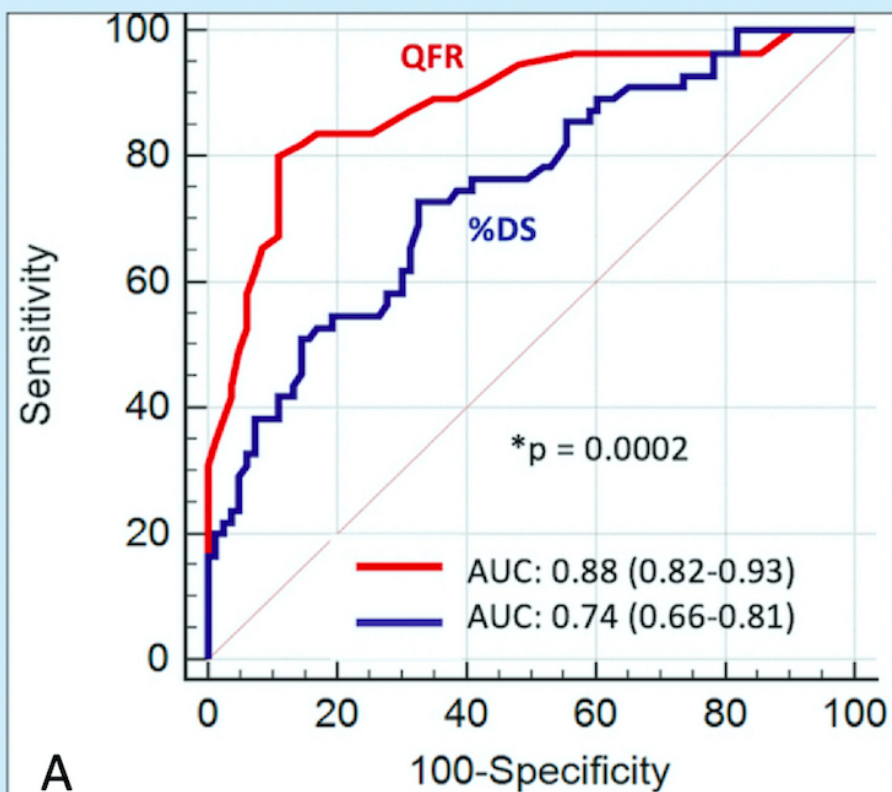
46 patients (58 vessels) excluded by core-lab

- 2 vessels with in-stent reestenosis
- 1 vessel with severe diffuse disease
- 3 vessels with severe overlapping
- 1 vessels with collateral circulation
- 15 ostial lesions
- 25 vessels without two optimal angiographic projections
- 1 vessels with severe foreshortening
- 10 vessels with poor image quality

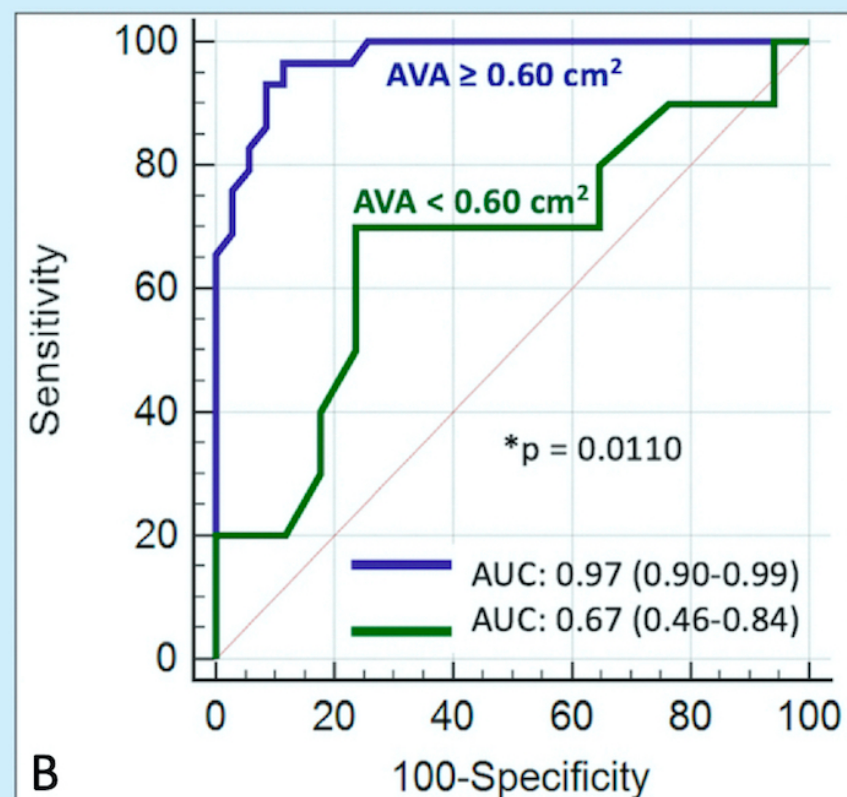


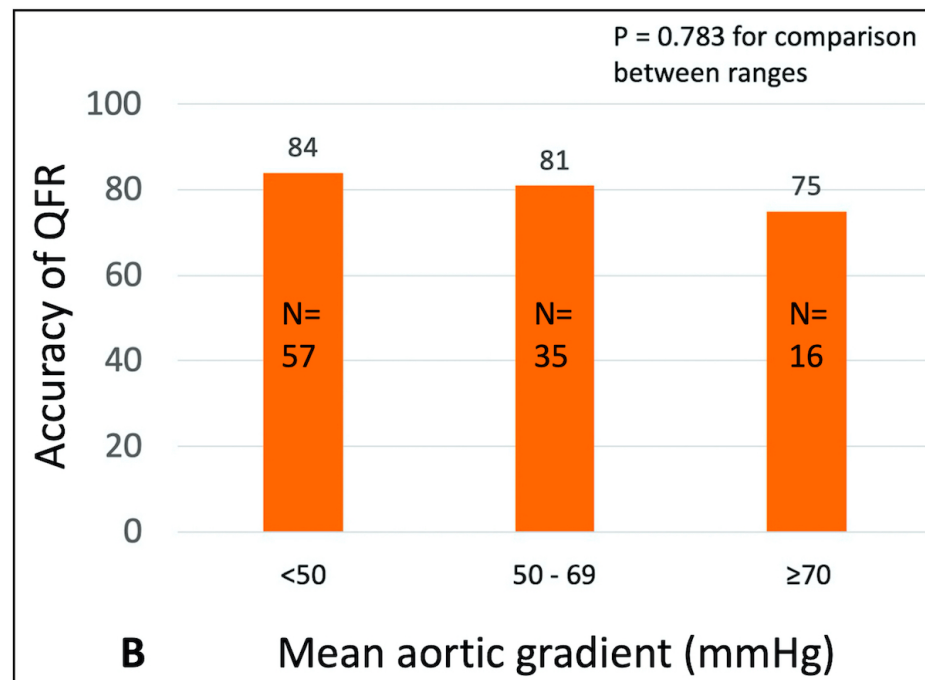
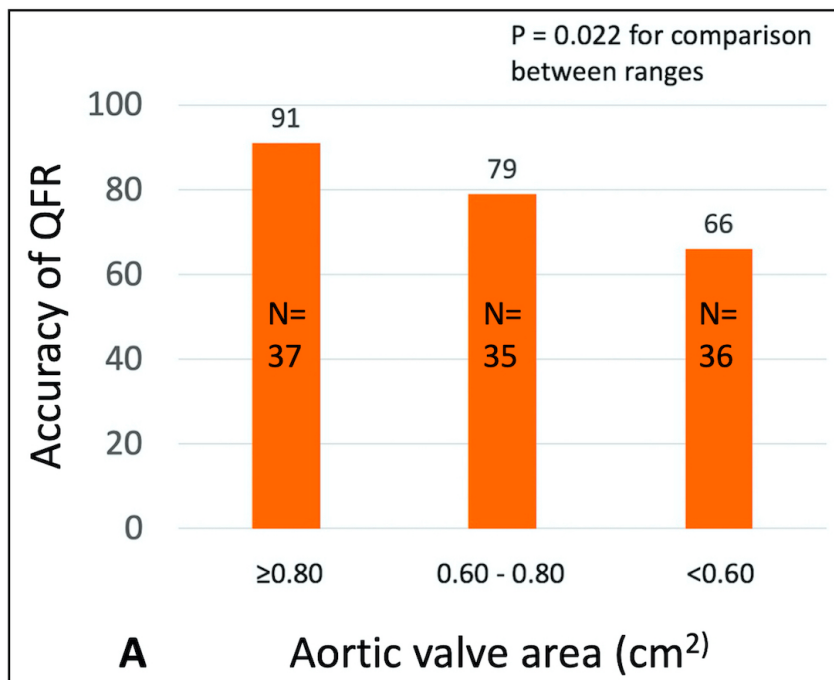
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Diagnostic yield of QFR and %DS in assessing the physiological relevance of coronary stenoses in SAS



Diagnostic yield of QFR according to AVA in SAS patients





Supplementary Material

Manuscript: Functional assessment of coronary stenosis with angiography-based Quantitative Flow Ratio compared with Fractional Flow Reserve in patients with severe aortic stenosis.

Authors: Mejía-Rentería et al.

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Invasive FFR assessment

Fractional flow reserve was measured following the routine manner of each participating center using a commercial pressure wire system. Nitroglycerin was administered at the operator's discretion according to patient-specific hemodynamic conditions prior to starting the physiological study. After equalization of pressures, the guidewire was advanced distal to the target coronary stenosis. Hyperemia was induced with adenosine either by intravenous administration (140-180 micrograms/kilogram/minute) or intra-coronary bolus (150-300 micrograms) according to operator criteria and routine practices at each center. During stable maximal hyperemia, FFR was calculated as the ratio between mean distal and mean proximal coronary pressure. The physiological study was completed by checking for pressure drift with the wire sensor located at the tip of the guiding catheter. For this study, an $\text{FFR} \leq 0.80$ was considered indicative of myocardial ischaemia.

Quantitative coronary analysis and QFR

QFR was calculated offline using the QAngio-XA 3D software (research edition, version 1.1, Medis, Leiden, the Netherlands) as described elsewhere [9]. Using the routine standard coronary angiography performed before TAVI, two angiographic projections separated by at least 25° with good image quality were selected according to the target vessel. In each of these two projections, the end-diastolic frame with adequate contrast opacification was selected. The analysts indicated three reference points along the target vessel with matching points in both selected projections. Additionally, the segment of interest in the vessel was selected from proximal to distal including the target lesion and the original location of the pressure-wire if available. A 3D reconstruction of the target vessel was then automatically obtained, and manual corrections of the vessel contours were made if necessary. For this study, the angiographical severity of coronary stenoses were graded by percent diameter stenosis (%DS) derived from 3D-QCA. Other parameters obtained from 3D-QCA were the reference vessel diameter, the minimum luminal diameter and lesion length. A fixed value of QFR (named fixed-QFR model), which resulted from computing 3D-QCA parameters with a fixed flow, was modelled to patient-

specific flow characteristics simulating hyperemic flow by using frame count analysis and the vessel lumen volume, finally obtaining so called “contrast-QFR” model (Supplementary Figure 1) [14]. For this study, the contrast-QFR model was the main QFR value to be analyzed and compared with FFR, named here just as “QFR”. A QFR value ≤ 0.80 was considered indicative of myocardial ischaemia.

Statistical analysis

Demographic baseline characteristics and aortic valve parameters were analyzed on a per-patient basis. The remaining parameters including physiological calculations were analyzed on a per-vessel basis using the generalized estimating equation method to adjust for intrasubject variability among patients with several vessels evaluated. Continuous variables are expressed as mean and standard deviation or median with interquartile range (IQR), as appropriate.

Categorical variables are presented as frequencies (percentages). Normality of distribution was verified by the Kolmogorov-Smirnov test. The accuracy of QFR in determining the functional stenosis relevance was evaluated according to the diagnostic categorization (dichotomous classification) with FFR using the cutoff ≤ 0.80 for both techniques. Sensitivity, specificity and predictive values for QFR were obtained from the receiver operating characteristics (ROC) analysis. The area under the curve (AUC) for 3D-QCA and QFR in assessing functional stenosis relevance was tested using FFR as the reference standard and compared using the DeLong method. Correlation and agreement between QFR and FFR were evaluated by Pearson (expressed as r value) and Bland-Altman analysis, respectively. SPSS statistics, version 23 (IBM Corp., Armonk, New York) and MedCalc software, version 17.6 (MedCalc Software, Ostend, Belgium) were used for statistical analysis. A p value < 0.05 was considered statistically significant.

Supplementary Figure Legends

Supplementary Figure 1

Title: QFR analysis of a coronary lesion in the presence of severe aortic stenosis

A mid left anterior descending coronary artery with intermediate lesion in a patient with severe aortic stenosis (A, B). From conventional angiography, a three-dimensional reconstruction of the target vessel was performed using two projections (A-C), matching the distal landmark with the location of the pressure-wire sensor (B, *). QFR value was 0.82 (C) and invasive FFR value was 0.85 (D) before transcatheter aortic valve implantation. FFR = fractional flow reserve; QFR = quantitative flow ratio; 3D-QCA = three-dimensional quantitative coronary angiography; %DS = percent diameter stenosis.

Supplementary Figure 2

Title: Correlation and agreement between QFR and FFR

A: Scatter plot diagram and linear regression for QFR and FFR values. B: Bland-Altman analysis showing mean absolute difference between QFR and FFR with 95% confidence limits. Abbreviations as in figure 1.

Supplementary Figure 3

Title: Best cutoff for %DS in predicting ischemic-causing coronary stenoses in SAS patients

Plot versus criterion values analysis derived from receiving operating characteristics method identified $\geq 49\%$ as the best cutoff for %DS (by 3D-QCA) in predicting an $\text{FFR} \leq 0.80$ (Youden Index $J = 0.4020$). Abbreviations as in supplementary figure 1.

Supplementary Figure 4

Title: Receiver-Operating Characteristic Curves for QFR and %DS according to FFR

Per-patient ROC analysis showing superiority of QFR over angiography in discriminating the functional relevance of coronary stenoses in patients with severe aortic stenosis, as judged by $\text{FFR} \leq 0.80$ ($p = 0.0005$ for comparison between AUC). AUC = area under the curve; QFR = quantitative flow ratio. Other abbreviations as in supplementary figure 1.

Supplementary Figure 5

Title: Receiver-Operating Characteristic Curves for contrast-QFR model vs. fixed-QFR model in presence of severe aortic stenosis

Per-vessel ROC analysis showing superiority of contrast-QFR model (c-QFR) over fixed-QFR model (f-QFR) in discriminating an $\text{FFR} \leq 0.80$ in presence of severe aortic stenosis. $P = 0.0027$ for comparison of area under the curve (AUC) between both models in the overall study population, $p = 0.3354$ for comparison of AUC between both models in critical aortic stenosis ($\text{AVA} < 0.60 \text{ cm}^2$) and $p = 0.0879$ for comparison of AUC between both models in severe aortic stenosis ($\text{AVA} \geq 0.60 \text{ cm}^2$). AVA= aortic valve area.

Supplementary Figure 6

Title: Distribution of left ventricle ejection fraction (LVEF) across ranges of mean aortic pressure gradient

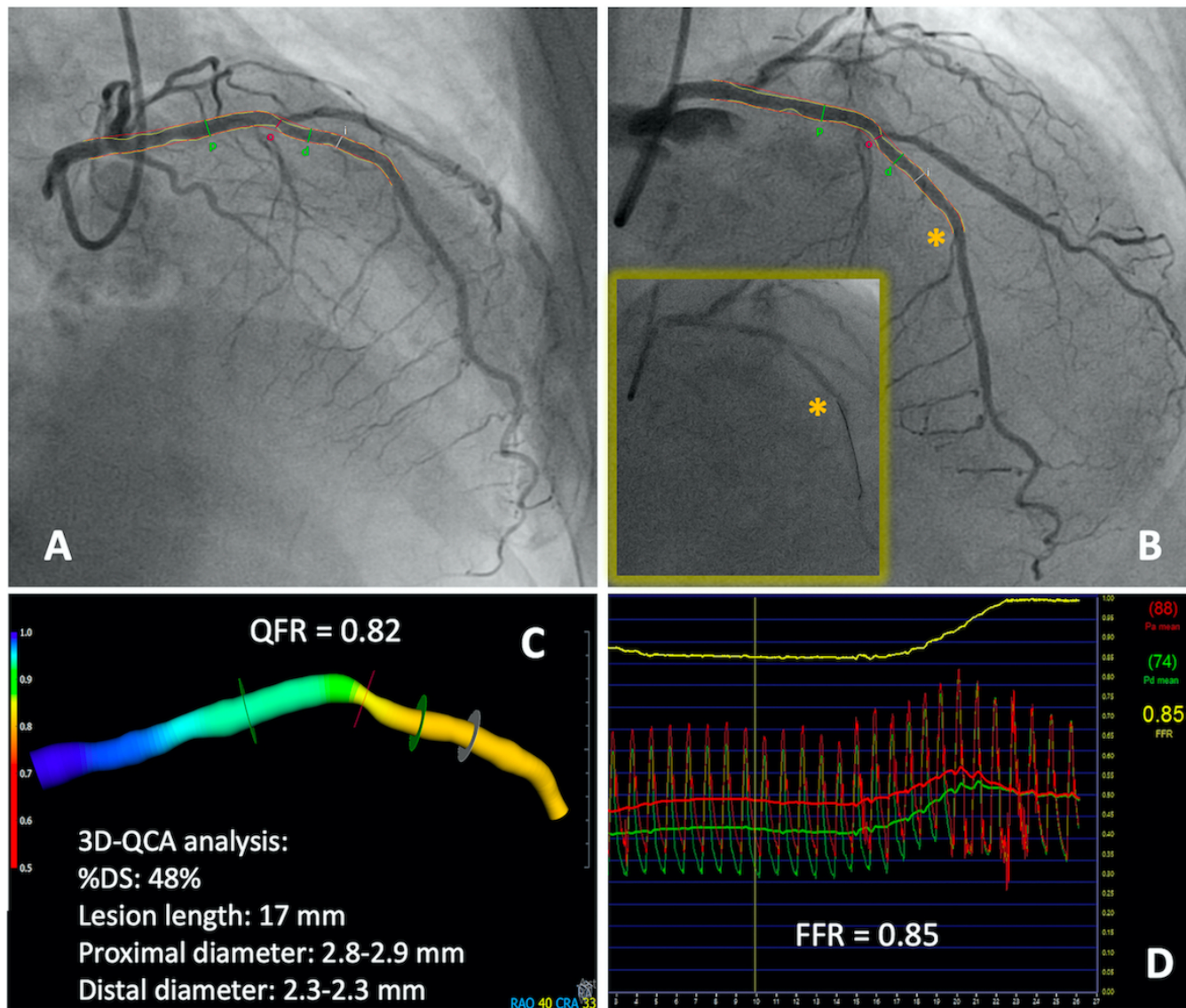
The Box-and-whisker plot displays values of LVEF across ranges of mean aortic pressure gradient. The central boxes represent the values from the lower to upper quartile (25 to 75 percentile) for each range of mean aortic gradient, and horizontal lines extends from the minimum to the maximum value. Outliers values corresponding to severely reduced LVEF are present in patients with lower mean aortic gradient values.

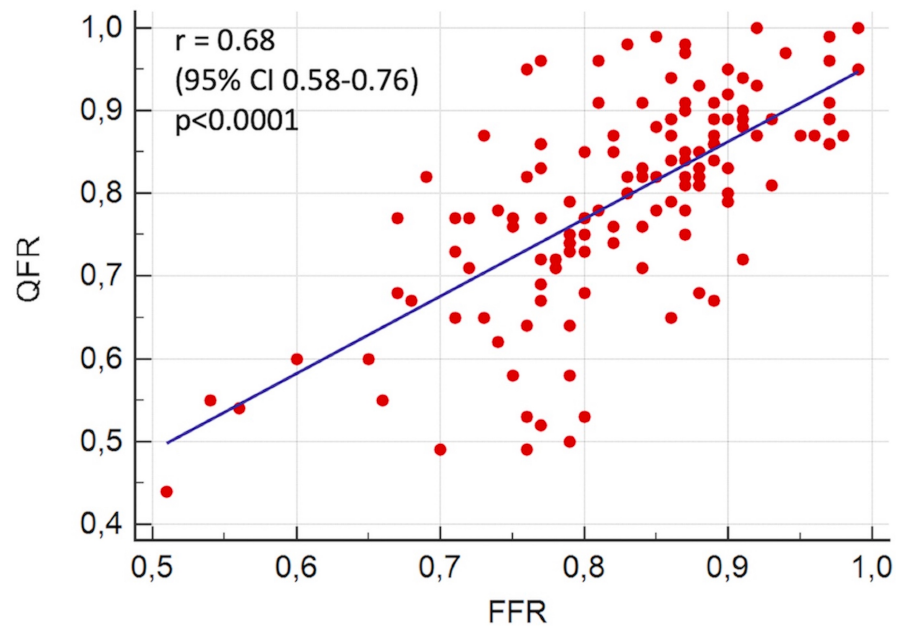
Supplementary Table

Clinical characteristics of the study population (N = 115)

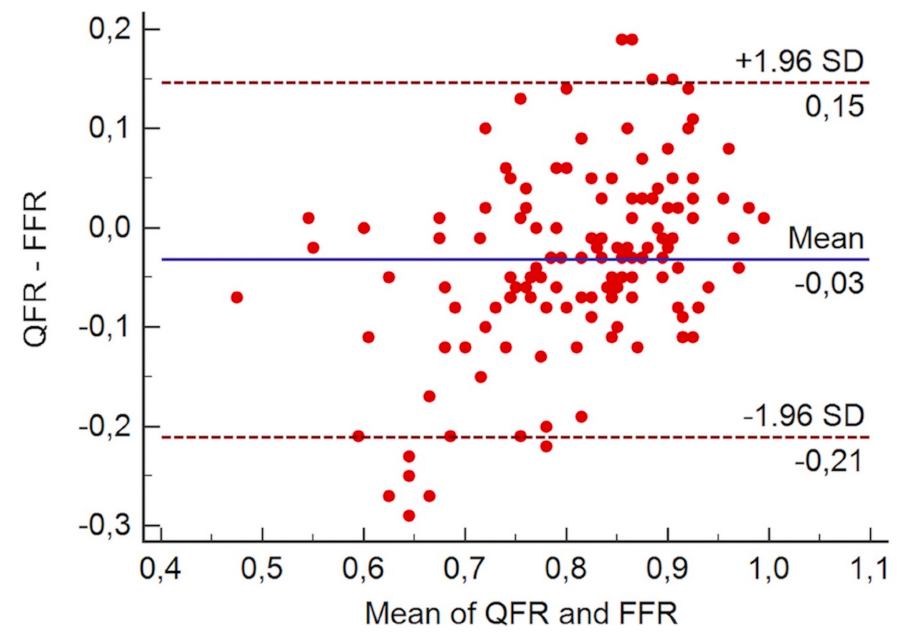
<i>Demographic data</i>	
Age, yrs	82 (75-86)
Male	54 (47)
Body mass index, Kg/m ²	25.8 (23.1-29.3)
Cardiovascular risk factors	
Hypertension	89 (77)
Diabetes	36 (31)
Dyslipidaemia	63 (55)
Current smoker	6 (5)
eGFR, mL/min/1.73 m ²	65.07 (52.8-93.3)
Previous myocardial infarction	12 (10)
NYHA functional class	
II	32 (34)
III and IV	62 (66)
<i>Echocardiographic characteristics</i>	
Aortic valve area, cm ²	0.68±0.22
Mean aortic gradient, mmHg	47.5±16.9
Left ventricular diameter in diastole, mm	44.6±6.9
Left ventricle ejection fraction, %	60 (50-60)

Values are mean ± SD, median (interquartile range) or n (%). eGFR = estimated glomerular filtration rate; NYHA = New York Heart Association.





A



B

