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Original article

Angiography-derived index versus fractional flow reserve for intermediate coronary lesions: a meta-analysis review

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ABSTRACT

Introduction and objectives: Assessment and treatment of intermediate coronary lesions, defined as those which represent 30%-90% of the vessel lumen, remains a clinical challenge. Physiological evaluation techniques, such as fractional flow reserve (FFR), non-adenosine-based methods, such as instantaneous wave-free ratio or resting full-cycle ratio, and angiography-derived physiological assessment techniques (ADPAT) have transformed the diagnostic landscape. This meta-analysis aimed to systematically review and compare the diagnostic performance of ADPAT and FFR evaluating intermediate coronary lesions.
Methods: We conducted a systematic review of comparative research on FFR and ADPAT from January through February 2024.
Results: A total of 27 studies were finally included in the meta-analysis for a total of 4818 patients and 5440 vessels. Overall, a strong correlation between the different ADPAT and FFR was observed (r = 0.83; 95%CI, 0.80-0.85), with a mean ADPAT value of 0.82; 95%CI, 0.81-0.83 and a mean FFR of 0.83; 95%CI, 0.82-0.85. The summary area under the curve for predicting significant FFR (≤ 0.80) was excellent at 0.947. The overall sensitivity rate was 85% (95%CI, 81-87) with a specificity rate of 93% (95%CI, 91-94). The positive predictive value was 86% (95%CI, 83-88) with a total negative predictive value of 92% (95%CI, 91-94).
Conclusions: ADPAT show good correlation and concordance with FFR for intermediate coronary lesion evaluation. However, due to unfavorable outcomes observed in the FAVOR III Europe trial[1] with quantitative flow ratio-guided revascularization, its clinical role should be reconsidered and potentially limited to scenarios where invasive assessment or adenosine use is not feasible. Further evaluation is warranted to confirm its diagnostic performance in broader clinical contexts.
Registered at PROSPERO: CRD420251042828.

Keywords: Clinical research. Fractional flow reserve. Angiographic/fluoroscopic. Meta-analysis.

Índice derivado de la angiografía frente a reserva fraccional de flujo en lesiones coronarias intermedias. Revisión de metanálisis

RESUMEN

Introducción y objetivos: La evaluación y el tratamiento de las lesiones coronarias intermedias, definidas como aquellas que comprometen entre el 30 y el 90% de la luz del vaso, continúan representando un desafío clínico. Las técnicas de evaluación fisiológica (como la reserva fraccional de flujo [RFF]), los métodos que no requieren adenosina (como el índice instantáneo libre de ondas o el índice de ciclo completo en reposo) y las técnicas de evaluación fisiológica derivadas de la angiografía (ADPAT) han transformado el panorama diagnóstico. Este metanálisis tuvo como objetivo revisar sistemáticamente y comparar el rendimiento diagnóstico de las ADPAT frente a la RFF en la evaluación de lesiones coronarias intermedias.
Métodos: Entre enero y febrero de 2024 se realizó una revisión sistemática de investigaciones comparativas entre RFF y ADPAT.
Resultados: Se incluyeron 27 estudios en el metanálisis, con un total de 4.818 pacientes y 5.440 vasos. En general, se observó una fuerte correlación entre las distintas ADPAT y la RFF (r = 0,83; IC95%, 0,80-0,85), con un valor medio de ADPAT de 0,82 (IC95%, 0,81-0,83) y un valor medio de FFR de 0,83 (IC95%, 0,82-0,85). El área bajo la curva resumen para predecir una RFF significativa (≤ 0,80) fue excelente, con un valor de 0,947. La sensibilidad global fue del 85% (IC95%, 81-87) y la especificidad fue del 93% (IC95%, 91-94). El valor predictivo positivo fue del 86% (IC95%, 83-88) y el valor predictivo negativo total fue del 92% (IC95%, 91-94).

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Conclusiones: Las ADPAT muestran una buena correlación y concordancia con la RFF en la evaluación de lesiones coronarias intermedias. Sin embargo, debido a los resultados desfavorables observados en el estudio FAVOR III Europe1 con la revascularización guiada por el índice cuantitativo de flujo, su papel clínico se debe reconsiderar y posiblemente limitar a escenarios en los que no sea factible realizar una evaluación invasiva ni utilizar adenosina. Se requiere una evaluación adicional para confirmar su rendimiento diagnóstico en contextos clínicos más amplios.
Registrado en PROSPERO: CRD420251042828.

Palabras clave: Investigación clínica. Reserva fraccional de flujo. Angiografía/fluoroscopia. Metanálisis.

Abbreviations

ADPAT: angiography-derived physiological assessment techniques. **AUC:** area under the curve. **FFR:** fractional flow reserve. **QFR:** quantitative flow ratio. **uFR:** Murray law-based quantitative flow reserve.

INTRODUCTION

Assessment and treatment of intermediate coronary lesions (those where percent diameter stenosis accounts for 30%-90% of the vessel lumen) remains a clinical challenge.[1] Over the past 10 years this field has undergone significant changes, primarily due to theoretical and technological advances in physiological evaluation techniques.[2,3]

Prior to the existence of these techniques, the assessment of intermediate lesions was based on the degree of relative narrowing of the vessel lumen vs healthy segments, being this reduction subjectively determined by the operator, without knowledge of its physiological repercussion.[2] The development of pressure guidewire methods, along with their validation and proven prognostic significance (particularly in the context of chronic coronary syndrome) from the late 1990s to the early 2000s,[4] has led to substantial progress in intermediate lesions evaluation, which has enabled a more accurate classification based on their clinical relevance.[5]

The initial method developed, and still considered the gold standard, is fractional flow reserve (FFR).[5] This technique estimates blood flow across a coronary lesion by measuring pressure differences.[6] To make this estimation between pressure and flow, maximal coronary vessel hyperemia, primarily achieved through adenosine infusion, is necessary.[6] FFR is defined as significant if flow difference across the lesion is > 20% (FFR ≤ 0.80).[6] Beyond merely identifying which lesions benefit from revascularization, FFR has shown improved survival vs revascularization based on relative narrowing assessment. Furthermore, it has allowed lesion exclusion where revascularization is deemed unnecessary, thus reducing stent implantation rates and any potential complications associated with both this procedure and antiplatelet therapy.[7]

Despite the clear benefits of using intracoronary physiology, the need for invasive pressure guidewires, IV adenosine (with its potential complications), the time required, and even the outright rejection by interventional cardiologist may have led to a lower than expected adoption.[8] These limitations triggered the appearance of non-adenosine-based methods, such as the instantaneous wave-free ratio (iFR) or resting full-cycle ratio.[9,10] These methods use a specific moment of the cardiac cycle (for example the iFR uses the diastolic wave-free period) where microvascular resistances are minimal, allowing correlation between pressures and flow without the use of adenosine.[11,12] However, despite eliminating this limitation, the use of pressure guidewires is still a barrier.[8]

Simultaneously with the development of these adenosine-free techniques, angiography-derived physiological assessment techniques (ADPAT) emerged, enabling the physiological evaluation of coronary lesions without the need for a guidewire or adenosine. These techniques, initially derived from those used in coronary lesion assessment in computational tomography,[13] are based on the computational evaluation of lesions through fluid dynamics in coronary angiography. Since then, multiple options have emerged including QFR, Murray law-based quantitative flow ratio (uFR), vessel fractional flow reserve (vFRR), fractional flow reserve derived from routine coronary angiography (FFRangio) and coronary angiography-derived fractional flow reserve (CaFFR). All of them have been validated and compared with the gold standard FFR in prospective direct comparative studies of diagnostic accuracy.[14-20]

The aim of this article was to provide a review of the different validation studies of ADPAT vs FFR and offer a meta-analysis on the accuracy of each option, both collectively and individually.

METHODS

Literature search strategy

We conducted a systematic review of comparative research on FFR and ADPAT from January through February 2024. The PubMed database was used to search for articles on concordance, agreement, and diagnostic accuracy. Multiple searches were conducted using the following algorithm: FFR/FFR permuted with each mainly commercialized tool (QFR, uFR, vFRR, FFRangio and CaFFR) while trying to avoid CT and articles developed mainly in acute coronary syndrome through the commands "NOT (CT) NOT ("acute coronary syndrome")". Date range was limited from January 2012 through December 2023. PRISMA statement guidelines were followed, and the review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration No. CRD420251042828.

Eligible criteria

A total of 4580 terms were identified through the entire search process. These terms and their combinations were carefully selected by 2 different operators to refine the search for articles comparing the main ADPAT from the main commercial vs FFR. Articles involving coronary computed tomography angiography and those where comparisons were mainly drawn within the context of acute coronary syndrome were also excluded by the operators. Based on these criteria, an initial pool of studies was established.

A total of 15 studies were subsequently excluded based on prespecified criteria, including those that specified the presence of patients

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with concurrent or treated aortic stenosis, had more than 25% of patients diagnosed with atrial fibrillation, or involved angiography-derived physiological assessments for coronary lesions conducted within the first 29 days of acute myocardial infarction (either on the culprit lesion or non-culprit lesions).

In cases where the time elapsed from myocardial infarction to angiography-derived evaluation was nonspecific; articles were also excluded if more than 30% of patients had undergone coronary angiography due to acute myocardial infarction.

Furthermore, studies specifying the presence of 10% or more patients with prior surgical revascularization were excluded, as were those where the comparison between angiography-based physiological assessment methods and FFR was conducted on mammary artery grafts, radial artery grafts, or saphenous vein grafts.

After applying the selection criteria, a total of 29 articles were initially chosen for analysis. However, 2 articles (FAST [virtual FFR])[21] and Ai et al.[22] were subsequently excluded because they did not provide or calculate sensitivity and specificity data from their analyses. Consequently, the final analysis included 27 articles.

Two articles were divided and included as different items in the analysis as they showed 2 different analyzed cohorts on their studies: Smit et al.,[23] where QFR was compared with the FFR in 2 cohorts: 1 with diabetes mellitus and the other without the disease; Zuo et al.[24] divided patients in 2 cohorts based on whether the vessel was severely calcified or not. The uFR was compared with the FFR in each group. Each cohort was included in our analysis. Finally, the study by Emori et al.[25] "Diagnostic accuracy of quantitative flow ratio for assessing myocardial ischemia in prior myocardial infarction," presented 2 distinct cohorts based on the presence of prior myocardial infarction (≥ 30 days from coronary angiography). Although one cohort depicted an acute coronary syndrome scenario, it fulfilled our inclusion criteria, leading to the inclusion of both cohorts in the final analysis.

Statistical and methodologic analysis

The homogeneity across studies was contrasted using the QH statistic. Regarding the low sensitivity of this test, $P < .10$ values were considered significant. To overcome this limitation, the I2 statistic was estimated as well, which measures the proportion of the total variation of the studies, explained by the heterogeneity and its 95% confidence interval (95%CI). A random effects model was used for all cases using the pooled method of DerSimonian Laird. If heterogeneity was present, meta-regression analyses were conducted to explore the sources of heterogeneity (figure 1 of the supplementary data). The presence of publication bias was tested using the Deek funnelplot (figure 2 of the supplementary data).

From the reported values of sensitivity, specificity, negative predictive value, positive predictive value, accuracy, and the number of vessels assessed, all 2×2 tables for the 0.8 cutoff point of the tests were constructed. Subsequently, pooled estimates for sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were derived from these data.[26]

The confidence intervals of sensitivity and specificity were calculated using the F distribution method to compute the exact confidence limits for the binomial proportion (x/n). The summary receive operator curve (SROC) was also calculated from which we drew all the points of sensitivity and 1-specificity and adjusted the weighted regression curve using Moses' Model. Spearman correlation coefficient between sensitivity and specificity was used to assessed constant diagnostic odds ratio (positive likelihood ratio and negative likelihood ratio) employing a symmetric SROC.[27] The area under curve (AUC) was computed by numeric integration of the curve equation using the trapezoidal method. Additionally, we applied the bootstrap methods for estimated AUC of multiple SROC. We provided the resultant bootstrap P values and 95%CI of the AUC for pairwise comparisons of the different methods (table 1 of the supplementary data). Furthermore, we provided an influence diagnostic method based on the AUC by performing leave-one-study-out analyses (table 2 of the supplementary data). Pearson correlation coefficients were transformed into Fisher's z-values to calculate variance and we performed a meta-analysis and calculated the 95%CI (figure 3 of the supplementary data). Fagan's Nomogram (figure 4 of the supplementary data) was used to graphically estimate how the result from a diagnostic test altered the probability of a patient having a disease. We assessed applicability and risk of bias based on the modified version of the QUADAS-2 tool[28] (figure 5A,B of the supplementary data). All analyses were conducted using R Statistical Software (v4.2.0; R Core Team 2022) and performed using dmetatools R package (1.1.1; Noma H 2023), mada R package (0.5.11; Sousa-Pinto 2022) and TeachingDemos R package (2.13; Greg Snow 2024).

RESULTS

Finally, a total of 27 articles were suitable for inclusion, as illustrated in figure 1. From these articles, a total of 4818 patients and 5440 vessels were added to the analysis. The population characteristics and mean cardiovascular risk factors are detailed in table 1 highlighting the existence of 3189 (66.18%) patients with hypertension, 2438 (50.6%) with dyslipidemia, and 1263 (26.2%) with diabetes. Notably, most patients included in the study were men (68.86% of the sample).

Thirteen of the selected articles were prospective in design. The most extensively studied vessel was the left anterior descending coronary artery (2921; 53.69%), followed by the right coronary artery (1075; 19.61%) and the left circumflex artery (772; 14.2%). Additionally, 89 left main coronary arteries were analyzed, accounting for 1.6% of all vessels. Angiography was primarily performed for stable angina (2483; 51.53%). Of note, while 1475 (30.61%) angiographies were prompted by acute coronary syndrome, only 333 (6.9% of the total) were performed in the context of acute myocardial infarction with or without ST-segment elevation, and the remaining 1142 in the context of unstable angina. Indications for cardiac catheterization are shown in table 2. The left anterior descending coronary artery was the most frequently studied vessel, accounting for 2921 patients (53.7% of the total studies). Proportions for other vessels are available in table 3.

The QFR[15-17,23,25,29-34] (QAngio XA 3D QFR, Medis Medical Imaging System; The Netherlands) was the most widely used software with a total of 13 patient cohorts from 11 articles, comprising 1987 patients and 2315 vessels, which accounts for 41.2% and 42.6% of the total, respectively. The correlation between QFR and FFR was excellent, showing an r = 0.82 (95%CI, 0.77-0.877). The overall sensitivity rate of QFR was 84% (95%CI, 80-88) with a specificity rate of 90% (95%CI, 87-93). The positive predictive value was 81% (95%CI, 77-84) with a total negative predictive value of 92% (95%CI, 90-94). The AUC for this technique was 0.937.

The second most analyzed technique, with a total of 5 articles, was FFRangio[14,35-38] (Cathworks FFRangio, Israel), where this technology was employed in 696 patients and 841 vessels (14.4% and

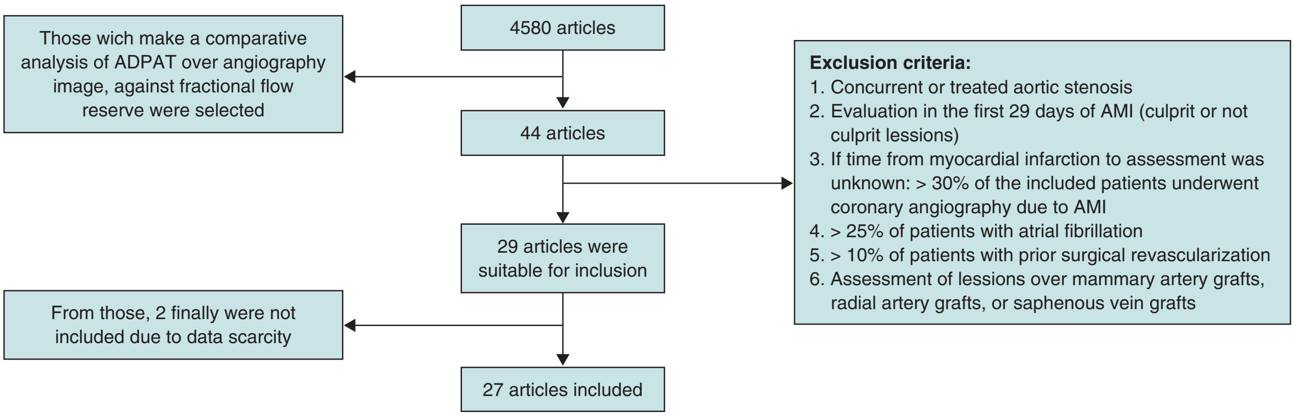

Figure 1. Selected articles flowchart and exclusion criteria. ADPAT, angiography-derived physiological assessment techniques; AMI, acute myocardial infarction.

Table 1. Patients' baseline characteristics

Patients' baseline characteristics (n = 4818)	
Characteristics (cohorts where this data is available)	**(± 95%CI) or %**
Mean age (26)	66.4 ± 1.3
Male (26)	3318 (68.9%)
Mean BMI (kg/m^2) (17)	26 ± 0.8
Hypertension (25)	3189 (66.2%)
Diabetes (25)	1263 (26.2%)
Dyslipidemia (21)	2438 (50.6%)
Mean LVEF (%) (10)	59.6 ± 3.3
Prior or current smoker (23)	1406 (29.2%)
Prior MI (20)	566 (11.7%)
Prior PCI (20)	1314 (27.3%)
Prior CABG (13)	47 (1%)

BMI, body mass index; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention. Data are expressed as mean value and standard deviation across the studies.

Table 2. Indications for cardiac catheterization

Indication for cardiac catheterization	(%)
Silent isquemia	323 (6.8)
Stable angina	2483 (51.5)
Acute coronary syndrome	1475 (30.6)
Unstable angina	1142 (23.7)
AMI	333 (6.9)
NSTEMI	204 (4.2)
STEMI	13 (0.3)
MI subtype not specified	116 (2.4)
Others	127 (2.6)

AMI, acute myocardial infarction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table 3. Number of studies per vessel performed across the different studies

Vessel characteristics (n = 5440)	(%)
Left main coronary artery	89 (1.7)
Left anterior descending coronary artery	2921 (53.7)
Diagonal branch	52 (1)
Ramus intermedius	54 (1)
Left circumflex artery	772 (14.2)
Obtuse marginal branch	108 (2)
Right coronary artery	1075 (19.8)
Posterolateral branch	7 (0.1)
Interventricular branch	8 (0.15)

15.45% of the total, respectively). The overall sensitivity rate of FFRangio was 90% (95%CI, 83-94) with a specificity rate of 95% (95%CI, 91-97). The positive predictive value was 90% (95%CI, 85-93) with a total negative predictive value of 94% (95%CI, 91-96).

vFFR (Pie Medical Imaging, The Netherlands) on the other hand, had an excellent correlation with FFR across the 3 included studies,[20,39,40] contributing 647 patients and 663 vessels to the analysis (representing 13.42% of patients and 11.96% of vessels). The mean sensitivity and specificity rates were 82% (95%CI, 72-89) and 0.94% (95%CI, 89-97), respectively. The summary positive predictive value was 89% (95%CI, 82-93), and the summary negative predictive value, 91% (95%CI, 86-94).

Following its recent validation in 2022, the uFR (AngioPlus, Pulse Medical Imaging Technology, China) is supported by only 2 articles,[19,24] one of which includes 2 cohorts based on vessel calcification. The uFR had a sensitivity rate of 80% (95%CI, 69-87) and a specificity rate of 0.94 (95%CI, 89-97). The summary positive predictive value was 85% (95%CI, 79-90), and the summary negative predictive value, 91% (95%CI, 87-94).

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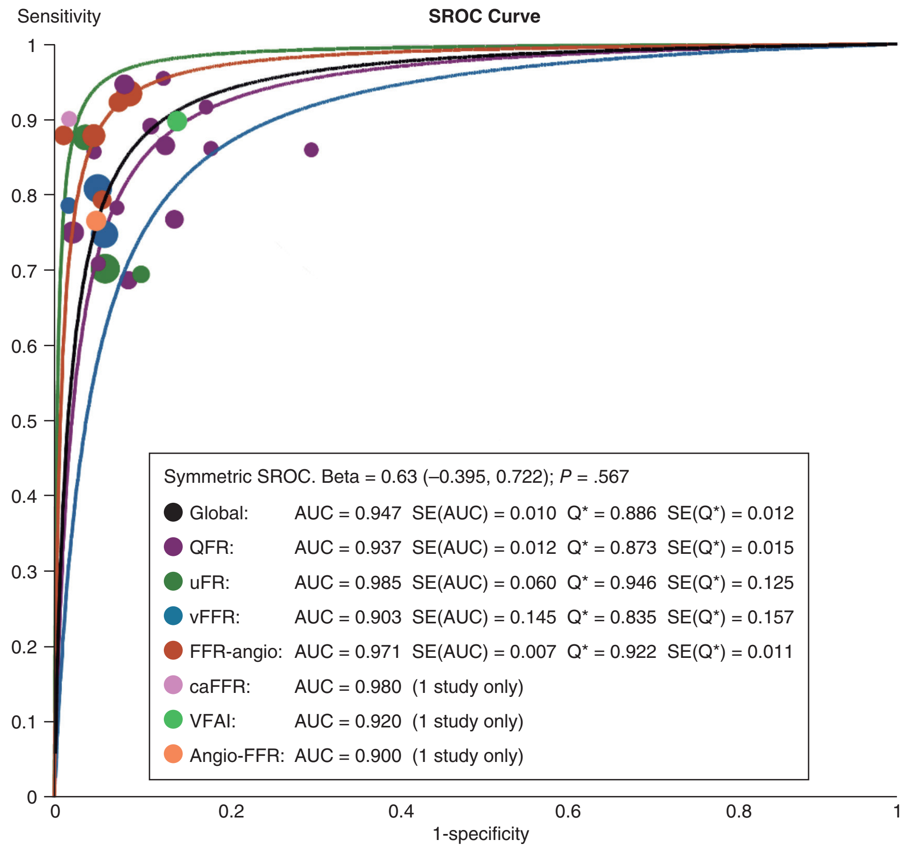

Figure 2. Summary receiver operating characteristic (SROC) curves and Q* index for subgroup analyses of software-derived coronary angiography-derived fractional flow reserve (caFFR); FFR, fractional flow reserve; QFR, quantitative flow ratio; uFR, Murray law-based quantitative flow reserve; VFAI, vessel fractional anatomy index; vFFR, vessel fractional flow reserve.

Only 1 article of CaFFR (Flashangio, Rainmed Ltd., China) was included.[18]

The analysis included 2 non-commercialized tools, VFAI[41] and AngioFFR,[42] which were not individually evaluated. Both were compared to FFR only once.

Overall, a strong correlation between the different ADPAT and FFR was observed (r = 0.83, 95%CI, 0.80-0.85), with a mean ADPAT value of 0.82 (95%CI, 0.81-0.83) (all the ADPAT set a value ≤ 0.80 for lesion significance) and a mean FFR of 0.83 (95%CI, 0.82-0.85).

The summary AUC for predicting significant FFR (≤ 0.80) was excellent at 0.947. The SROC for the different ADPAT is shown in figure 2.

The overall sensitivity rate was 85% (95%CI, 81-87) with a specificity rate of 93% (95%CI, 91-94). The positive predictive value was 86% (95%CI, 83-88) with a total negative predictive value of 92% (95%CI, 91-94). The main commercially available ADPAT values of sensibility, specificity, positive predictive value and negative predictive value are shown in figure 3 and figure 4.

DISCUSSION

Key findings

Our key findings were: *a)* ADPAT emerge as a reliable and practical method for assessing the physiological significance of intermediate coronary lesions, which is consistent with previous literature.[44-46] ADPAT consistently demonstrates agreement with the current gold standard (FFR) regarding mean values and lesion classification, without vasodilator medication or pressure guidance; *b)* By summarizing the diagnostic capabilities of each ADPAT from the included studies, we were able to perform the first direct comparison of various angiography-based methods for evaluating coronary lesions. We presented the main commercially available options and their respective diagnostic accuracies relative to FFR. Additionally, an overview of these techniques was provided; *c)* We also included innovative methods, such as uFR, based on Murray's Law, while offering a unique approach by using a single projection to estimate lesion significance, potentially overcoming a significant limitation of current techniques, which often require specific projections and a certain quality image.

The overall results confirmed that different ADPAT serve as an appropriate method for evaluating intermediate coronary lesions, as they demonstrated a strong correlation with FFR. This correlation extended to sensitivity, specificity, and predictive values as illustrated in figure 4. Notably, the studies exhibited homogeneity without significant discrepancies in their weighting within the analysis, as observed through the resampling techniques employed.

In comparative analysis, while ADPAT exhibit adequate sensitivity and positive predictive values regarding lesion significance, their specificity and negative predictive value exceed 90%. This high specificity allows ADPAT to more accurately identify physiologically non-significant lesions, thereby avoiding unnecessary revascularization.

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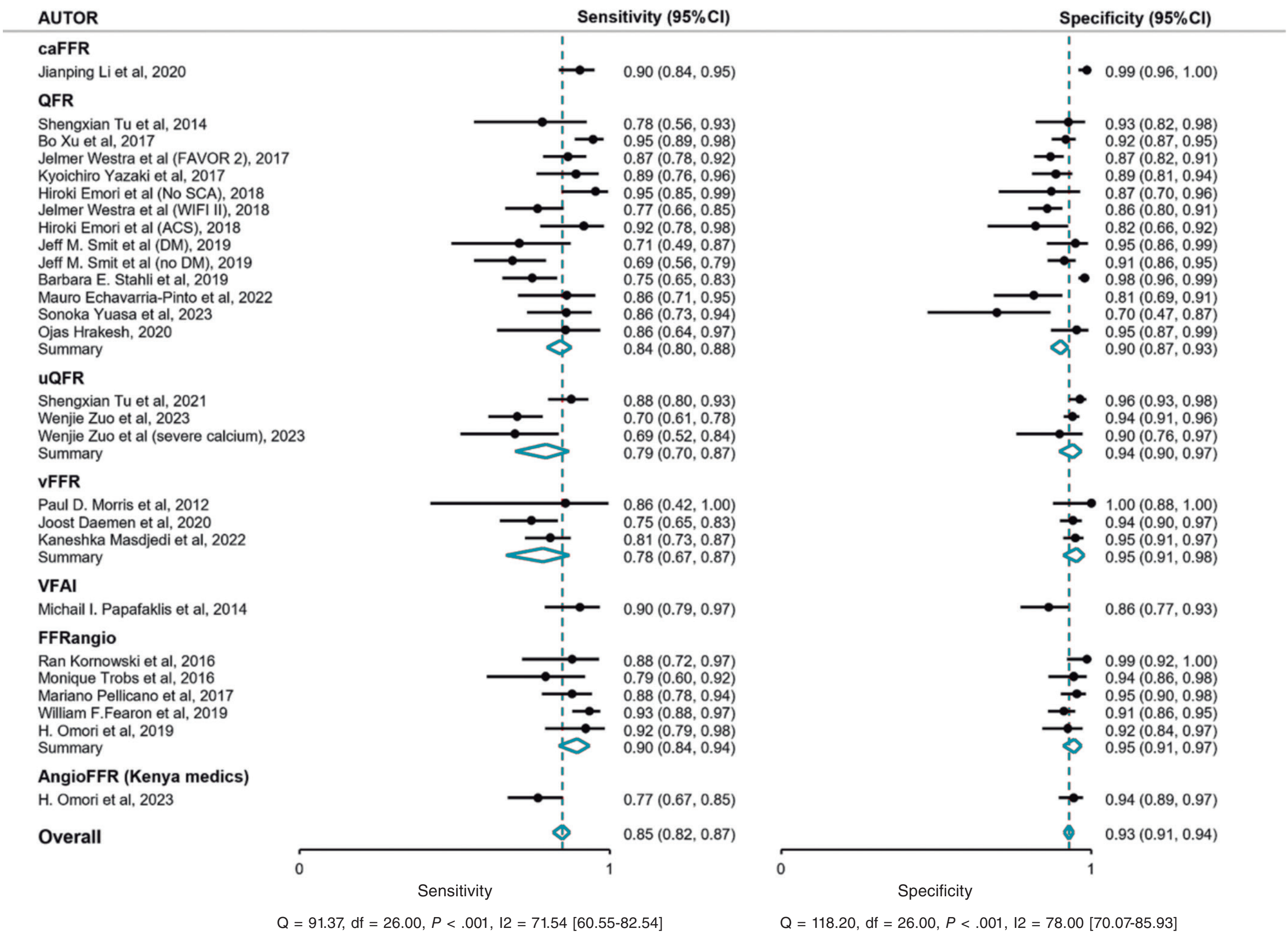

Figure 3. Forest plots and summary statistics for sensitivity and specificity estimates from a meta-analysis of FFR across different indices, using a random-effects model. 95%CI, 95% confidence interval; caFFR, coronary angiography–derived fractional flow reserve; FFR, fractional flow reserve; QFR, quantitative flow ratio; uFR, Murray law-based quantitative flow reserve; VFAI, vessel fractional anatomy index; vFFR, vessel fractional flow reserve. Xu et al.,[16] 2017; Fearon et al.,[36] 2019; Yuasa et al.,[33] 2023; Morris et al.,[39] 2013; Westra et al.,[29] 2018; Echavarría-Pinto et al.,[31] 2022; Stähli et al.,[34] 2019; Omori et al.,[35] 2019; Westra et al.,[17] 2018; Li et al.,[18] 2020; Pellicano et al.,[14] 2017; Emori et al.,[25] 2018; Tu et al.,[15] 2014; Zuo et al.,[24] 2024; Tu et al.,[19] 2021; Omori et al.,[42] 2023; Hrakesh et al.,[32] 2020; Kornowski et al.,[37] 2016; Masdjedi et al.,[20] 2022; Tröbs et al.,[38] 2016; Yazaki et al.,[30] 2017; Smit et al.[23] 2019; Daemen et al.,[43] 2022; and Papafaklis et al.,[41] 2014.

From a technical standpoint, it was notable that these results were primarily obtained from assessments of the left anterior descending coronary artery (53.6%), with only 1 dedicated study on the left main coronary artery. Despite this, left main coronary arteries contributed a significant proportion (1.66%) to the overall analysis, showcasing proficient classification of significant lesions (AUC = 0.82) and indicating the feasibility of applying tools in this context.

QFR was the most frequently included tool in the analysis, representing 13 out of 27 cohorts. Despite multiple validations vs the FFR in diverse contexts, most studies align closely, demonstrating a correlation between QFR and FFR.

Comparing results across different tools, minimal differences were observed, with FFRangio and CaFFR showing slightly superior overall results vs other methods. However, it's important to note that the results of the CaFFR are based solely on validation articles, and when considering only validation studies, results among tools are very similar.

Although QFR is frequently studied, its results might require more robust validation because there are limited articles on FFRangio, especially on chronic coronary syndrome in patient groups like those with left main disease or diabetes.

While ADPAT have been validated vs the FFR in various clinical scenarios, such as severe aortic stenosis, atrial fibrillation, or non-culprit coronary lesions in acute coronary syndrome, the inclusion of these scenarios in our analysis could potentially bias the results due to variations in study characteristics and the unique features of each disease affecting lesion assessment.

The limitation of this study stems from including a large proportion of pivotal studies for each analyzed tool, which were not performed under real-world clinical conditions. Consequently, the applicability of their results may be restricted, as demonstrated by a recent study from independent laboratories comparing the 5 main non-hyperemic indices with FFR under real-life conditions.[47]

Although the study demonstrated a good correlation between the indices and FFR, the levels of diagnostic accuracy reported in the pivotal studies were not achieved.

In this regard, QFR has been recently evaluated vs the FFR in the FAVOR III Europe trial,[1] which included 2000 patients who were

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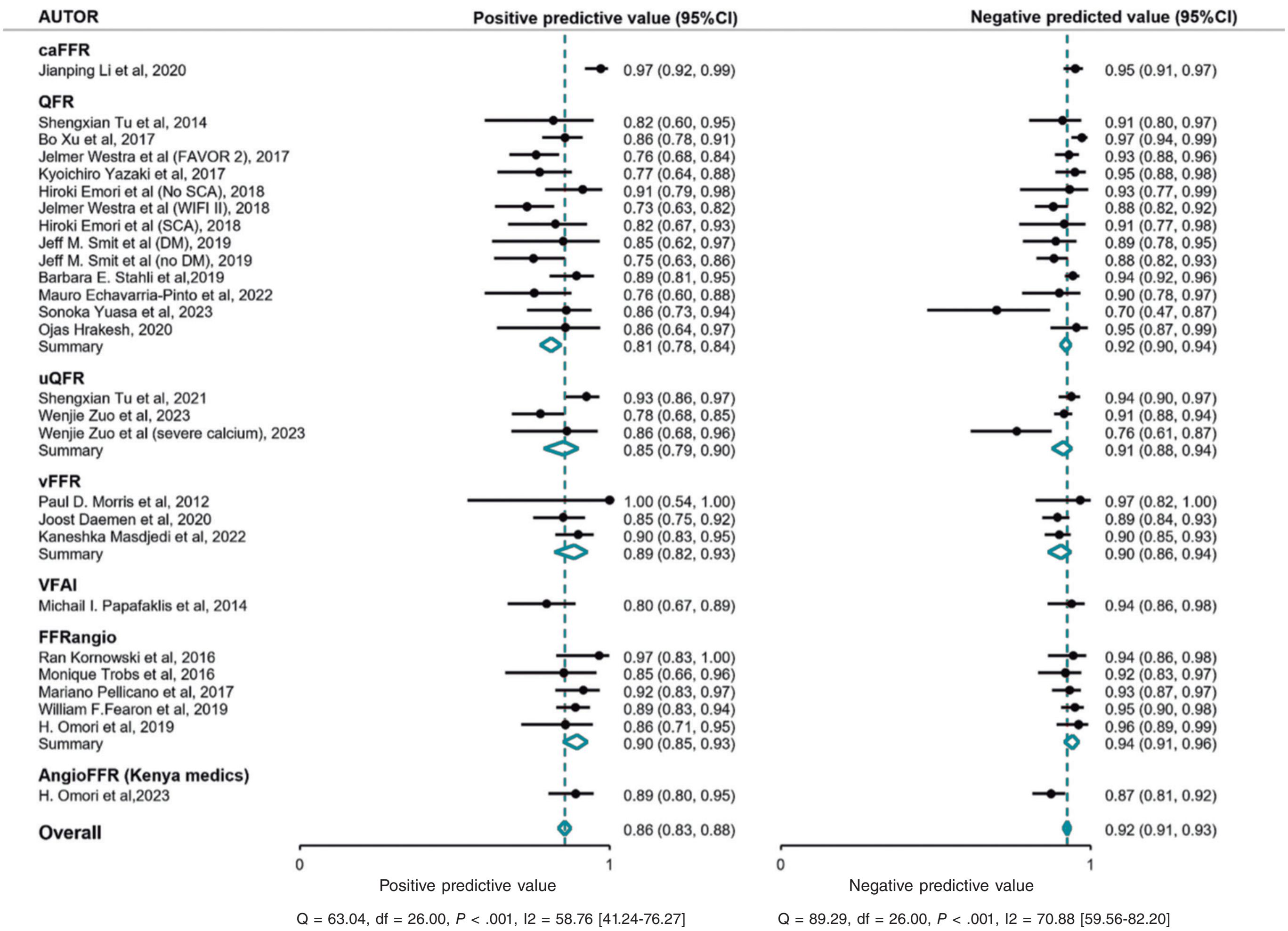

Figure 4. Forest plots and summary statistics for positive predictive value (PPV) and negative predictive value (NPV) estimates from a meta-analysis of FFR across different indices, using a random-effects model. 95%CI, 95% confidence interval; caFFR, coronary angiography–derived fractional flow reserve; FFR, fractional flow reserve; QFR, quantitative flow ratio; uFR, Murray law-based quantitative flow reserve; VFAI, vessel fractional anatomy index; vFFR, vessel fractional flow reserve. Xu et al.,[16] 2017; Fearon et al.,[36] 2019; Yuasa et al.,[33] 2023; Morris et al.,[39] 2013; Westra et al.,[29] 2018; Echavarría-Pinto et al.,[31] 2022; Stähli et al.,[34] 2019; Omori et al.,[35] 2019; Westra et al.,[17] 2018; Li et al.,[18] 2020; Pellicano et al.,[14] 2017; Emori et al.,[25] 2018; Tu et al.,[15] 2014; Zuo et al.,[24] 2024; Tu et al.,[19] 2021; Omori et al.,[42] 2023; Hrakesh et al.,[32] 2020; Kornowski et al.,[37] 2016; Masdjedi et al.,[20] 2022; Tröbs et al.,[38] 2016; Yazaki et al.,[30] 2017; Smit et al.,[23] 2019; Daemen et al.,[43] 2022; and Papafaklis et al.,[41] 2014.

randomized (1:1) to QFR-guided or FFR-guided treatment of intermediate lesions. The results showed that the QFR-guided group had higher rates of mortality, myocardial infarction, and unplanned revascularization at 12 months.

Although these findings may initially seem discouraging, they do not contradict the results of our study, in which non-hyperemic indices demonstrated superior performance over conventional angiography in the functional classification of lesions. Therefore, their use remains valuable in clinical scenarios where invasive assessment with a pressure guidewire or the use of adenosine is not feasible or contraindicated.

Of note, while QFR is currently the most widely used non-hyperemic index, it is the only one that has been evaluated in clinical trials with hard clinical endpoints vs FFR. Other tools with promising results are still to be investigated in this context.

CONCLUSIONS

Substantial correlations and concordances have been demonstrated between ADPAT and FFR. These techniques have also shown accurate categorization of lesions deemed significant by the current gold standard (FFR). However, the results of the FAVOR III Europe study[1] indicate that QFR–guided revascularization, compared with FFR-guided revascularization, is associated with higher rates of mortality, myocardial infarction, and unplanned revascularization. Therefore, the current role of ADPAT requires re-evaluation.

In this context, the use of QFR may be most appropriate when invasive assessment using a pressure guidewire is not feasible or when adenosine is contraindicated. Additionally, due to the unique characteristics of other clinical scenarios, further reviews are warranted to evaluate the diagnostic accuracy of this index.

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ETHICAL CONSIDERATIONS

The present study was conducted in full compliance with the clinical practice guidelines set forth in the Declaration of Helsinki

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for clinical research and was approved by the ethics committees of the reference hospital (*Hospital Clínico Universitario de Valladolid*) and other participant centers. Possible sex- and gender-related biases were also taken into consideration according to the SAGER recommendations.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the writing of this text.

AUTHORS' CONTRIBUTIONS

J. Ruiz-Ruiz and C. Cortés-Villar participated in the study design, data analysis, manuscript drafting, and critical revision. C. Fernández-Cordón and M. García-Gómez contributed to data collection and results analysis. A. Lozano-Ibáñez and D. Carnicero-Martínez contributed to data gathering. S. Blasco-Turrión and M. Carrasco-Moraleja contributed to the statistical analysis. J.A. San Román-Calvar and I.J. Amat-Santos performed the final review and approved the version for publication.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M25000523.

REFERENCES

1. Andersen BK, Sejr-Hansen M, Maillard L, et al. Quantitative flow ratio versus fractional flow reserve for coronary revascularisation guidance (FAVOR III Europe): a multicentre, randomised, non-inferiority trial. *Lancet*. 2024;404:1835-1846.
2. Patil CV, Beyar R. Intermediate coronary artery stenosis: Evidence-based decisions in interventions to avoid the oculostenotic reflex. *Int J Cardiovasc Intervent*. 2000;3:195-206.
3. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974;33:87-94.
4. De Bruyne B, Paulus WJ, Vantrimpont PJ, Sys SU, Heyndrickx GR, Pijls NHJ. Transstenotic coronary pressure gradient measurement in humans: In vitro and in vivo evaluation of a new pressure monitoring angioplasty guide wire. *J Am Coll Cardiol*. 1993;22:119-126.
5. Sousa-Uva M, Neumann FJ, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur J Cardio-thoracic Surg*. 2019;55:4-90.
6. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2011;365:213-224.
7. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease. *N Engl J Med*. 2012;367:991-1001.
8. Johnson NP, Koo BK. Coronary Psychology: Do You Believe? *JACC Cardiovasc Interv*. 2018;11:1492-1494.
9. De Waard GA, Di Mario C, Lerman A, Serruys PW, Van Royen N. Instantaneous wave-free ratio to guide coronary revascularisation: Physiological framework, validation and differences from fractional flow reserve. *EuroIntervention*. 2017;13:450-458.
10. Svanerud J, Ahn JM, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: The Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention*. 2018;14:806-814.
11. Davies JE, Sen S, Dehbi H-M, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*. 2017;376:1824-1834.
12. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017;376:1813-1823.
13. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *Jama*. 2012;308:1237-1245.
14. Pellicano M, Lavi I, De Bruyne B, et al. Validation study of image-based fractional flow reserve during coronary angiography. *Circ Cardiovasc Interv*. 2017;10:E005259.
15. Tu S, Barbato E, Köszegi Z, et al. 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;7:768-777.
16. Xu B, Tu S, Qiao S, et al. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. *J Am Coll Cardiol*. 2017;70:3077-3087.
17. Westra J, Andersen BK, Campo G, et al. 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.
18. Li J, Gong Y, Wang W, et al. Accuracy of Computational Pressure-Fluid Dynamics applied to Coronary Angiography to Derive Fractional Flow Reserve – FLASH FFR. *Cardiovasc Res*. 2020;116:1349-1356.
19. Tu S, Ding D, Chang Y, Li C, Wijns W, Xu B. Diagnostic accuracy of quantitative flow ratio for assessment of coronary stenosis significance from a single angiographic view: A novel method based on bifurcation fractal law. *Catheter Cardiovasc Interv*. 2021;97(S2):1040-1047.
20. Masdjedi K, Tanaka N, Van Belle E, et al. Vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study. *EuroIntervention*. 2022;17:1498-1505.
21. Masdjedi K, van Zandvoort LJC, Balbi MM, et al. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: The FAST study. *EuroIntervention*. 2021;16:591-599.
22. Ai H, Zheng N, Li L, et al. Agreement of Angiography-Derived and Wire-Based Fractional Flow Reserves in Percutaneous Coronary Intervention. *Front Cardiovasc Med*. 2021;8:654392.
23. Smit JM, El Mahdiui M, van Rosendael AR, et al. Comparison of Diagnostic Performance of Quantitative Flow Ratio in Patients With Versus Without Diabetes Mellitus. *Am J Cardiol*. 2019;123:1722-1728.
24. Zuo W, Sun R, Xu Y, et al. Impact of calcification on Murray law-based quantitative flow ratio for physiological assessment of intermediate coronary stenoses. *Cardiol J*. 2024;31:205-214.
25. Emori H, Kubo T, Kameyama T, et al. Diagnostic accuracy of quantitative flow ratio for assessing myocardial ischemia in prior myocardial infarction. *Circ J*. 2018;82:807-814.
26. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. *Bmj*. 2001;323:157.
27. Walter SD. Properties of the summary receiver operating characteristic (SROC) curve for diagnostic test data. *Stat Med*. 2002;21:1237-1256.
28. Whiting PF, Reitsma JB, Leeflang MMG, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155:529-536.
29. Westra J, Tu S, Winther S, et al. 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;11:1-8.
30. Yazaki K, Otsuka M, Kataoka S, et al. Applicability of 3-dimensional quantitative coronary angiography-derived computed fractional flow reserve for intermediate coronary stenosis. *Circ J*. 2017;81:988-992.
31. Echavarría-Pinto M, Van de Hoef TP, Pacheco-Beltran N, et al. Diagnostic agreement of quantitative flow ratio with fractional flow reserve in a Latin-American population. *Int J Cardiovasc Imaging*. 2022;38:1423-1430.
32. Hrakesh O, Hay M, Lim RY, et al. Comparison of diagnostic performance between quantitative flow ratio, non-hyperemic pressure indices and fractional flow reserve. *Cardiovasc Diagn Ther*. 2020;10:442-452.
33. Yuasa S, Lauri FM, Mejia-Renteria H, et al. Angiography-derived functional assessment of left main coronary stenoses. *Catheter Cardiovasc Interv*. 2023;101:1045-1052.
34. Stähli BE, Erbay A, Steiner J, et al. Comparison of resting distal to aortic coronary pressure with angiography-based quantitative flow ratio. *Int J Cardiol*. 2019;279:12-17.
35. Omori H, Witberg G, Kawase Y, et al. Angiogram based fractional flow reserve in patients with dual/triple vessel coronary artery disease. *Int J Cardiol*. 2019;283:17-22.
36. Fearon WF, Achenbach S, Engstrom T, et al. Accuracy of Fractional Flow Reserve Derived from Coronary Angiography. *Circulation*. 2019;139:477-484.

37. Kornowski R, Lavi I, Pellicano M, et al. Fractional Flow Reserve Derived From Routine Coronary Angiograms. *J Am Coll Cardiol*. 2016;68: 2235-2237.
38. Tröbs M, Achenbach S, Röther J, et al. Comparison of Fractional Flow Reserve Based on Computational Fluid Dynamics Modeling Using Coronary Angiographic Vessel Morphology Versus Invasively Measured Fractional Flow Reserve. *Am J Cardiol*. 2016;117:29-35.
39. Morris PD, Ryan D, Morton AC, et al. Virtual fractional flow reserve from coronary angiography: Modeling the significance of coronary lesions. Results from the VIRTU-1 (VIRTUal fractional flow reserve from coronary angiography) study. *JACC Cardiovasc Interv*. 2013;6:149-157.
40. Neleman T, Masdjedi K, Van Zandvoort LJC, et al. Extended Validation of Novel 3D Quantitative Coronary Angiography-Based Software to Calculate vFFR: The FAST EXTEND Study. *JACC Cardiovasc Imaging*. 2021;14: 504-506.
41. Papafaklis MI, Muramatsu T, Ishibashi Y, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: Comparison with pressure wire - fractional flow reserve. *EuroIntervention*. 2014;10:574-583.
42. Omori H, Kawase Y, Mizukami T, et al. Diagnostic Accuracy of Artificial Intelligence-Based Angiography-Derived Fractional Flow Reserve Using Pressure Wire-Based Fractional Flow Reserve as a Reference. *Circ J*. 2023;87:783-790.
43. Scoccia A, Tomaniak M, Neleman T, Groenland FTW, Plantes ACZ des, Daemen J. Angiography-Based Fractional Flow Reserve: State of the Art. *Curr Cardiol Rep*. 2022;24:667-678.
44. Cortés C, Carrasco-Moraleja M, Aparisi A, et al. Quantitative flow ratio—Meta-analysis and systematic review. *Catheter Cardiovasc Interv*. 2021;97: 807-814.
45. Faria D, Hennessey B, Shabbir A, et al. Functional coronary angiography for the assessment of the epicardial vessels and the microcirculation. *EuroIntervention*. 2023;19:203-221.
46. Leone AM, Campo G, Gallo F, et al. Adenosine-Free Indexes vs. Fractional Flow Reserve for Functional Assessment of Coronary Stenoses: Systematic Review and Meta-Analysis. *Int J Cardiol*. 2020;299:93-99.
47. Ninomiya K, Serruys PW, Kotoku N, et al. Anonymous Comparison of Various Angiography-Derived Fractional Flow Reserve Software With Pressure-Derived Physiological Assessment. *JACC Cardiovasc Interv*. 2023;16:1778-1790.

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