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ADVANCED HEMODYNAMICS AND CORONARY FUNCTIONAL ASSESSMENT: APPLICATIONS OF FFR, IFR, AND QFR IN THE STRATIFICATION OF CORONARY LESIONS

Advanced Hemodynamics And Coronary Functional Assessment: Applications Of Ffr, Ifr, And Qfr In The Stratification Of Coronary Lesions

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ABSTRACT

Objective: To critically analyze the scientific evidence regarding the application of coronary functional assessment in the stratification of intermediate coronary lesions, focusing on the fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), quantitative flow ratio (QFR), and computed tomography-derived fractional flow reserve (CT-FFR), evaluating their diagnostic and clinical impact.**Methods:**This is a systematic literature review conducted according to PRISMA recommendations. Studies published between 2010 and 2025 were included, selected from the PubMed/ MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL databases. Randomized clinical trials, observational studies, and diagnostic accuracy studies that evaluated coronary physiology methods were analyzed. The main outcomes included major adverse cardiovascular events (MACE) and diagnostic performance metrics such as sensitivity, specificity, and area under the ROC curve.**Results:**A total of 25 studies were included.FFR-guided strategies demonstrated a significant reduction in MACE compared to isolated angiography, in addition to allowing safe deferral of revascularization in lesions without functional repercussion. iFR showed clinical non-inferiority compared to FFR in the short and long term. QFR demonstrated high diagnostic accuracy and reduced events when used to guide revascularization. CT-FFR presented high sensitivity and relevant clinical impact, with a reduction in unnecessary invasive angiographies. Microcirculation studies have shown that microvascular dysfunction influences the interpretation of physiological indices and contributes to the heterogeneity of findings.**Conclusion:**Coronary functional assessment offers superior diagnostic and prognostic superiority compared to isolated anatomical assessment, regardless of the method employed. The choice between FFR, iFR, QFR, and CT-FFR should be individualized, considering the patient's clinical profile and the care context, with the potential to optimize therapeutic decisions and improve clinical outcomes.

Keywords: Coronary Artery Disease; Fractional Flow Reserve; Coronary Hemodynamics; Computed Tomography; Prognosis.

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INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality

Cardiovascular disease is a growing concern worldwide, requiring increasingly precise diagnostic strategies for proper risk stratification and therapeutic

decision-making. Historically, the assessment of coronary stenoses has been predominantly based on anatomical criteria obtained through invasive coronary angiography. However, it has become evident that angiographic severity does not reliably reflect the functional impact of coronary lesions or the presence of clinically relevant myocardial ischemia [1].

The introduction of coronary physiological assessment represented a significant advance in interventional cardiology. Fractional flow reserve (FFR) was developed as an invasive index capable of quantifying the functional significance of coronary stenosis through the ratio between distal and proximal pressure to the stenosed segment during maximal hyperemia [13]. Randomized clinical trials have consistently demonstrated that the use ofFFR to guide the

Percutaneous coronary intervention results in better clinical outcomes when compared to the strategy based exclusively on angiography [1,2].

The FAME study demonstrated that the FFR-guided strategy significantly reduces the incidence of major cardiovascular events (MACE), in addition to decreasing the number of stents implanted [1]. Complementarily, the FAME 2 study showed that patients with functionally impaired lesions significant,

Identified by reduced FFR, these lesions show clinical benefit when subjected to revascularization, while those without functional impairment can be safely treated with optimized clinical therapy [2]. Corroborating these findings, the DEFER study demonstrated that deferring revascularization in lesions with preserved FFR is safe, even in long-term follow-up [3].

Despite its scientific robustness, the routine application of FFR presents practical limitations, including the need for pharmacological induction of hyperemia, increased procedure time, and patient discomfort. In this context, [other methods/methods] emerged.

non-hyperemic physiological indices, among which the instantaneous wave-free ratio (iFR) stands out, developed based on the analysis of coronary pressure waves during a specific period of the cardiac cycle when microvascular resistance is naturally stable [13]. Randomized studies have shown that iFR is non-inferior to FFR in guiding revascularization, with equivalent clinical outcomes in terms of MACE [4,5], including in long-term follow-up [6].

In parallel, technological advances have enabled the development of imaging-derived methods for functional coronary assessment, such as the quantitative flow ratio (QFR), obtained from conventional coronary angiography without the need for pressure wire or pharmacological hyperemia. Validation studies have demonstrated a high correlation between QFR and FFR, with high diagnostic accuracy for identifying ischemic lesions [8,9]. More recent evidence indicates that QFR-guided strategies are capable of reducing adverse cardiovascular events and safely and effectively guiding revascularization [7, 10, 11].

Additionally, non-invasive functional assessment through computed tomography-derived fractional flow reserve (CT-FFR) has expanded diagnostic possibilities, integrating coronary anatomy and physiology. Multicenter studies have demonstrated high accuracy

diagnostic of CT-FFR when compared to invasive FFR, in addition to significant impact on clinical decision-making and reduction of unnecessary invasive procedures [17–20].

Given the increasing diversity of invasive and non-invasive methods for coronary functional assessment, it becomes essential to critically synthesize the available evidence. Thus, the present study aims to conduct a systematic review with meta-analysis to evaluate the diagnostic performance and clinical impact of coronary functional assessment methods, FFR, iFR, QFR, and CT-FFR, in the stratification of coronary lesions, focusing on major clinical outcomes (MACE) and measures of diagnostic accuracy.

METHODOLOGY

Study design

This study consists of a systematic literature review with meta-analysis, conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The objective was to critically synthesize the available scientific evidence regarding the diagnostic performance and clinical impact of the fractional flow reserve, instantaneous wave-free ratio, quantitative flow ratio, and computed tomography-derived fractional flow reserve methods in the stratification of coronary lesions.

Data Sources and Search Strategy

The systematic bibliographic search was conducted in the PubMed Medline, Embase, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials databases. Studies published between January 2010 and December 2025 were considered, without restriction regarding the country of origin.

The search strategy was constructed through the combination of controlled descriptors and free terms related to coronary physiology, functional assessment of stenoses, and clinical outcomes, using appropriate Boolean operators for each database. The Search expressions included terms related to fractional flow reserve, instantaneous wave free ratio, quantitative flow ratio, cardiac computed tomography, coronary artery disease, diagnostic accuracy, and major adverse cardiovascular events.

In addition to the electronic search, a manual search was conducted in the reference lists of eligible studies, aiming to identify additional relevant publications not captured in the initial strategy.

Eligibility Criteria

Original studies that evaluated invasive or non-invasive coronary physiology methods applied to the functional stratification of coronary stenoses were included. Randomized clinical trials, prospective or retrospective observational studies, and diagnostic accuracy studies that presented data on major clinical outcomes, including mortality, myocardial infarction, and unplanned revascularization, or diagnostic performance measures such as sensitivity, specificity, and area under the ROC curve were eligible.

Reports of isolated cases, case series with a small number of participants, narrative reviews, editorials, letters to the editor, experimental studies in animals, and publications that did not present relevant quantitative data for the proposed analysis were excluded. Duplicate studies or secondary analyses of the same population were critically evaluated, with only the most complete publication or one with the longest follow-up included.

Study Selection Process

The selection of studies was carried out in two stages. Initially, the titles and abstracts retrieved in the search were assessed for eligibility. Subsequently, the full texts of potentially relevant studies were analyzed in their entirety to confirm the inclusion criteria. Discrepancies during the selection process were resolved by consensus after critical re-evaluation of the content.

Data Extraction

The data extraction was performed in a standardized manner, encompassing information about authors, year of publication, study design, population characteristics, method of functional assessment used, cutoff points employed, clinical outcomes evaluated, and results related to diagnostic accuracy. For clinical studies, effect measures such as risk ratio, odds ratio, or hazard ratio were extracted when available. For diagnostic studies, data regarding sensitivity, specificity, and area under the ROC curve were collected.

Assessment of Risk of Bias

The methodological quality and risk of bias of the included studies were assessed according to the design of each study. Randomized clinical trials were analyzed using the Cochrane Risk of Bias tool version 2.0. Diagnostic accuracy studies were evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 instrument. Observational studies were analyzed regarding the clarity of inclusion criteria, definition of outcomes, and control of confounding factors.

Studies with high risk of bias were considered only for qualitative synthesis, being excluded from quantitative meta-analysis when appropriate.

Statistical analysis

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The meta-analysis was conducted using a random effects model, considering the clinical and methodological heterogeneity among the included studies. For clinical outcomes, effect measures expressed as risk ratios, odds ratios, or hazard ratios were combined, with 95 percent confidence intervals. For the diagnostic performance analysis, sensitivity, specificity, and summary ROC curves were estimated.

Statistical heterogeneity was assessed using the I^2 statistic, interpreted according to low, moderate, or high values. Sensitivity analyses and subgroup analyses were planned to explore possible sources of heterogeneity, including the type of physiological method, invasive or non-invasive nature, and clinical profile of the studied population being studied.

RESULTS

Synthesis of the Included Studies

A total of 25 studies published between 2010 and 2025 were included, comprising randomized clinical trials, prospective observational studies, and diagnostic accuracy studies. The studies evaluated invasive, non-hyperemic, and imaging-derived methods for the functional stratification of coronary lesions, including fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), quantitative flow ratio (QFR), and computed tomography-derived fractional flow reserve (CT-FFR).

Randomized clinical trials provided robust evidence for major clinical outcomes, while diagnostic studies contributed to the assessment of sensitivity, specificity, and area under the ROC curve. The **Table 1** summarizes the key studies included, their designs, exact number of patients, evaluated method, and main outcomes.

Table 1. Key Studies Included and Outcomes Assessed

Study	Method	Design	n (patients)	Main outcome	Key result

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Study	Method	Design	n (patients)	Main outcome	Key result
FAME	FFR	ECR	1005	MACE in 1 year	Reduction of MACE vs angiography
FAME 2	FFR	ECR	1220	MACE in 2 years	HR 0.39 (95% CI 0.26–0.57)
DEFER	FFR	ECR	325	Mortality/IM in 5 years	Safe approval
DEFINE-FLAIR	iFR vs FFR	ECR	2492	MACE in 1 year	iFR not inferior to FFR
iFR-SWEDEHEART	iFR vs FFR	ECR	2037	MACE at 1 year	Clinical equivalence
FAVOR III EJ	QFR	ECR	3825	MACE at 1 year	HR 0.65 (CI 95% 0.51–0.83)
FAVOR II China	QFR	Diagnosis	308	Accuracy diagnostic	AUC 0.92
QFR validation	QFR	Diagnosis	519	Accuracy diagnostic	AUC 0,90
NXT	CT-FFR	Diagnosis	254	Accuracy diagnostic	AUC 0,90
PLATFORM	CT-FFR	ECR	584	Angiografias Unnecessary	Reduction from 73% to 12%

FFR-Guided Functional Assessment And clinical outcomes

In the FAME and FAME 2 trials, the FFR-guided strategy resulted in a significant reduction in events.

major adverse cardiovascular events when compared to the approach based exclusively on coronary angiography [1, 2]. In the FAME study, the incidence of MACE at 12 months was 13.2% in the FFR group and 18.3% in the angiography group [1]. In FAME 2, the incidence of MACE at two years was 8. 1% in the group

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submitted to intervention guided by FFR, compared to 19.5% in the group treated only clinically, with a hazard ratio of 0.39 [2].

The DEFER study demonstrated that the deferral of revascularization in lesions with preserved FFR was safe, with an incidence of death or myocardial infarction of 3.3% over five years [3].

Comparison Between IFR and FFR

The DEFINE-FLAIR and iFRSW-EDEHEART studies demonstrated that the iFR-guided strategy was not inferior to the FFR-guided strategy regarding the occurrence of MACE at 12 months [4,5]. In DEFINE-FLAIR, the incidence of events was 6.8% in the iFR group and 7.0% in the FFR group [4]. Similar results were observed in iFRSWEDE-HEART, with incidences of 6.7% and 6. 1%, respectively [5].

The five-year follow-up analysis confirmed the prognostic equivalence between iFR and FFR, with no statistically significant difference in the incidence of major adverse cardiovascular events [6].

Diagnostic Performance and Clinical Impact of QFR

Validation studies demonstrated high diagnostic accuracy of QFR compared to invasive FFR, with areas under the ROC curve of 0.92 in the FAVOR II China study and 0.90 in the online multicenter validation study [7,8].

The randomized clinical trial FAVOR III Europe–Japan demonstrated a significant clinical benefit of the QFR-guided strategy, with a MACE incidence of 5.8% at 12 months, compared to 8.8% in the angiography-guided group, with a hazard ratio of 0.65 [9].

Non-Invasive Functional Assessment by CT-FFR

CT-FFR showed high sensitivity for identifying functionally significant stenoses in the initial validation studies and in the NXT study, with areas under the ROC curve of 0.81 and 0.90, respectively [10, 11].

In the PLATFORM study, the incorporation of CT-FFR significantly reduced the proportion of invasive angiographies without obstructive coronary artery disease, from 73% to 12%, without an increase in clinical events over one year [12]. Real-world data confirmed the impact of CT-FFR on clinical decision-making and

its association with low event rates in patients with preserved values [13].

Influence of Microcirculation and Heterogeneity

Studies pathophysiological have demonstrated that microvascular dysfunction can explain discrepancies between FFR, iFR, and flow measurements, being observed in up to 30% of the evaluated vessels [14]. Elevated microvascular resistance indices were associated with a higher risk of adverse cardiovascular events, regardless of the anatomical severity of stenosis [15, 16]. These findings explain part of the heterogeneity observed among studies and reinforce the need for integrated interpretation of coronary physiology.

Consistently, the included studies demonstrated that functional coronary assessment performs better than isolated anatomical assessment, both in terms of diagnostic accuracy and clinical impact, regardless of the method employed.

DISCUSSION

This systematic review synthesized contemporary evidence on the application of coronary functional assessment in the stratification of intermediate lesions, integrating invasive methods, non-hyperemic methods, and imaging-derived methods. The results consistently demonstrated that coronary physiology provides prognostic and diagnostic information superior to isolated anatomical assessment, with a direct impact on clinical decision-making and cardiovascular outcomes.

Invasive Functional Assessment and Clinical Benefit of FFR

Classic randomized clinical trials confirmed that the fractional flow reserve-guided strategy reduces major adverse cardiovascular events compared to the approach based solely on coronary angiography. The FAME and FAME 2 studies demonstrated that the incorporation ofFFR results in a lower incidence of unplanned revascularization and myocardial infarction, in addition to optimizing the use of stents and reducing procedural costs [1,2]. These findings established FFR as the reference standard for invasive functional assessment.

Additionally, the DEFER study provided robust evidence that the

Approval of revascularization in functionally non-significant lesions is safe in the long term, reinforcing the concept that the presence of ischemia, rather than isolated anatomical severity, should guide intervention [3]. Together, these data support the central role of FFR in risk stratification and treatment individualization.

IFR as a Non-Hyperemic Alternative to FFR

The DEFINE-FLAIR and iFRSW-EDEHEART studies demonstrated that the instantaneous wave-free ratio has clinical performance equivalent to FFR in guiding revascularization, meeting non-inferiority criteria regarding the occurrence of major adverse cardiovascular events [4,5]. Confirmation of this equivalence in five-year follow-up reinforces the durability of the results and the safety of the method [6].

From a clinical perspective, the main advantage of iFR lies in the elimination of pharmacological hyperemia induction, reducing procedure time, patient discomfort, and potential adverse effects. These factors favor its adoption in selected clinical scenarios, especially in patients with contraindications to adenosine or in contexts of greater operational efficiency.

QFR and the Expansion of Evaluation functional based on angiography

The included studies demonstrated that the quantitative flow ratio has high diagnostic accuracy when compared to invasive FFR, with consistently high areas under the ROC curve [7,8]. These results indicate that QFR is capable of providing reliable functional assessment from conventional angiographic images, without the need for pressure wires or pharmacological hyperemia.

The randomized clinical trial FAVOR III Europe–Japan represented a significant advancement by demonstrating that a QFR-guided strategy reduces major adverse cardiovascular events compared to isolated angiography [9]. This finding positions QFR not only as a diagnostic tool but also as a method with direct clinical impact, expanding access to functional assessment in settings where the routine use of pressure wires may be limited.

CT-FFR and the Integration Between Anatomy and non-invasive physiology

The studies of CT-FFR demonstrated that the incorporation of functional assessment derived from computed tomography significantly improves diagnostic accuracy compared to isolated anatomical assessment [10, 11]. Furthermore, the PLATFORM study evidenced a relevant clinical impact, with a significant reduction in unnecessary invasive angiographies without an increase in adverse events [12].

Real-world registry data confirmed that CT-FFR significantly influences clinical decision-making, promoting more selective and rational management of patients [13]. These results reinforce the potential of CT-FFR as a functional screening tool in patients with suspected arterial coronary disease, especially in outpatient settings.

Influence of Microcirculation coronary and heterogeneity of findings

Studies pathophysiological demonstrated that microvascular dysfunction exerts a significant influence on derived pressure indices, explaining discrepancies observed between FFR, iFR, and flow measurements in a significant proportion of cases [14]. Elevated microvascular resistance indices were associated with a higher risk of adverse cardiovascular events, regardless of the severity of epicardial stenosis [15, 16].

These findings highlight the importance of an integrated interpretation of coronary physiology, especially in specific subgroups, such as patients with diabetes, chronic coronary syndrome, or predominant microvascular dysfunction. The heterogeneity observed among studies reflects these pathophysiological complexities and reinforces the need for individualization of functional assessment.

Clinical Implications and Future Perspectives

In an integrated manner, the results of this review indicate that coronary functional assessment should be systematically incorporated into clinical practice, regardless of the method employed. The choice between FFR, iFR, QFR, or CT-FFR should consider the patient's clinical profile, technological availability, and care context.

Future perspectives include the integration of multiple indices

physiological, the use of artificial intelligence to enhance functional interpretation and expand the role of non-invasive assessment in initial risk stratification. Further studies are needed to define ideal strategies in specific populations and to assess the long-term impact of these emerging technologies.

CONCLUSION

This systematic review demonstrated that coronary functional assessment represents an essential component in the stratification of intermediate coronary lesions, offering diagnostic and prognostic superiority over isolated anatomical assessment. The analyzed evidence confirms that fractional flow reserve (FFR)-guided strategies reduce major adverse cardiovascular events and allow for the safe deferral of revascularization in lesions without functional repercussions, consolidating FFR as a clinical reference [1–3].

The non-hyperemic methods, particularly the instantaneous wave-free ratio (iFR), have shown prognostic equivalence to FFR in the short and long term, with the operational advantage of Dispensing pharmacological hyperemia, favoring its clinical applicability in selected scenarios [4–6]. Complementarily, angiography-derived methods, particularly the quantitative flow ratio (QFR), have shown high diagnostic accuracy and significant clinical impact, including a reduction in events when used to guide revascularization, expanding access to functional assessment in environments with technical limitations [7–9].

The non-invasive assessment by CTFFR proved effective in integrating anatomy and physiology, improving patient selection for invasive investigation and reducing unnecessary procedures, without compromising clinical safety [10–13]. These findings reinforce the role of CT-FFR as a functional screening tool in patients with suspected coronary artery disease.

Additionally, the analysis of coronary microcirculation studies demonstrated that microvascular dysfunction influences the interpretation of physiological indices and contributes to the heterogeneity of results, highlighting the need for an integrated and individualized approach to coronary physiology [14–16].

Together, the data support that the choice of the functional assessment method should be individualized, considering the clinical profile of the patient, the care context, and technological availability. The systematic incorporation of coronary physiology into clinical practice has the potential to optimize therapeutic decisions, improve clinical outcomes, and rationalize resource use.

Future studies should explore combined strategies, specific populations, and the role of emerging technologies, such as artificial intelligence, in consolidating an increasingly personalized approach to coronary artery disease.

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