*REC Interv Cardiol. 2025;7(3):169-177*
https://doi.org/10.24875/RECICE.M25000511

**Original article**

# Functional assessment in acute coronary syndrome: a systematic review of acute versus staged interventions

Federico Vergni,[a,*] Silvia Buscarini,[b] Leonardo Ciurlanti,[a] Filippo Luca Gurgoglione,[c] Francesco Pellone,[a] and Mario Luzi[d]

[a] *Department of Interventional Cardiology, Hospital of Macerata, Macerata, Italy*
[b] *Department of Cardiology, Hospital of Fermo, Fermo, Italy*
[c] *Department of Cardiology, University Hospital of Parma, Parma, Italy*
[d] *Department of Cardiology, Hospital of Macerata, Macerata, Italy*

## ABSTRACT

***Introduction and objectives:*** Several tools have been implemented to assess the functional significance of coronary lesions. Their reliability in the management of acute coronary syndrome (ACS) might be affected by alterations in the acute phase that go beyond the affected area. Our main objective was to evaluate the reliability of invasive physiological indices for non-culprit lesions (NCL) in patients with ACS.
***Methods:*** We conducted a systematic review across ClinicalTrials.gov, Embase, Google Scholar, PubMed, and Web of Science from inception through 5 December 2024. Additionally, a citation analysis and web searches were conducted.
***Results:*** A total of 20 articles, with 4379 patients were included in the analysis. The main study design is a cohort study. The following methods were compared between acute and staged interventions: *a)* angiography-derived; *b)* hyperemic; and *c)* non-hyperemic indices. A significant difference in fractional flow reserve, instantaneous wave-free ratio, and quantitative flow ratio was found in one or more articles. There were no articles reporting any important changes in the Murray law-based quantitative flow ratio, resting distal-to-aortic coronary pressure ratio, or vessel fractional flow reserve. However, these indices rely on retrospective and/or limited data. All significant variations were observed in cohorts of ST-segment elevation myocardial infarction. Unlike quantitative flow ratio, the fractional flow reserve and instantaneous wave-free ratio demonstrated consistent directions of change towards lower and higher values, respectively. Prospective cohorts and randomized controlled trials including non-ST-segment elevation acute coronary syndrome did not prove the existence of significant differences between acute and follow-up fractional flow reserve.
***Conclusions:*** Physiological methods lack complete reliability for evaluating NCL during acute ST-segment elevation myocardial infarction. However, considering directions of change, fractional flow reserve is suitable for guiding the revascularization of acute positive NCL. Conversely, instantaneous wave-free ratio can be used to defer the revascularization of negative NCL. In non-ST-segment elevation acute coronary syndrome, fractional flow reserve is appropriate for assessing NCL within the acute phase.

*Keywords:* Fractional flow reserve. Instantaneous wave-free ratio. Quantitative flow ratio.

# Evaluación funcional en el síndrome coronario agudo: una revisión sistemática del escenario agudo frente al diferido

## RESUMEN

***Introducción y objetivos:*** Se han implementado varias herramientas para evaluar la importancia funcional de las lesiones coronarias. Su fiabilidad en el síndrome coronario agudo (SCA) podría verse afectada por perturbaciones en la fase aguda que se extienden más allá de la zona afectada. Nuestro objetivo principal fue evaluar la fiabilidad de los índices fisiológicos invasivos para las lesiones no culpables (LNC) en pacientes con SCA.
***Métodos:*** Se realizó una revisión sistemática en ClinicalTrials.gov, Embase, Google Scholar, PubMed y Web of Science, desde el inicio hasta el 06/12/2024. Además, se hizo un análisis de citas y búsquedas en la web.
***Resultados:*** Se incluyeron en el análisis 20 estudios, que abarcaban 4.379 pacientes. El principal diseño de estudio es el de cohorte. Se compararon los siguientes métodos entre procedimientos agudos y diferidos: *a)* índices derivados de la angiografía; *b)* índices hiperémicos; y *c)* índices no hiperémicos. En uno o más artículos se hallaron diferencias significativas en la reserva fraccional de flujo, el índice diastólico instantáneo sin ondas y el cociente de flujo cuantitativo. Ningún artículo informó de cambios importantes en el cociente de flujo cuantitativo basado en la ley de Murray, el cociente de presión coronaria distal-aórtica en reposo o la reserva fraccional de flujo del vaso. Sin embargo, estos estudios se basan en datos retrospectivos o limitados. Todas las variaciones

*** Corresponding author.**
E-mail address: vergni95@gmail.com (F. Vergni).

Received 16 January 2025. Accepted 1 April 2025. Online 28 May 2025.

significativas se observaron en cohortes de pacientes con infarto de miocardio con elevación del segmento ST. A diferencia del cociente de flujo cuantitativo, la reserva fraccional de flujo y el índice diastólico instantáneo sin ondas mostraron direcciones de cambio coherentes, hacia valores más bajos y más altos, respectivamente. Las cohortes prospectivas y los ensayos controlados aleatorizados que incluyeron pacientes con infarto de miocardio sin elevación del segmento ST no encontraron diferencias importantes entre la reserva fraccional de flujo aguda y la diferida.
***Conclusiones:*** Los métodos fisiológicos no tienen una total fiabilidad para evaluar la gravedad de las LNC durante el infarto agudo de miocardio con elevación del segmento ST. Sin embargo, teniendo en cuenta las direcciones del cambio, la reserva fraccional de flujo es adecuada para guiar la revascularización de una LNC positiva en la fase aguda. Por el contrario, el índice diastólico instantáneo sin ondas se puede utilizar para aplazar la revascularización de una LNC con valoración negativa. En el SCA sin elevación del segmento ST, la reserva fraccional de flujo es adecuada para evaluar una LNC en la fase aguda.

*Palabras clave:* Reserva fraccional de flujo. Índice diastólico instantáneo sin ondas. Cociente de flujo cuantitativo.

**Abbreviations**

**ACS:** acute coronary syndrome. **FFR:** fractional flow reserve. **iFR:** instantaneous wave-free ratio. **NCL:** non-culprit lesions. **QFR:** quantitative flow ratio.

## INTRODUCTION

The optimal strategy and timing of complete revascularization in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease remains unclear, and current recommendations are controversial.[1] According to 2023 European Society of Cardiology (ESC) guidelines, complete revascularization, based solely on angiographic severity, is recommended in "stable" STEMI patients.[2] Conversely, the 2023 Asia-Pacific Expert Consensus Document suggested a treatment strategy of non-culprit lesions (NCL) based on angiographic severity and invasive physiological assessment with fractional flow reserve (FFR) or non-hyperemic pressure ratios for patients with STEMI.[3]

FFR and non-hyperemic pressure ratios may be inaccurate in acute coronary syndrome (ACS), as hyperemic flow may be reduced due to microcirculatory dysfunction, while the resting flow may be higher due to neurohumoral compensatory mechanisms.[4]

Angiography-derived indices are additional physiological tools. They need ≥ 1 angiographic projections plus frame count analysis and/or aortic pressure that may also be different in the acute setting.

Furthermore, drugs such as hypolipidemic agents may promote plaque regression, potentially impacting the results of physiological assessment after a few months into therapy.[5]

Our main objective was to evaluate the changes in invasive physiological measurements of NCL between the acute and staged phases of ACS.

Secondly, we aimed to evaluate the effects of different therapies on physiological measurements.

## METHODS

### Eligibility criteria

We included studies that evaluated the physiology of NCL during acute and staged interventions for ACS. Studies conducted on assessments following percutaneous coronary interventions of non-culprit vessels, or with patients with chronic coronary syndrome were excluded.

Case reports, conference abstracts, commentaries, editorials, and reviews were excluded as well. An initial protocol was registered in PROSPERO with registration No. CRD42024574683.

### Search strategy, and study selection

We conducted the search across ClinicalTrials.gov, Embase (via Ovid), Google Scholar, PubMed, and Web of Science from inception through 26 April 2024 (initial search). We used the "Review articles" filter in Google Scholar and the "Topic" field in Web of Science. No language restrictions were applied.

Duplicates were removed using Deduplicator (SR-Accelerator) software. Title/abstract and full text screening was conducted independently by 2 authors using Rayyan software.

Back in July, 2 authors conducted a backward and forward citation analysis of the included articles using Citationchaser software.

The search strings were repeated in 6 December 2024 (in Embase, sources with invalid date limits were excluded). Simultaneously, we looked into any online conference news on imaging modalities and physiological measurements.[6] Additionally, we looked into the "Slide Library" section using the "2024" filter on another web page.[7]

Finally, we manually reviewed the references of the articles included after the initial search.

All discrepancies were resolved by consensus.

Selection process was recorded in sufficient detail to complete a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.[8]

### Data extraction

The following data were extracted from each article: *a)* study characteristics; *b)* population characteristics; *c)* type of physiological index(es); *d)* follow-up duration; *e)* primary endpoint.

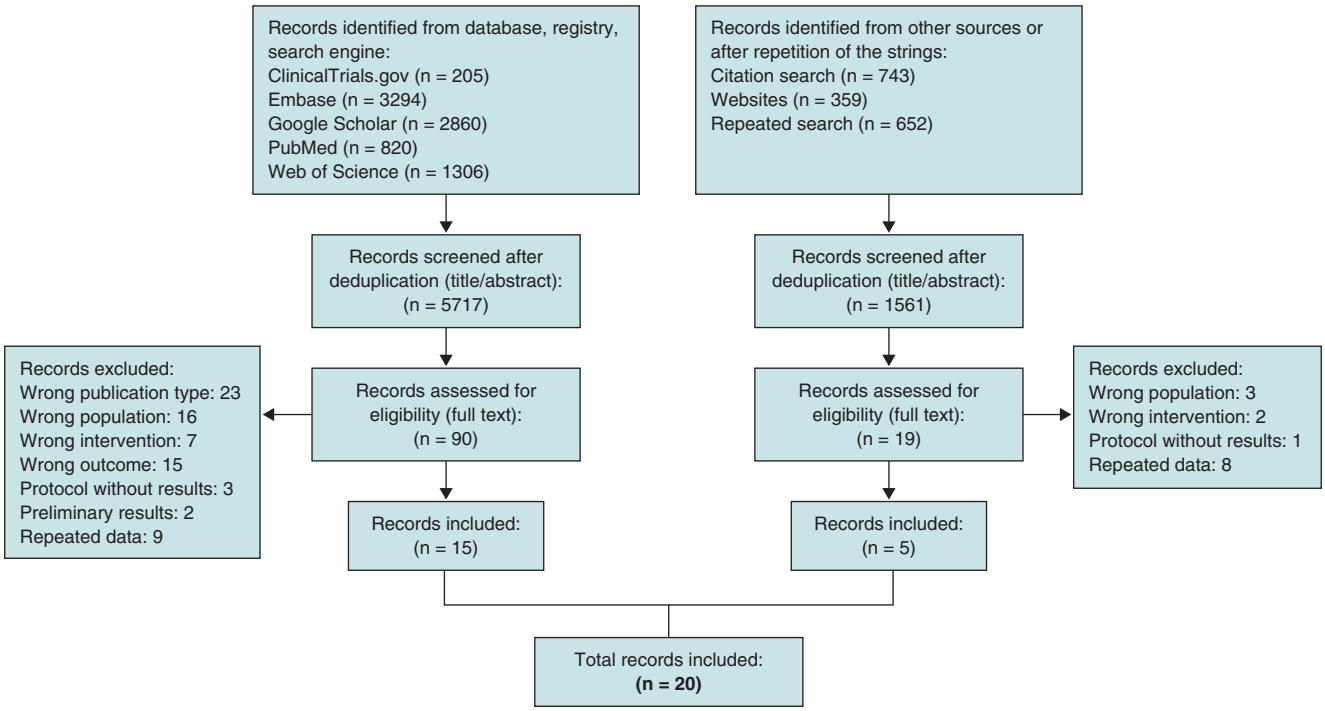


**Figure 1.** PRISMA flow diagram. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

The primary endpoint was the variation between acute and staged indices regarding statistical significance, mean difference (MD), and disagreement on revascularization decision.

One author extracted the data, and another one checked it independently. We contacted the authors of eligible studies when clarifications were needed.

### Risk of bias assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools,[9-11] as appropriate.

Two authors independently assessed the risk of bias for each study. We used red for high, yellow for moderate, and green for low risk of bias based on positive answers being ≤ 49%, 50%-69%, or ≥ 70%.

### Data synthesis

We conducted a descriptive synthesis of the evidence. Results from data extraction were shown in separate tables based on risk of bias, or bubble charts. Some data were rounded to the nearest integer (age, diameter of stenosis of NCL, and follow-up) or 2 decimal places (MD).

Unless otherwise specified, *P* values < .05 were considered statistically significant. When MDs were unreported, they were estimated by calculating the difference between staged and acute mean values. When required, a formula for estimating the means was applied.[12]

In bubble charts, the size of the bubbles represents the number of patients or lesions if the former was not reported. Acute −/staged + disagreement indicates an acute value above the threshold, with the staged value below the revascularization cut-off. Acute +/staged − disagreement represents the opposite.

## RESULTS

### Characteristics of the articles, participants, and indices

Results of the search and selection processes are shown in figure 1. Extracted data are shown in table 1 and table 2.

A total of 20 articles were included[13-32] (1 article in the form of a conference presentation).[19] Publication years went from 2010 through 2024. The total number of reported patients was 4379.

In every publication, the patients are predominantly men and non-diabetic. The main clinical presentation was STEMI, except for 3 studies.[19,29,31]

The following methods were assessed: a) angiography-derived: Murray law-based quantitative flow ratio (muQFR), quantitative flow ratio (QFR), vessel FFR (vFFR); b) hyperemic (FFR); and c) non-hyperemic indices: instantaneous wave-free ratio (iFR), resting distal-to-aortic coronary pressure ratio ($P_d/P_a$). When reported, the FFR was obtained using adenosine.

Reported patients for each index are as follows: 2340 (muQFR), 1187 (QFR), 710 (FFR), 243 (iFR), 92 (vFFR), and 73 (resting $P_d/P_a$).

### Risk of bias

The studies mainly used an observational (cohort) design. Cohort studies on angiography-derived methods were retrospective, except for 1 article on QFR.[28] Those on FFR and non-hyperemic indices were prospective, except for 2 substudies.[22,26]

QFR was also evaluated by 1 quasi-experimental study[27] and 1 randomized controlled trial.[13]

Finally, the FFR was assessed by 2 randomized controlled trials, in samples with predominance of non-ST-segment elevation myocardial infarction (NSTEMI).[19,31,33]

**Table 1.** Extracted data of studies with low risk of bias

| First author | Patients (No.) | Age (years) | STEMI (%) | PDS of NCL (%) | Type of index | Follow-up (days) | Comparison across measurements | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *P*-value | Mean difference (staged–acute value) |
| Bär[13] | 94[a] | 59 ± 10 | 53 | 37 ± 8 | cQFR | 365 | NR | 0.00 |
| | 99[b] | 58 ± 8 | 54 | 37 ± 8 | | | NR | – 0.01 |
| Cortés[14] | 88 | 68 ± 11 | 100 | 59 ± 12 | cQFR | 6 ± 4 | S | + 0.06 |
| Erbay[15] | 321 | 66 [58-76] | 50.5[c] | 47 [36-57] | cQFR | 49 [42-58] | NS | + 0.01 |
| Hou[16] | 2256 | 64 ± 6 | 100 | 65 ± 9 | muQFR | (7-45) | NS | 0.00 |
| Huang[17] | 92 | 65 ± 10 | 100 | (30-80) | vFFR | 15 [3-30] | NS | 0.00 |
| Kirigaya[18] | 50 | 63 ± 11 | 100 | 46 ± 13 | cQFR | 14 ± 5 | NS | + 0.01 |
| Mensink[19] | 150[d] | 64 ± 9 | 35.3 | NR | FFR | 84 | NR | 0.00 |
| Musto[20] | 50 | 68 ± 11 | 100 | 58 ± 12 | FFR | 6 ± 2 | NS | 0.00 |
| | | | | | iFR | | NS | 0.00 |
| Ntalianis[21] | 101 | 63 ± 12 | 74.2 | 56 ± 14 | FFR | 35 ± 4 | NS | 0.00 |
| Sejr-hansen[22] | NR[e] | NR | 100 | 56 [48-66] | cQFR | 13 [7-31] | NS | – 0.02 |
| | | | | | iFR | | S | + 0.02 |
| Shukla[23] | 31 | 56 ± 8 | 100 | 78 ± 9 | FFR | 18 ± 4 | S | – 0.01 |
| Thim[24] | 120 | 66 ± 11 | 100 | 50 [41-59] | iFR | 16 [5-32] | S | + 0.03 |
| Van der Hoeven[25] | 73 | 61 ± 10 | 100 | 55 ± 13 | FFR | 31 ± 6 | S | – 0.03 |
| | | | | | iFR | | NS | + 0.01 |
| | | | | | Resting $P_d/P_a$ | | NS | + 0.01 |
| Wang[26] | 70 | 62 | 100 | NR | QFR | 30 | NS | – 0.01 |
| | | | | | FFR | | S | – 0.03 |
| Zhao[27] | 102[f] | 66 ± 6 | 100 | 64 ± 5 | cQFR | 365 | NR | + 0.01 |
| | 253[g] | 65 ± 6 | | 64 ± 6 | | | NR | – 0.01 |

cQFR, contrast quantitative flow ratio; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; muQFR, Murray law-based QFR; NCL, non-culprit lesions; NR, not reported; NS, non-significant; $P_d/P_a$, distal-to-aortic coronary pressure ratio; QFR, quantitative flow ratio; PDS, percent diameter stenosis; S, significant; STEMI, ST-segment elevation myocardial infarction; vFFR, vessel fractional flow reserve.
Data are expressed as mean, mean ± standard deviation or median [interquartile range] or (range) (age, PDS of NCL, follow-up).
[a] Statin + alirocumab subgroup.
[b] Statin + placebo subgroup.
[c] Percentage of ST-segment elevation acute coronary syndrome.
[d] Overall population (statin + evolocumab or placebo subgroups).
[e] No. of lesions analyzed: 70.
[f] Statin + evolocumab subgroup.
[g] Statin monotherapy subgroup.

Results are shown in table 1 of the supplementary data, table 2 of the supplementary data, and table 3 of the supplementary data. There were no studies with high risk of bias.

## Primary endpoint

### *Statistical significance*

There were no articles on relevant changes in muQFR,[16,30] resting $P_d/P_a$,[25] and vFFR[17] at the follow-up.

A significant difference in FFR, iFR, and QFR was found in 3, 2, and 1 article(s),[14,22-26] respectively. In 1 study, the difference in QFR was non-significant, with a significance threshold of .001.[28]

These variations were seen in cohorts of STEMI patients.[14,22-26] Studies including non-ST-segment elevation acute coronary syndrome (NSTEACS) did not show any relevant differences regarding the QFR[15] or the FFR.[19,21,29,31]

A total of 4 articles[20,22,25,26] evaluated > 1 method. The iFR and FFR were both stable in the study by Musto et al.,[20] while the iFR was more stable than the FFR in a different article.[25] The QFR was compared to both the FFR[26] and the iFR.[22] Unlike these indices, the QFR did not show any significant changes in staged phases.[22,26]

## Mean differences

The most valued indices showed varying results. muQFR had MD values close to 0 in both studies.[16,30]

**Table 2.** Data drawn from studies with moderate risk of bias

| First author | Patients (No.) | Age (years) | STEMI (%) | PDS of NCL (%) | Type of index | Follow-up (days) | Comparison across measurements | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | *P*-value | Mean difference (staged–acute value) |
| Barauskas[28] | 79 | NR | 100 | (35-75) | QFR | ≥ 91 | NS[a] | – 0.02 |
| Jo[29] | 115 | 60 ± 12 | 32.2 | NR | FFR | 182 | NS | – 0.01 |
| Li[30] | 84 | 60 ± 11 | 100 | (50-90) | muQFR | 8 ± 2 | NS | 0.00 |
| Park[31] | 60[b] | 57 ± 11 | 30 | NR | FFR | 182 | NS | – 0.02 |
| | 60[c] | 59 ± 10 | 33.3 | NR | | | NS | – 0.01 |
| Spitaleri[32] | 31 | 64 ± 12 | 100 | 59 ± 13 | cQFR | (3-4) | NS | 0.00 |

cQFR, contrast quantitative flow ratio; FFR, fractional flow reserve; muQFR, Murray law-based QFR; NCL, non-culprit lesions; NS, non-significant; NR, not reported; PDS, percent diameter stenosis; QFR, quantitative flow ratio; STEMI, ST-segment elevation myocardial infarction.
Data are expressed as ≥ lower limit or mean or mean ± standard deviation or (range) (age, PDS of NCL, follow-up).
[a] Level of significance was set at $P < .001$.
[b] Ticagrelor subgroup.
[c] Clopidogrel subgroup.

QFR variations were observed at both lower[22,26,28] and higher values.[14,15,18] Conversely, the FFR and the iFR varied towards smaller and greater values, respectively.[22-26,29,31] Their MDs ranged from – 0.02 to + 0.06 (QFR), – 0.03 to 0.00 (FFR), and 0.00 to + 0.03 (iFR).[14,19-21,24,25,28] MD values of 0.01 were observed more often.

In STEMI patients, the MDs of the FFR, the iFR, and the QFR were close to 0 only in studies with mean follow-ups of < 1 week.[20,32] In studies including NSTEACS, the FFR MDs were close to 0 after longer mean follow-ups (> 1 month).[19,21] Furthermore, Ntalianis et al. showed a greater stability of FFR in patients with NSTEMI (MD, 0.00) vs those with STEMI (MD, – 0.02).[21]

### *Disagreement*

Disagreement in the indication for revascularization is shown in figure 2. MDs of 0.01 resulted in variable disagreements: 5%-18%.[15,18,23,25]

Unlike the QFR, the FFR and the iFR consistently showed a higher frequency of one type of disagreement: acute – /staged + for FFR,[21,23,25] and acute + /staged – for iFR.[24,25]

### Secondary endpoint

A total of 4 studies compared the effects of different drugs on the physiological parameters.[13,19,27,31]

Ticagrelor (which can increase the levels of adenosine) was compared to clopidogrel and no significant differences were found in the FFR of non-culprit vessels after 6 months of treatment.[31]

Another 3 studies compared a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (eg, alirocumab or evolocumab) plus high-intensity statin (HIST) (eg, rosuvastatin 20 mg/day) vs statin-only therapy.[13,19,27]

In a nonrandomized study, the QFR values were significantly higher in the evolucumab group at 12 months.[27] However, in 2 randomized studies, no significant differences were observed across the 2 treatment groups in the QFR at 12 months or in the FFR at 3 months, respectively.[13,19]

## DISCUSSION

The main findings of this systematic review are these: firstly, in STEMI patients, the muQFR, resting $P_d/P_a$, and vFFR indices remained relatively stable in retrospective and/or small studies. The FFR, iFR, and QFR showed variability between acute and staged phases. Secondly, the FFR did not change significantly in prospective cohorts or randomized controlled trials including NSTEACS. Thirdly, the QFR was more stable than both the FFR and the iFR in direct comparisons, although only the FFR and the iFR exhibited consistent directions of change. Fourthly, PCSK9 inhibitors added to HIST did not influence physiological measurements compared with HIST in randomized controlled trials.

The muQFR demonstrated stability in a large sample of patients. This index is based on a single angiographic view, unlike other angiography-based methods that require 2 angiographic projections. This characteristic might reduce observer variability and enhance reliability. Future prospective and comparative studies are needed to confirm the validity of this method.

Although low variations for FFR, iFR, and QFR were observed in cohorts of STEMI patients,[20,32] these studies were limited by short-term follow-ups. Thim et al. found a non-significant change in the iFR with 5-day follow-ups, whereas there were significant changes with ≥ 5 day follow-ups.[24] Therefore, physiological disarrangements initiated at the acute moment of STEMI might still exist if a staged procedure is conducted close to the index event.[24,25]

Angiographic, hemodynamic, and microcirculatory variables may alter acute physiologic assessment and account for the higher reliability of the FFR in NSTEACS vs STEMI.

In patients with microvascular dysfunction, epicardial blood flow cannot increase sufficiently during maximal hyperemia, thus causing a reduced pressure gradient across the stenotic lesion,[29] and higher FFR values.

In STEMI patients, microcirculatory indices (coronary flow reserve and index of microcirculatory resistance) were significantly worse during the acute phase, along with a higher FFR.[25] Conversely, studies including NSTEACS did not show any significant differences in the coronary flow reserve and/or index of microcirculatory resistance at the follow-up.[21,29,31]

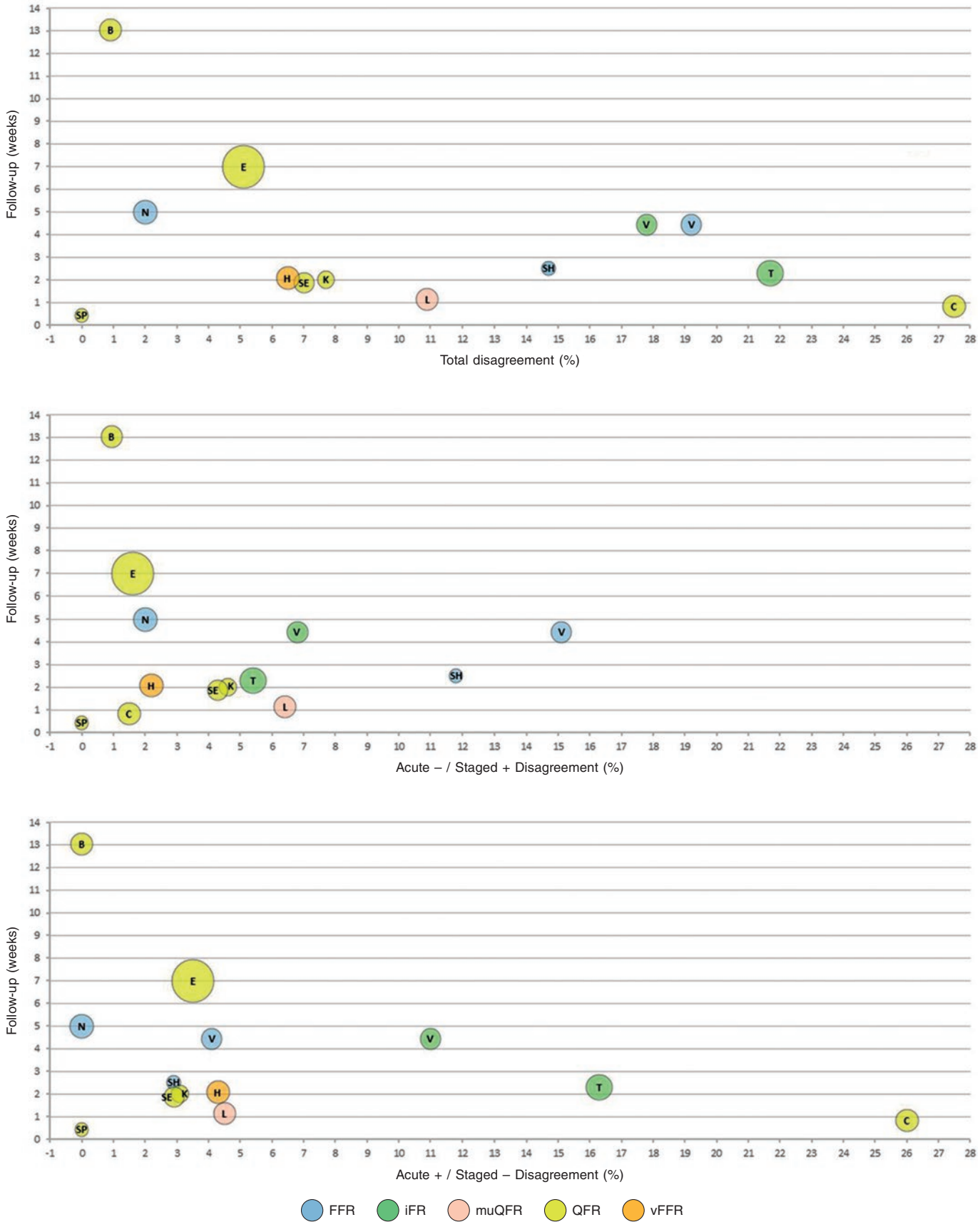


**Figure 2.** Disagreement between acute and staged values in the indication for PCI. B, Barauskas; C, Cortés; E, Erbay; FFR, fractional flow reserve; H, Huang; iFR, instantaneous wave-free ratio; K, Kirigaya; L, Li; muQFR, Murray law-based QFR; N, Ntalianis; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; SE, Sejr-Hansen; SH, Shukla; SP, Spitaleri; T, Thim; V, van der Hoeven; vFFR, vessel fractional flow reserve.

Furthermore, STEMI patients showed greater acute angiographic severity, along with lower QFR or iFR values,[14,22] which may be attributed to vasoconstriction typically occurring during the acute phase.

Consequently, the FFR seems more reliable in NSTEACS vs STEMI due to reduced acute microcirculatory impairment and/or vasoconstriction.

Literature trials support the use of the FFR in NCL of NSTEMI during the acute phase (eg, within the index hospitalization).[34,35] In contrast, acute FFR-guided complete revascularization did not show any significant benefits in terms of death or myocardial infarction in STEMI patients.[36-39]

The higher stability of QFR when directly compared to the FFR or the iFR was limited to a small number of patients in post-hoc substudies.[22,26] A MD of 0.01 sometimes led to non-trivial disagreement on revascularization decision,[25] likely due to baseline values being near the cut-off. Therefore, it is essential to have an index which remains stable or demonstrates consistent changes, such as the FFR and the iFR. Similarly, these indices demonstrated a greater frequency of a specific type of disagreement (methodological variations–wire positioning–may explain the less frequent cases of disagreement).[24]

Therefore, the FFR and the iFR could be considered in the acute STEMI as an alternative to delayed assessments,[25] considering that the FFR tends to decrease and the iFR tends to increase. The FFR could guide the revascularization of positive lesions (FFR ≤ 0.80).[25] In patients with a FFR > 0.80, acute iFR assessment can be used to delay the revascularization of negative NCL (iFR > 0.89).[24] In the remaining cases (iFR ≤ 0.89), some authors suggested a staged reevaluation.[24] At least 5 days after the index procedure should go by. This was the minimum time needed to observe the initial resolution of acute physiological disturbances.[24]

Finally, when plaques are correctly identified as functionally negative, they may still be vulnerable and associated with adverse events. NCL exhibiting thin-cap fibroatheromas as defined by optical coherence tomography, and having a muQFR ≤ 0.80, showed the highest event rate,[40] which suggests that imaging can offer additional prognostic information.

PCSK9 inhibitors have shown minimal impact on coronary physiology, despite greatly reducing low-density lipoprotein-cholesterol (LDL-C) levels. A large treatment effect on HIST only,[19] minor flow limitation at baseline, and microvascular compensation may account for this finding.[13]

However, combining alirocumab with HIST resulted in a greater increase in cap thickness of fibroatheromas vs statin monotherapy as assessed by optical coherence tomography.[41] Moreover, lower LDL-C levels after an ACS are associated with the occurrence of fewer cardiovascular events.[2] Therefore, PCSK9 inhibitor treatment is recommended in patients who do not reach their LDL-C target despite maximum tolerated statin and ezetimibe therapy.[2]

### Limitations

The wide variety of indices to assess coronary physiology has led to a lack of evidence on some of them; similarly, few studies made direct comparisons among such indices.

Our evaluations are mainly based on observational studies with a very different follow-ups.

Angiography-based methods frequently exhibited bias due to their retrospective analysis. Some patients were excluded because of the poor quality of angiographies or anatomic issues, such as ostial lesion or severe vascular tortuosity. Some angiographies were not obtained optimally according to the specific acquisition guide.

## CONCLUSIONS

The assessment of functional indices for NCL during the initial procedure for STEMI is not absolutely reliable. This evidence is due to potential variability of the FFR, the iFR, and the QFR outside the acute phase. Although variation was not significant for muQFR, resting Pd/Pa, and vFFR, retrospective and/or limited data limit the generalizability of these findings.

Both the FFR and the iFR showed consistent directions of change. Therefore, during an acute STEMI, the FFR can guide the revascularization of positive NCL, while the iFR can help defer revascularization of negative NCL. A negative FFR with a positive iFR should be reevaluated.

The FFR shows robust data supporting its use in NLC of NSTEMI during the acute phase, meaning that it is a more reliable index for initial ACS procedures.

## DATA AVAILABILITY

Search string for Google Scholar: "acute coronary syndrome"|"myocardial infarction" "fractional flow reserve"|FFR| "hyperemic ind"|"resting ind"|iFR|"instantaneous wave-free ratio"| "angiography-based ind"|"angiography-derived ind"|QFR|"quantitative flow ratio"|OFR staged|repeated|later. The remaining search strings are available upon request.

## FUNDING

None declared.

## ETHICAL CONSIDERATIONS

Ethical committee and patient's informed consent: not applicable. We followed the SAGER guidelines with respect to possible sex/gender bias.

## STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Microsoft Copilot was used to help edit the English version of the text.

## AUTHORS' CONTRIBUTIONS

F. Vergni designed the work. F. Vergni, S. Buscarini, L. Ciurlanti, and F.L. Gurgoglione contributed to data acquisition (screening, and/or extraction). F. Vergni, and L. Ciurlanti conducted the critical appraisal. F. Vergni, and S. Buscarini contributed to data interpretation. F. Vergni, and F.L. Gurgoglione drafted, edited and reviewed the work. F. Vergni, S. Buscarini, L. Ciurlanti, F.L. Gurgoglione, F. Pellone, and M. Luzi approved the final version for publication.

## CONFLICTS OF INTEREST

None declared.

**WHAT IS KNOWN ABOUT THE TOPIC?**

- The role of physiological assessment of NCL in patients with ACS is still under discussion because its reliability might be flawed due to alterations of both the hyperemic and resting flow in the acute phase.

**WHAT DOES THIS STUDY ADD?**

- In NSTEACS, it is appropriate to use the FFR for the acute evaluation of NCL. Regarding STEMI, a hybrid approach with both acute FFR and iFR can be considered, with delayed reassessment for doubtful NCL.

## SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M25000511.

## REFERENCES


1. Benatti G, Gragnano F, Vignali L, Calabrò P, Gurgoglione FL, Niccoli G. Timing and modality of complete revascularization in patients presenting with ST-segment elevation myocardial infarction and multivessel coronary artery disease. *Int J Cardiol*. 2023;380:6-11.
2. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720-3826. Published correction appears in Eur Heart J. 2024;45:1145.
3. Koo BK, Hwang D, Park S, et al. Practical Application of Coronary Physiologic Assessment: Asia-Pacific Expert Consensus Document: Part 2. *JACC Asia*. 2023;3:825-842.
4. Mejía-Rentería H, Lee JM, van der Hoeven NW, et al. Coronary Microcirculation Downstream Non-Infarct-Related Arteries in the Subacute Phase of Myocardial Infarction: Implications for Physiology-Guided Revascularization. *J Am Heart Assoc*. 2019;8:e011534.
5. Takenaka H, Okamura T, Miyazaki Y, et al. Serial changes in the quantitative flow ratio in patients with intermediate residual stenosis after percutaneous coronary intervention. *Heart Vessels*. 2022;37:363-373.
6. Cardiovascular Research Foundation. Conference News. Available at: https://www.tctmd.com. Accessed 30 Mar 2025.
7. Clinical Trial Results. Slide Library. Available at: https://clinicaltrialresults.org. Accessed 30 Mar 2025.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
9. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: systematic reviews of etiology and risk. In: Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. Adelaide: JBI; 2020.
10. Barker TH, Habibi N, Aromataris E, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for quasi-experimental studies. *JBI Evid Synth*. 2024;22:378-388.
11. Barker TH, Stone JC, Sears K, et al. The revised JBI critical appraisal tool for the assessment of risk of bias for randomized controlled trials. *JBI Evid Synth*. 2023;21:494-506.
12. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
13. Bär S, Kavaliauskaite R, Otsuka T, et al. Impact of alirocumab on plaque regression and haemodynamics of non-culprit arteries in patients with acute myocardial infarction: a prespecified substudy of the PACMAN-AMI trial. *EuroIntervention*. 2023;19:e286-e296.
14. Cortés C, Rodríguez-Gabella T, Gutiérrez H, et al. Quantitative flow ratio in myocardial infarction for the evaluation of non-infarct-related arteries. The QIMERA pilot study. *REC Interv Cardiol*. 2019;1:13-20.
15. Erbay A, Penzel L, Abdelwahed YS, et al. Feasibility and diagnostic reliability of quantitative flow ratio in the assessment of non-culprit lesions in acute coronary syndrome. *Int J Cardiovasc Imaging*. 2021;37:1815-1823.
16. Hou S, Zhu X, Zhao Q, et al. Quantitative flow ratio-guided staged percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. *Heliyon*. 2024;10:e39335.
17. Huang J, Groenland FTW, Scoccia A, et al. Acute-setting vs. staged-setting vessel fractional flow reserve of intermediate non-culprit lesions in patients with ST-segment elevation myocardial infarction (FAST STAGED study). *Int J Cardiol Heart Vasc*. 2023;45:101192.
18. Kirigaya H, Okada K, Hibi K, et al. Diagnostic performance and limitation of quantitative flow ratio for functional assessment of intermediate coronary stenosis. *J Cardiol*. 2021;77:492-499.
19. Mensink F, Los J, van Geuns RJ. Functional and morphological changes of significant non-culprit coronary artery stenosis by extensive LDL-C reduction with PCSK9 inhibitors. Results of the randomized, placebo-controlled FITTER trial. In: ESC Congress 2024; 2024 30 August - 2 September; London, United Kingdom. Available at: https://clinicaltrialresults.org/slide-library/.
20. Musto C, De Felice F, Rigattieri S, et al. Instantaneous wave-free ratio and fractional flow reserve for the assessment of nonculprit lesions during the index procedure in patients with ST-segment elevation myocardial infarction: The WAVE study. *Am Heart J*. 2017;193:63-69.
21. Ntalianis A, Sels JW, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv*. 2010;3:1274-1281.
22. Sejr-Hansen M, Westra J, Thim T, et al. Quantitative flow ratio for immediate assessment of nonculprit lesions in patients with ST-segment elevation myocardial infarction-An iSTEMI substudy. *Catheter Cardiovasc Interv*. 2019;94:686-692.
23. Shukla A, Dwivedi SK, Chandra S, et al. Reliability of Fractional Flow Reserve in Non-Infarct-Related Arteries in ST-Segment Elevation Myocardial Infarction Patients Undergoing a Pharmaco-Invasive Approach. *Cureus*. 2024;16:e52668.
24. Thim T, Götberg M, Fröbert O, et al. Nonculprit Stenosis Evaluation Using Instantaneous Wave-Free Ratio in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2017;10:2528-2535.
25. van der Hoeven NW, Janssens GN, de Waard GA, et al. Temporal Changes in Coronary Hyperemic and Resting Hemodynamic Indices in Nonculprit Vessels of Patients With ST-Segment Elevation Myocardial Infarction. *JAMA Cardiol*. 2019;4:736-744.
26. Wang L, Travieso A, van der Hoeven N, et al. Improved Nonculprit Stenosis Assessment in Patients With ST-Segment Elevation Myocardial Infarction Using Quantitative Flow Ratio. *JACC Cardiovasc Interv*. 2023;16:1828-1830.
27. Zhao Q, Sun S, Zhou F, Yue J, Luo X, Qu X. The Inhibition of Evolocumab on Non-Infarct-Related Artery Disease in Patients with ST-Elevation Myocardial Infarction. *Int J Gen Med*. 2023;16:2771-2781.
28. Barauskas M, Žiubrytė G, Jodka N, Unikas R. Quantitative Flow Ratio for Assessment of Non-Culprit Coronary Artery Lesions During Percutaneous Coronary Intervention (PCI) in 79 Patients Diagnosed with ST-Elevation Myocardial Infarction (STEMI): A Study from a Single Center in Lithuania. *Med Sci Monit*. 2023;29:e939360.
29. Jo YS, Moon H, Park K. Different Microcirculation Response Between Culprit and Non-Culprit Vessels in Patients With Acute Coronary Syndrome. *J Am Heart Assoc*. 2020;9:e015507.
30. Li X, Mi L, Duan J, Tao L, Xu X, Wang G. Murray law-based quantitative flow ratio for assessment of nonculprit lesions in patients with ST-segment elevation myocardial infarction. *Cardiol J*. 2024;31:522-527.
31. Park K, Cho YR, Park JS, Park TH, Kim MH, Kim YD. Comparison of the Effects of Ticagrelor and Clopidogrel on Microvascular Dysfunction in Patients With Acute Coronary Syndrome Using Invasive Physiologic Indices. *Circ Cardiovasc Interv*. 2019;12:e008105.
32. Spitaleri G, Tebaldi M, Biscaglia S, et al. Quantitative Flow Ratio Identifies Nonculprit Coronary Lesions Requiring Revascularization in Patients With ST-Segment-Elevation Myocardial Infarction and Multivessel Disease. *Circ Cardiovasc Interv*. 2018;11:e006023.
33. Mensink FB, Los J, Oemrawsingh RM, et al. Functional and morphological improvement of significant non-culprit coronary artery stenosis by LDL-C reduction with a PCSK9 antibody: Rationale and design of the randomized FITTER trial. *Heliyon*. 2024;10:e38077.

34. Biscaglia S, Guiducci V, Escaned J, et al. Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction. *N Engl J Med*. 2023;389: 889-898.
35. Lee JM, Kim HK, Park KH, et al. Fractional flow reserve versus angiography-guided strategy in acute myocardial infarction with multivessel disease: a randomized trial. *Eur Heart J*. 2023;44:473-484.
36. Böhm F, Mogensen B, Engstrøm T, et al. FFR-Guided Complete or Culprit-Only PCI in Patients with Myocardial Infarction. *N Engl J Med*. 2024; 390:1481-1492.
37. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376:1234-1244.
38. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. *Lancet*. 2015;386:665-671.
39. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. *N Engl J Med*. 2021;385:297-308.
40. Xu X, Fang C, Jiang S, et al. Functional or anatomical assessment of non-culprit lesions in acute myocardial infarction. *EuroIntervention*. 2025; 21:e217-e228.
41. Räber L, Ueki Y, Otsuka T, et al. Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial. *JAMA*. 2022;327:1771-1781.