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MANAGEMENT OF ACUTE CORONARY SYNDROMES (H JNEID, SECTION EDITOR)

# The Role of Fractional Flow Reserve and Instantaneous Wave-Free Ratio Measurements in Patients with Acute Coronary Syndrome

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## Abstract

**Purpose of Review** The role of fractional flow reserve to guide revascularization in patients with stable angina is well established. The instantaneous wave-free ratio (iFR) is an emerging adenosine-free resting index that is non-inferior to FFR and has potential to streamline the functional evaluation of coronary artery disease. The feasibility and utility of intracoronary physiology in patients with acute coronary syndrome (ACS) is unclear. This review will discuss the physiological principles and validity of using FFR and iFR in patients presenting with ACS. We will also provide an overview of the available evidence for their role in guiding revascularization in this patient group.

**Recent Findings** The use of intracoronary physiology in culprit lesions of patients presenting with STEMI is not recommended and its accuracy is uncertain in patients with NSTEMI. In contrast, the physiological assessment of non-culprit vessels with FFR and IFR is a reliable measure of lesion-specific ischemia. Recent studies have demonstrated that FFR-guided revascularization of non-culprit lesions improves clinical outcomes although the role of iFR in this patient cohort is unknown.

**Summary** Physiology-guided revascularization of non-culprit ACS lesions improves clinical outcomes. Future studies investigating the complementary role of plaque morphology, biomechanics, and systemic inflammation may provide clinicians with a more comprehensive framework to guide treatment decisions.

**Keywords** Acute coronary syndrome · Fractional flow reserve · Instantaneous wave-free ratio · Coronary artery disease · Intracoronary physiology

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## Introduction

Culprit-vessel revascularization by percutaneous coronary intervention is a gold-standard therapy for patients presenting with acute coronary syndromes (ACS) [1, 2]. Ongoing morbidity and mortality, however, remain high, driven largely by the risk of myocardial re-infarction. In addition, as many as 50% of patients with ST-elevation myocardial infarction (STEMI) who have multivessel disease have a significantly higher risk of subsequent events compared to patients with STEMI and single-vessel disease [3]. Not surprisingly, the prognostic benefit of culprit vessel-only versus complete revascularization in ACS has been of widespread interest and the target of several large studies. Earlier data from large pooled analyses had suggested that concomitant revascularization of non-infarct-related arteries in patients with STEMI at the time of presentation portends worse outcomes [4, 5]. However, recent prospective randomized trials including PRAMI (preventive angioplasty in acute myocardial infarction) and CVLPRIT (complete versus lesion-only primary PCI) provided the first-available evidence of benefit for complete revascularization [6, 7].

The systemic inflammatory state of patients presenting with ACS can lead to diffuse vasoconstriction and spasm at the site of lesions. This has led to uncertainty about the accuracy of angiographic assessment of non-culprit lesions given the potential for overestimation of stenosis severity. This, along with the limitations of subjective and poorly reproducible visual angiographic assessment of coronary lesions [8], has led to the exploration of using pressure-based physiologically guided assessment using FFR and iFR to better guide revascularization on the basis that these tools can better discriminate ischemia-provoking lesions compared to anatomical assessment [9, 10]. While there is a plethora of evidence demonstrating that physiologically guided PCI is superior to angiographically guided PCI, the majority of validation and trial data is in cohorts of patients with stable coronary artery disease [11–13].

The use of invasive physiological assessment is less established in patients in the context of ACS. The accuracy and validity of such pressure-based indices have been questioned given the systemic inflammatory states which lead to altered microcirculatory milieu and the potential for higher resting distal pressures and blunted hyperemic response [14]. Notwithstanding, there is a growing body of evidence which demonstrates that functionally guided PCI to non-infarct-related arteries may offer better outcomes [15••, 16].

In this review, we will discuss the physiological principles of both hyperemia-dependent and resting pressure-based indices and their validity in patients presenting with ACS. We will also provide an overview of the available evidence for their role in guiding revascularization in this patient group.

## Physiological Principles and Validity of FFR and IFR in Acute Coronary Syndrome

### Physiological Principles of FFR

Fractional flow reserve is an invasive measure of the hemodynamic significance of a coronary stenosis. It is defined as the ratio of the mean perfusion pressures distal to a stenosis (Pd), obtained via a coronary pressure wire, divided by the mean aortic pressure (Pa) as assessed from the guiding catheter (Fig. 1). It is performed under vasodilator stress to induce maximal hyperemia, a state in which microvascular resistance is minimized and constant, and coronary flow becomes proportional to perfusion pressure [17]. In addition to stenosis severity, FFR is also determined by lesion length, presence of collateral flow, and the degree of subtended viable myocardium [17]. The latter is particularly relevant in patients with a history of ACS, as an angiographically severe stenosis subtending scarred myocardium may be hemodynamically insignificant as the coronary flow required in the myocardium is significantly lower resulting in a smaller pressure gradient and a higher value of FFR during hyperemia (Fig. 2).

Fractional flow reserve was initially validated using a cutpoint of $\leq 0.75$ to define ischemia [18]. To be more inclusive of a stenosis that may be truly hemodynamically significant at the expense of reducing specificity, a cutpoint of $\leq 0.80$ was subsequently utilized in clinical trials to guide revascularization decisions [12, 19]. In light of the variation in FFR thresholds, a 'gray zone' of between 0.75 and 0.80 has been proposed in which clinical decision making should be guided by additional factors such as patient symptoms, myocardium at risk, or findings from other investigations [17]. Although clinical trials interpreted FFR in a rigid dichotomous manner for values either above or below 0.80 [12, 19], recent evidence supports the interpretation of FFR as a risk continuum, with lower values representing a greater severity of ischemia, a higher rate of clinical events, and greater benefit from revascularization [20, 21]. Even in patients with non-functionally significant FFR values, this continuous relationship is maintained with a higher likelihood of adverse events in those with low-normal values (0.81 to 0.85) compared to those with a near normal FFR [20].

There are several important steps in accurately performing and interpreting FFR. (1) Any size guiding catheter can be used; however, it is important to ensure that the catheter is co-axially engaged and adequately sized in relation to the coronary ostium in order to avoid pressure dampening and erroneous FFR values [17]. (2) Intracoronary administration of nitrates should be performed routinely to ensure maximal vasodilatation of the epicardial artery. (3) Hyperemia is then induced to ensure maximal vasodilation of the microvasculature and is typically achieved with intravenous or intracoronary administration of adenosine. (4) The position of the pressure sensor along the

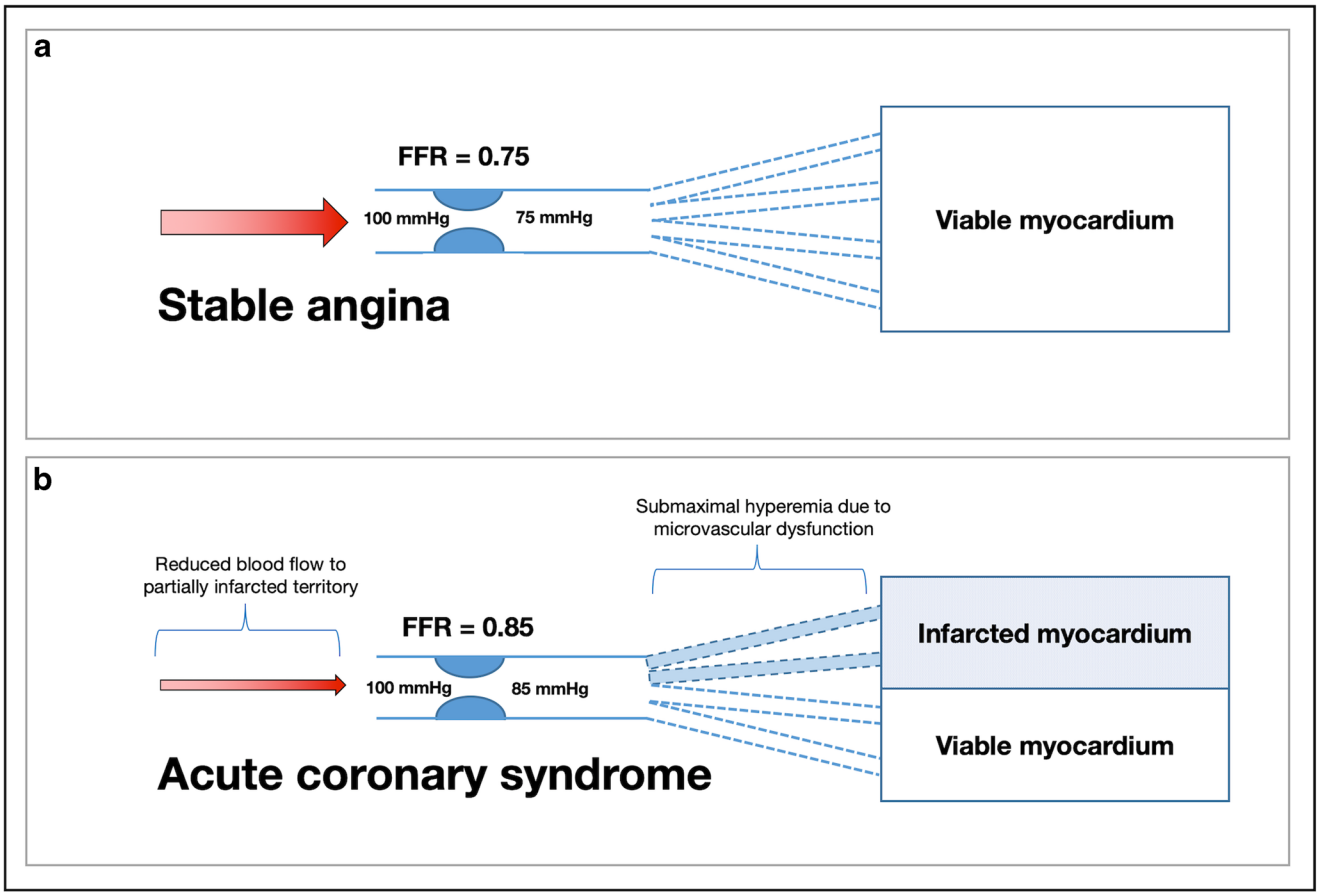


**Fig. 1** Schematic representation of the relationship between FFR, microvascular function, and viable myocardium. **a** Fractional flow reserve is influenced by the degree of subtended viable myocardium and ability to achieve maximal hyperemia. **b** In the setting of ACS, FFR may be underestimated as a consequence of reduced viable myocardium and microvascular dysfunction contribute to reduced coronary blood flow and pressure loss across a stenosis. ACS = acute coronary syndrome; FFR = fractional flow reserve

course of the vessel can also influence the interpretation of FFR. It is recommended to place the pressure sensor distal as possible and then perform a pullback of the wire back to the guide during hyperemia. Firstly, this permits assessment of signal drift, a common source of error during FFR measurements. Secondly, the pressure wire pullback also facilitates a comprehensive assessment of pressure loss across the vessel and the identification of focal, diffuse, or tandem lesions [17]. While intracoronary adenosine provides equivalent hyperemia, its clinical utility is limited by the transient nature of hyperemia;

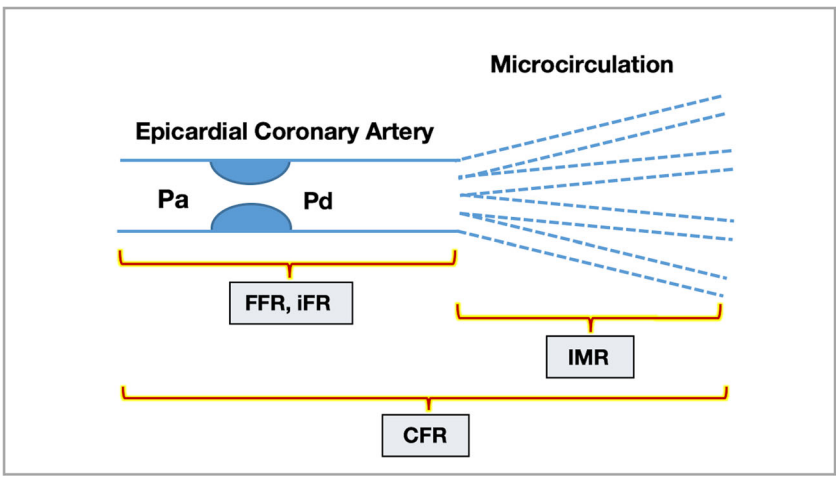


**Fig. 2** Schematic representation of commonly used physiological indices. Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) specifically assess the epicardial artery. The index of microvascular resistance (IMR) interrogates the microvascular resistance independent of epicardial system. Coronary flow reserve (CFR) assesses both the epicardial artery and microcirculation

hence, pullback assessment in diffuse disease or tandem lesions will not be possible [22].

## FFR in Culprit STEMI Lesions

The accuracy of FFR is dependent on the ability to achieve maximal hyperemia, which may be impaired in ACS due to transient damage to the microvasculature [23]. A combination of distal embolization, inflammation, tissue edema, and vasoconstriction all potentially limit the maximal hyperemic flow in the culprit vessel contributing to an underestimation of lesion severity and falsely negative FFR value [24]. Accordingly, culprit vessel FFR in patients presenting with STEMI is not recommended [25]. The time required for recovery of the microcirculation in culprit ACS lesions is also unclear. Initial studies including both STEMI and NSTEMI patients demonstrated that FFR performed early post-ACS could accurately identify reversible ischemia and viable myocardium on SPECT imaging [26, 27]. A more recent study in STEMI patients measured FFR and the index of microvascular resistance (IMR) at baseline and at serial time points [24]. The microvascular function as measured by IMR demonstrated significant reduction both at 24 h following ACS with continued improvement through to 6-month follow-up which was reflected with a reduction in FFR values [24]. These findings suggest that although FFR can potentially identify clearly ischemic culprit lesions early post-STEMI, the delayed recovery of the microvasculature may lead to underestimation of lesion severity and misclassification, particularly in FFR values within the diagnostic gray zone. In addition, given that plaque rupture or erosion are frequently encountered in this setting [28, 29], it is not clear that the residual hemodynamic significance of the lesion should guide revascularization but rather anatomic or inflammatory features of on-going plaque instability that may drive recurrent events and might inform revascularization decisions. Therefore, FFR measurement is currently not recommended for guiding revascularization decisions in culprit vessels in patients with STEMI.

## FFR in Culprit NSTEMI Lesions

In patients with NSTEMI, less transient microvascular dysfunction is expected compared with STEMI [30]. Layland et al. demonstrated that the resistive reserve ratio, a measure of vasodilatory capacity of the microcirculation and IMR measured in the culprit vessels of NSTEMI patients did not differ from those with stable CAD and was significantly lower than in culprit vessels of STEMI patients [23]. Although these data imply that the measurement of FFR in the culprit vessel of NSTEMI patients may be reliable, an important caveat is that measurements were performed at a mean duration of 4 days from symptom onset [23]. This is in contrast to conventional clinical practice where NSTEMI patients are often invasively evaluated within 24 h of admission [31], a time frame in which there may remain microvasculature dysfunction. Similarly, to patients with STEMI, those with NSTEMI may have underlying ruptured or eroded plaques and thus the hemodynamic paradigm alone may not be sufficient to inform revascularization decisions. Therefore, further studies are needed to evaluate the validity of culprit-vessel FFR performed acutely in patients presenting with NSTEMI.

## FFR in Non-Culprit ACS Lesions

The assessment of non-culprit lesions with FFR has shown to be reliable even when assessed during the index procedure. Ntalianis et al. demonstrated in a multicenter study of 101 patients, excellent reproducibility of FFR measured in non-culprit vessels of STEMI ($n = 75$) and NSTEMI patients ($n = 26$) at time of ACS and at follow-up 35 days later ($r = 0.91$, $P < 0.0001$) (Fig. 3) [32••]. Using an animal model, Lee et al. demonstrated that FFR and IMR in non-culprit vessels were maintained despite increasing microvasculature damage in the culprit vessel territory [14]. Recently, in patients presenting with ACS, FFR and IMR were assessed in 59 non-culprit vessels and matched to a control group of vessels in patients with stable angina. Reassuringly, in the ACS cohort, the microvascular resistance and hyperemic response to adenosine were comparable to patients with stable angina [33•]. These findings provide mechanistic support for the reliability of FFR measurements in non-culprit vessels of ACS patients.

## Physiological Principles of iFR

The instantaneous wave-free ratio (iFR) is an emerging adenosine-free resting index that has the potential to streamline the functional evaluation of CAD. iFR is calculated from the ratio of the mean distal to aortic pressure in a period of diastole in which the microvascular resistance is lowest and stable (the wave-free period) [34]. Studies investigating iFR have demonstrated good agreement with FFR and comparable diagnostic performance for detecting ischemia in patients with stable CAD [34–36]. An iFR of $\leq 0.89$ has been determined as the optimal cut-off for hemodynamic significance which is further supported by clinical outcome data demonstrating non-inferiority to FFR [37, 38].

## iFR in Culprit and Non-Culprit ACS Lesions

The validity of using iFR in culprit vessel STEMI patients is as yet undefined. Theoretically, resting flow should also be reduced in the acute setting and therefore non-hyperemic indices such as iFR may not be an accurate measure of culprit lesion severity. In non-culprit ACS lesions, conflicting studies exist on the validity of IFR. A small study showed that the concordance and correlation between iFR and FFR were comparable to

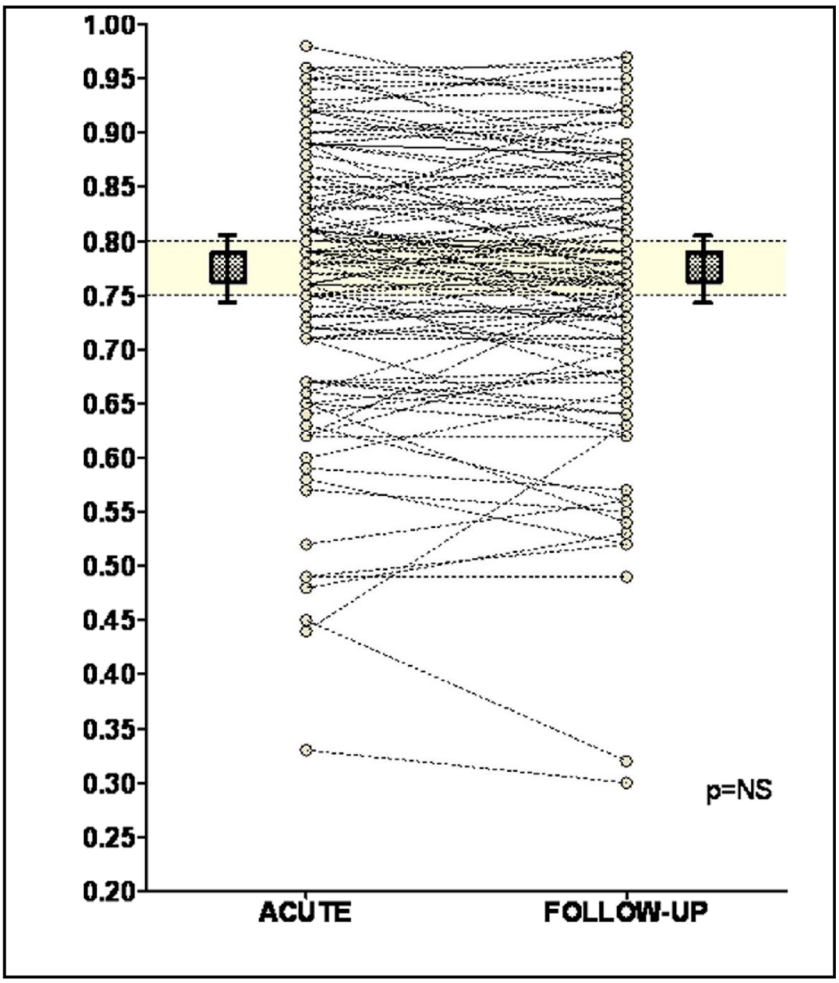


**Fig. 3** Plot of FFR values of non-culprit coronary artery stenosis measured acutely in acute coronary syndrome and at follow-up. The FFR value of the non-culprit stenoses did not change between the acute and follow-up measurements in patients with acute coronary syndrome (0.77 ± 0.13 vs. 0.77 ± 0.13, respectively, $p$ = NS). FFR = fractional flow reserve; NS = non-significant (reprinted from: Ntalianis A et al. JACC Cardiovasc Interv 2010;3:1274–1281, with permission from Elsevier) [32••]

patients with stable CAD [39]. Similarly, Choi et al. found that FFR and iFR values were similar in non-culprit ACS lesions compared to patients with stable CAD and similar stenosis severity. More recently, several comprehensive physiological studies have demonstrated that resting coronary flow in non-culprit ACS lesions is significantly higher than patients with stable CAD [33•, 40]. This may have important implications on the accuracy of resting indices such as iFR in ACS patients, as an increase in resting flow would potentially exaggerate the pressure loss across a lesion, overestimating its functional significance. Taken together these data support that iFR measurements in the non-culprit vessel following an ACS are likely valid, particularly in the deferral of lesions. Although, until larger clinical studies provide clarity, caution is advised in interpreting iFR in setting of large myocardial infarctions or with values around the diagnostic threshold (≤ 0.89).

## Physiology-Guided Revascularization in ACS

Culprit-vessel revascularization in patients presenting with STEMI reduces morbidity and mortality [1, 2]. Up to 50% of patients in this cohort are identified to have angiographically significant multi-vessel disease and is associated with a higher incidence of mortality and myocardial infarction compared to STEMI patients with single-vessel disease [41, 42]. Historically, there has been uncertainty in the strategy and timing of revascularization for non-culprit lesions. Large registry analyses initially alluded to a higher mortality for multivessel PCI at the time of index procedure compared with staged revascularization [5, 43]. Accordingly, clinical practice guidelines recommended against revascularization of non-culprit lesions during primary PCI [44]. Subsequent randomized trials (PRAMI and CVLPRIT) demonstrated superior outcomes for complete revascularization of non-culprit lesions during the index procedure, although assessment of lesion severity was based on angiography alone [6, 7].

It is well established that angiographic assessment of lesion severity does not correlate well with functional significance [9, 10]. The FAME trial demonstrated that two-thirds of lesions with > 50% stenosis on angiography demonstrated no evidence of ischemia [10]. Conversely, mild angiographic stenosis in vessels supplying a large myocardial territory (i.e., left main, left anterior descending artery) is not infrequently

associated with ischemia [45, 46]. Therefore, the visual-functional mismatch associated with angiography may lead to inappropriate treatment with additional cost and risk to patients [12].

In patients with stable CAD, physiology-guided revascularization with FFR reduces the risk of adverse cardiac events compared to angiography-guided PCI or medical therapy [12, 19, 47]. The benefit of FFR observed in these landmark trials was driven predominantly by reduction in unplanned revascularization, although the trials were not powered to observe differences in 'hard' endpoints of cardiac death and myocardial infarction [12, 19]. This limitation was addressed with a recent patient-level meta-analysis of 2400 patients which demonstrated that in stable CAD, FFR-guided revascularization significantly reduces the incidence of myocardial infarction compared to medical therapy alone [48].

The application of coronary physiology to non-culprit lesions in patients with STEMI has been evaluated in several landmark clinical trials (Table 1). The DANAMI-3 PRIMULTI trial recruited 627 patients presenting with STEMI and identified to have ≥ 1 clinically significant coronary stenosis [15••]. Following successful treatment of the infarct-related artery, patients were randomized 1:1 to no further invasive treatment or complete FFR guided revascularization performed prior to discharge (median 2 days, IQR 2–4). At a median follow-up of 27 months, a strategy of complete FFR guided revascularization was associated with a 40.9% relative risk reduction (RRR) in the primary endpoint of all-cause mortality, non-fatal reinfarction, and ischemia-driven revascularization (HR 0.56; 95% CI 0.38 to 0.83; $P = 0.004$) (Fig. 4a) [15••]. The COMPARE-ACUTE was a similar study except that FFR and non-culprit revascularization was performed at time of index procedure [16]. The study included 885 patients randomized in a 1:2 ratio to undergo complete FFR-guided revascularization or only treatment of the infarct-related artery. FFR-guided revascularization at time of index procedure was associated with a 62% RRR in the composite primary endpoint of death from any cause, nonfatal MI, revascularization, and cerebrovascular events at 12 months (HR 0.35; 95% CI 0.22 to 0.55; $P < 0.001$) (Fig. 4b) [16]. The benefit of complete revascularization in both these studies was driven by reduced repeat revascularization with no difference in mortality or myocardial infarction. The COMPLETE and FULL-REVASC trials (Table 1) are currently in progress and will hopefully provide more definitive guidance on the impact of FFR in improving hard clinical endpoints in STEMI patients with multi-vessel disease [49, 50].

On the basis of these trials, the European Society of Cardiology now assigns a class IIa and the American College of Cardiology a class IIb recommendation for routine non-culprit lesion revascularization prior to hospital discharge in patients presenting with STEMI [51, 52]. An important limitation in these trials was the exclusion of patients with cardiogenic shock. Notably, the recently published CULPRIT-SHOCK trial demonstrated a 7.3% absolute increase in 30-day mortality in patients presenting with ACS and cardiogenic shock who underwent immediate multivessel PCI compared with culprit-only revascularization [53]. Although immediate revascularization decisions were not guided by invasive physiology, on the strength of these findings, clinical practice guidelines now recommend (class III) against the immediate treatment of non-culprit lesions in hemodynamically unstable patients presenting with ACS [54].

Two clinical trials have assessed the utility of FFR in guiding revascularization in patients presenting with non-ST elevation myocardial infarction (NSTEMI). The FAME study enrolled 328 patients with unstable angina or NSTEMI out of a total 1005 patients with multi-vessel disease [55]. FFR-guided revascularization in the ACS cohort was associated with a 5.1% absolute risk reduction in the composite primary endpoint of death, MI, or revascularization) compared with angiographic guidance at 2 years, similar to that observed in patients with stable CAD. An important caveat is that these findings were based on a subgroup analysis that was not powered to detect superiority of FFR over angiographic guidance. The FAMOUS-NSTEMI trial assessed the feasibility of FFR-guided revascularization in both culprit and non-culprit lesions in patients presenting with NSTEMI [56]. The study reported no difference in 12-month clinical outcomes in patients ($n = 350$) randomized to FFR or angiographic guided PCI. Although FFR guidance changed revascularization strategy in 22% of patients and was associated with lower rates of coronary revascularization [56], taken together, the use of FFR in patients with NSTEMI has not been demonstrated to improve clinical outcomes. Both the FAME sub-analysis and FAMOUS-NSTEMI trial were underpowered and highlight the need for larger studies to ascertain the role of intracoronary physiology in this high-risk cohort.

How about data comparing the performance of FFR versus resting indices in the physiological assessment of non-culprit lesions in patients with ACS? DEFINE-FLAIR and iFR-SWEDEHEART are two landmark trials which demonstrated that a strategy of iFR-guided revascularization was non-inferior to FFR for 1-year clinical outcomes and was associated with a reduction in procedural time, patient discomfort, and cost [37, 57]. The majority of patients presented with stable CAD (72%, 3262/4529) with only 2% enrolled with STEMI [37, 57]. A pooled analysis of both trials compared the safety of deferring coronary revascularization with FFR versus iFR in stable CAD and ACS cohorts [58]. Although overall outcomes between FFR and iFR were comparable, deferral with FFR in the ACS subgroup was associated with a higher rate of clinical events compared to FFR deferral in stable CAD. In contrast, deferral with iFR yielded similar outcomes regardless of clinical presentation. A potential explanation for this disparity is that the hyperemic response required for FFR assessment may be blunted

**Table 1** Landmark trials for FFR/iFR-guided revascularization in acute coronary syndrome

| | No. of patients | ACS type | Culprit or non-culprit | Intervention | Timing of FFR/iFR-based treatment | Follow-up (months) | Outcome |
|---|---|---|---|---|---|---|---|
| DANAMI-3 PRIMULTI (2015) | 627 | STEMI | Non-culprit | Complete FFR guided revascularization vs. no further treatment prior to discharge | Before hospital discharge [median 2 days (IQR 2–4) post index procedure] | 27 | MACE: 13% vs 22% ($p = 0.004$) IDR: 5% vs 17% ($p < 0.001$) MI: 5% vs 5% ($p = 0.87$) Death: 5 vs 4% ($p = 0.43$) |
| COMPARE ACUTE (2017) | 885 | STEMI | Non-culprit | Complete FFR guided revascularization vs. no further treatment prior to discharge | During or within 72 h of index procedure (83% during index procedure) | 12 | MACE: 7.8% vs 20.5% ($p < 0.001$) UR: 6.1% vs 17.5% ($p < 0.001$) AMI: 2.4% vs 4.7% ($p = 0.1$) Death: 1.4% vs 1.7% ($p = 0.70$) |
| FAME (ACS COHORT) (2011) | 328 | NSTEMI and UA | Culprit and non--culprit | FFR vs. Angiographically guided PCI in Multi-vessel CAD ($\geq 50\%$ stenosis in at least 2 vessels) | During index procedure | 24 | MACE: 21.3% vs 26.4% CABG or repeat PCI: 13.3% vs 14% MI: 8% vs 13.5% Death: 2.7% vs 4.5% ($p$ = not significant for all) |
| FAMOUS-NSTEMI (2014) | 350 | NSTEMI | Culprit and non--culprit | FFR vs. Angiographically guided PCI in each vessel with > 30% stenosis | Median 3 (IQR 2–5) days from the index episode of myocardial ischaemia. | 12 | Patients treated by OMT alone: 13.2 vs 22.7% ($p = 0.022$) FFR guidance changed treatment (PCI, OMT, or CABG)—21.6% MACE: 7.4% vs 9.2% ($p = 0.56$) |
| DEFINE-FLAIR and iFR-SWEDEHEART (ACS COHORT) (2018) | 440 | NSTEACS and STEMI | Non-culprit | Deferral of PCI on basis of FFR or IFR for Stable vs ACS patients | In NSTEACS: at index procedure, in STEMI: > 48 h after Primary PCI | 12 | MACE: FFR (HR 0.52; 0.27–1.0) iFR (HR 0.74; 0.38–1.42) *P* value for interaction: 0.46 |
| Ongoing trials | | | | | | | |
| COMPLETE *(Due 2019)* | 4042 | STEMI | Non-culprit | Angiographically or FFR guided PCI of non-culprit vessels vs. culprit-only PCI | | 48 | Co-primary outcomes: Composite of CV death and new MI, Composite of CV death, new MI or IDR |
| FULL-REVASC *(Due 2021)* | 4052 | STEMI or very high risk NSTEMI | Non-culprit | FFR-guided PCI of non-culprit vessels. vs. culprit-only PCI | | 12 | Combined endpoint of all-cause mortality and myocardial infarction |

/*MI* myocardial Infarction, *CV* cardiovascular, *IDR* ischemia-driven revascularization, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non ST-elevation myocardial infarction, *NSTEACS* non ST-elevation acute coronary syndrome, *MACE* major adverse cardiovascular events, *UR* urgent revascularization, *HR* hazard ratio

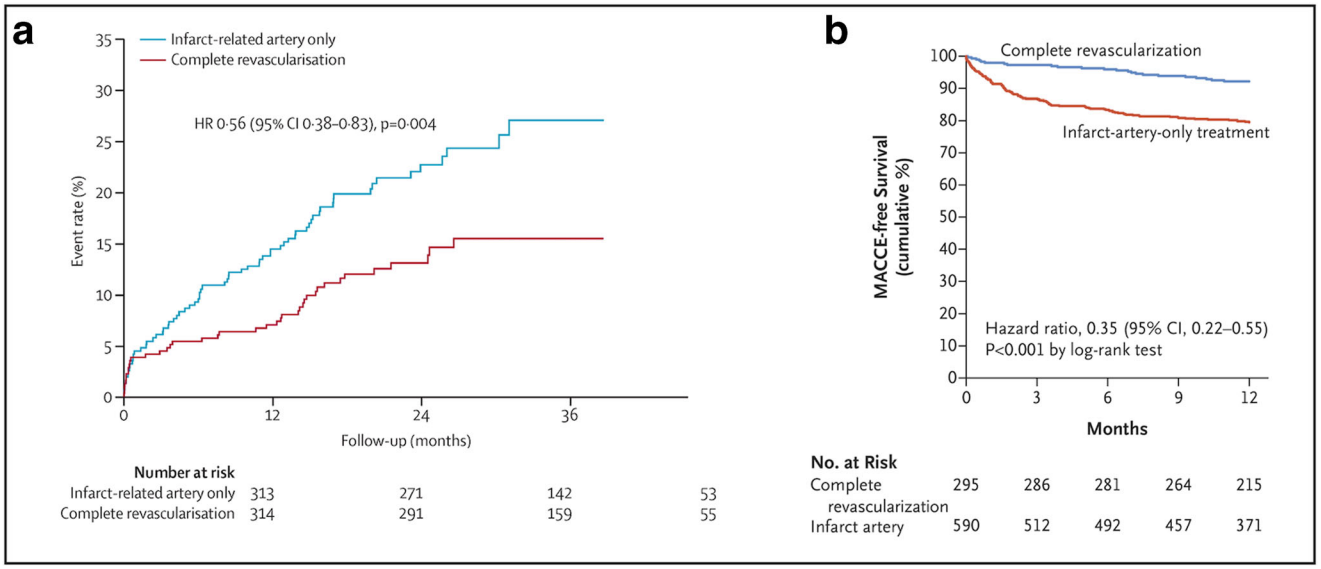


**Fig. 4** Landmark clinical trials comparing strategy of complete revascularization to infarct artery only treatment in patients with ST elevation myocardial infarction. In patients with presenting with ST-elevation myocardial infarction the DANAMI-3 PRIMULTI (**a**) and COMPARE-ACUTE (**b**) trials both demonstrated reduced adverse cardiac events in patients randomized to complete revascularization of non-culprit lesions compared to only treatment of the infarct-related artery (**a** reprinted from The Lancet: Engstrøm T et al. Lancet 2015;386:665–671, with permission from Elsevier) [15••] (**b** reprinted from: Smits PC et al. N Engl J Med 2017;376(13):1234–1244. Copyright © 2017 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society) [16]

in ACS due to microvascular dysfunction and therefore underestimates lesion severity [59]. Overall, the inherent limitations of a subgroup analysis preclude drawing definitive conclusions on the utility of one physiological tool over the other, but rather highlight the need for further research to improve the safety of deferring revascularization in patients presenting with ACS.

## Future Directions

The current approach for treating culprit lesions in patients with ACS is to aggressively revascularize these lesions. Future clinical studies in patients with STEMI and NSTEMI should focus on combining high-resolution anatomic and biomechanical plaque characteristics using intravascular ultrasound or optimal coherence tomography imaging with physiologic measurements to identify the clinical and plaque features that determine the natural history of *mild and intermediate* culprit lesions. Subsequently, patients and plaques with *mild and intermediate* culprit lesions with high-risk features should be randomized to PCI versus aggressive medical therapy. Similar studies could be performed in non-culprit lesions of patients with STEMI and NSTEMI. Furthermore, computational techniques using angiography, intravascular imaging, and computerized tomography will continue to be developed for lesion and vessel assessment of both culprit and non-culprit lesions in patients with acute coronary syndromes.

## Conclusion

In patients presenting with ACS, the physiological assessment of non-culprit vessels with FFR or IFR provides clinicians with a reliable measure of lesion-specific ischemia. Similar to patients with stable CAD, incorporating invasive physiology to guide the treatment of non-culprit lesions in ACS improves clinical outcomes by predominantly reducing the incidence of urgent revascularization. Importantly, the risk of subsequent myocardial infarction in this cohort is dependent on factors beyond the burden of ischemia. Future studies investigating the complementary role of plaque morphology, biomechanics, and systemic inflammation may provide clinicians with a more comprehensive framework to guide both revascularization and medical therapy, with the potential to deliver a more focused and impactful treatment to this high-risk patient population.

## Compliance with Ethical Standards

**Conflict of Interest** Abdul Rahman Ihdayhid reports consulting fees from Boston Scientific.

Habib Samady reports grants and personal fees from Philips, grants from Abbott Vascular, and grants from Gilead; and he is a Co-Founder of COVANOS. In addition, Dr. Samady has a pending patent for Computational physiology related.

Jin-Sin Koh, John Ramzy, Arnav Kumar, Michael Michail, and Adam Brown declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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