



REVIEW

Contemporary Use of Coronary Physiology in Cardiology

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ABSTRACT

Coronary angiography has a limited ability to predict the functional significance of intermediate coronary lesions. Hence, physiological assessment of coronary lesions, via fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR), has been introduced to determine their functional significance. An accumulating body of evidence has consolidated the role of

physiology-guided revascularization, particularly among patients with stable ischemic heart disease. The use of FFR or iFR to guide decision-making in patients with stable ischemic heart disease and intermediate coronary lesions received a class I recommendation from major societal guidelines. Nevertheless, the role of coronary physiology testing is less clear among certain patients' groups, including patients with serial coronary lesions, acute coronary syndromes, aortic stenosis, heart failure, as well as post-percutaneous coronary interventions. In this review, we aimed to discuss the utility and clinical evidence of coronary physiology (mainly FFR and iFR), with emphasis on those specific patient groups.

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Key Summary Points

Why carry out this study?

The role of coronary physiology testing is less clear among certain patients' groups with coronary artery disease.

What did the study ask?

What is the available evidence regarding the utility of coronary physiology testing in patients with serial coronary lesions, acute coronary syndrome (ACS), aortic stenosis (AS), heart failure, as well as post-percutaneous coronary intervention (PCI)?

What was learned from the study?

In patients with serial non-left main coronary lesions, instantaneous wave-free ratio (iFR) is the preferred modality for assessing coronary physiology.

The use of fractional flow reserve (FFR) in evaluating non-culprit lesions among patients with ST-elevation myocardial infarction is feasible and would reduce adverse events compared with culprit-only approach.

A post-PCI FFR or iFR can predict adverse events, but the role of physiology-guided optimization approach in improving clinical outcomes is being evaluated. In patients with acute heart failure, FFR-guided revascularization is feasible in most patients.

In patients with AS, borderline values of FFR are harder to interpret, and should be re-evaluated after treatment of AS.

INTRODUCTION

It has been long recognized that anatomical assessment of coronary artery disease (CAD) via coronary angiography has a limited ability to

predict the functional significance of coronary disease [1, 2]. In light of the growing focus on the appropriateness of coronary stenting in stable ischemic heart disease (SIHD), there has been interest in coronary physiology as a means to inform clinical decision-making. Fractional flow reserve (FFR) is the ratio between mean distal coronary pressure and mean aortic pressure during maximal hyperemia, which was initially introduced as a surrogate for relative coronary flow reserve (CFR). Due to accumulating evidence for its clinical role, cost-effectiveness and reproducibility, the use of FFR has been integrated in the current era to guide decision-making in patients evaluated for coronary revascularization. Non-hyperemic indices, such as instantaneous wave-free ratio (iFR), have also been introduced into the intracoronary physiology toolbox, promoted by its simplistic use and supported by initial validation studies against FFR [3, 4]. Coronary physiology evaluation is more established among patients with stable ischemic heart disease (SIHD) [5–8]. However, among certain patients' groups, the role of coronary physiology testing is less clear, including patients with acute coronary syndromes (ACS), aortic stenosis, heart failure as well as cases of serial coronary lesions and post-percutaneous coronary intervention (PCI). In this review, we aimed to discuss the utility and clinical evidence of coronary physiology (mainly FFR and iFR), with emphasis on those specific patient groups. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Physiological Testing with FFR and iFR

FFR is a coronary pressure-derived estimate of coronary flow impairment. Due to narrowing of an epicardial vessel, there occurs a drop in perfusion pressure as a result of viscous and expansion losses, which could be determined by Poiseuille's law and Bernoulli's equation [1, 9, 10]. Administration of a vasodilating drug causes abolition of vasomotor tone and decreased microvascular resistance. Under this

condition, blood flow across a stenotic vessel is assumed to be maximal, producing the maximal achievable flow. Based on simultaneous measurement of mean aortic, distal coronary, and central venous pressure (P_a , P_d , and P_v , respectively) during pharmacological vasodilation, FFR can be estimated as $P_d \cdot P_v / P_a \cdot P_v$, which is approximated to P_d/P_a , presuming low central venous pressure [9, 10]. Many studies have validated the accuracy of FFR in identifying coronary stenoses that are associated with myocardial ischemia based on non-invasive stress testing. The role of FFR has then evolved to be gold standard for invasive physiological assessment of coronary lesion severity, and even become the reference test for novel intracoronary diagnostic modalities, in the setting of SIHD. Furthermore, the reproducibility of FFR is independent of changes in blood pressure, heart rate, and contractility [1, 11, 12].

Nonetheless, the clinical application of FFR must keep in consideration several concepts for coronary hemodynamics. First, the concept of FFR assumes that under maximal hyperemia the coronary resistance is negligible, and coronary pressure becomes proportional with coronary flow. However, such an assumption is not uncommonly incorrect. Achievement of maximal vasodilation would be limited among patients with microvascular disease, diffuse CAD and with concomitant intake of caffeine or sympathomimetic drugs. Second, FFR represents a pressure-derived simulation for relative CFR but it does not provide absolute measurement of coronary flow. Absolute coronary flow is the major determinant for adequate myocardial metabolism, but not coronary perfusion pressure. Studies have demonstrated that myocardial contractility remains stable even in conditions of decreased perfusion pressure, up to $FFR < 0.45$, provided there is stable coronary flow. Indeed, myocardial ischemia as angina, ST depression > 1 mmHg or stress induced dysfunction, is determined mainly by absolute coronary flow, which are rarely present during FFR testing. Furthermore, studies demonstrated that the relationship between FFR and CFR is not linear, and discordance does occur in 30–40% of cases. For example, in cases with epicardial stenosis severe enough to generate a

pressure gradient with abnormal FFR, a high basal coronary flow and intact microvasculature could still maintain CFR that is above the ischemic threshold. Similarly, patients with diffuse CAD and low CFR might still have normal FFR. As such, optimal assessment of intracoronary physiology and hemodynamics should ideally include evaluating coronary blood flow. Third, FFR for a specific artery depends on the supplied myocardial mass [13]. Failure to quantify myocardial mass at risk is a limitation of FFR.

In contrast to hyperemic physiological testing during FFR, non-hyperemic coronary physiological testing techniques are available and variably validated. Among these, the most commonly used is the iFR (instantaneous wave Free Ratio). iFR is calculated using a Philips® algorithm incorporating the resting mean P_d/P_a ratio calculated during a certain period of diastole, the so-called wave-free period. The wave-free period exists at the mid-to-end diastole, and has been proposed to have relatively higher coronary flow as well as stable and low microvascular resistance compared with the rest of the cardiac cycle [14]. Nevertheless, a true “wave-free” period in the cardiac cycle is physiologically not possible, as the coronary pressure waveform is composed of various waves resulting from forward and backward traveling pressure waves [15–17]. Moreover, the instantaneous pressure-flow ratio measurement during iFR validation studies is conceptually confounded since Ohm’s law pertains to averaged pressure and flow only [15–17]. Finally, studies have demonstrated the wave-free myocardial resistance still falls considerably with vasodilation, arguing that this measurement is not inherently minimized [18].

In the IDEAL (Iberian–Dutch–English) study, 567 intracoronary pressure and flow velocity assessments were analyzed from 301 patients during the whole cardiac cycle and the diastolic wave-free period. Data from the IDEAL study showed that with progressive coronary stenosis severity, trans-stenotic pressure gradient increased during rest and hyperemia, and this was mainly determined by compensatory vasodilatory changes in microvascular resistance [18]. As such, iFR has been proposed to

identify ischemia-producing coronary stenoses at resting states [4]. The use of iFR relies on the measurement of pressure gradient during resting conditions, which makes it unfavorably sensitive to hemodynamic changes in baseline coronary flow [19]. Also, iFR values has smaller gradient compared with FFR, which makes it more prone to measurement noise or drift during wire pullback [19]. Other proposed resting tests include: resting mean P_d/P_a ratio during full cardiac cycle; diastolic pressure ratio (dPR) which represents resting mean P_d/P_a ratio during diastole; resting full cycle ratio (RFR) which represents ratio of lowest P_d/P_a ratio independent of the timing during cardiac cycle [20].

Current Data for the Use of FFR and iFR

The normal value of FFR is 1.0, for every patient and every coronary artery. FFR for a stenotic vessel is expressed as a decimal or fraction of this value [1]. Studies suggested that a cut-off value for $FFR < 0.75$ showed higher specificity to correlate with inducible ischemia, whereas stenoses cutoff of > 0.80 showed highest sensitivity to correlate with inducible ischemia [7, 10, 21]. A cut-off value ≤ 0.80 is now the recommended criterion for a hemodynamically significant lesion that may be treated with percutaneous intervention [2].

The clinical benefits for FFR-guided revascularization among patients with SIHD have been established [5–8]. The utility of FFR was evaluated in the DEFER trial where 181 patients with stable coronary artery disease (CAD) and intermediate coronary stenosis ($> 50\%$ on visual assessment) underwent randomization to PCI or deferral of PCI if their $FFR \geq 0.75$ [8]. At 5-year follow-up, there was no significant difference in the composite outcome of cardiac death and acute myocardial infarction between the groups, although the deferred group had numerically lower events (3.3 vs. 7.9%, $p = 0.21$). However, at 15 years there was a statistically significant lower rate of myocardial infarction in the FFR group (reference – 2.2 vs. 10%; $p = 0.03$) [22].

The FAME randomized controlled trial (RCT) exclusively included patients who had coronary

artery stenoses of $\geq 50\%$ of the vessel diameter in at least two major epicardial coronary arteries, and if clinical data and angiographic appearance suggested candidacy for PCI [23]. FAME excluded patients with significant left main coronary artery (LMCA) disease and those with non-ST elevation myocardial infarction (NSTEMI) and creatinine kinase > 1000 U/I within the prior 5 days to enrollment [24]. Eligible patients were randomized into FFR-guided PCI (if $FFR \leq 0.80$) versus angiography-guided PCI. FFR-guided PCI reduced the risk of major adverse cardiac events (MACE) at 1 year compared with angiography-guided PCI (relative risk [RR] 0.72; 95% confidence interval [CI] 0.54–0.96) [24]. At 2-year assessment, there was a trend to lower risk of MACE with FFR-guidance (RR 0.80; 95% CI 0.62–1.02) [23, 25]. The FAME-2 trial randomized 1220 patients who had at least one stenosis in a major coronary artery with a $FFR \leq 0.80$ to undergo FFR-guided PCI or to receive medical therapy alone. The study demonstrated lower MACE among the PCI versus medical therapy groups (hazard ratio [HR] 0.39; 95% CI 0.26–0.57), which was driven by fewer urgent revascularizations in the PCI group [26].

The use of iFR in evaluating the significance of coronary lesions has been evaluated in the two landmark studies, iFR-SWEDEHEART (The Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) and DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization). These demonstrated non-inferior 1-year clinical outcomes with iFR versus FFR-guided revascularization, with the added benefit of lower procedural time and patient discomfort (as adenosine is not needed) with iFR guidance [27, 28]. Most recently, the 5-year data from the DEFINE-FLAIR study were presented and showed consistent non-inferiority with iFR versus FFR-guided revascularization in the primary outcome of MACE; however, iFR-guided revascularization had higher events in the secondary endpoint of all-cause mortality [29].

The recent American College of Cardiology/American Heart Association joint committee guidelines gives a Class I recommendation for

using FFR or iFR to guide the decision to proceed with PCI in patients with angina and angiographically intermediate stenosis [6]. The European Society of Cardiology guidelines gives a Class I recommendation for using FFR or iFR to evaluate intermediate stenoses when evidence of ischemia is not available, and gives a Class IIa recommendation for FFR-guided PCI in patients with multivessel disease undergoing PCI [30].

USE OF FFR IN SPECIFIC GROUPS OF PATIENTS

FFR in Acute Coronary Syndrome

There has been controversy regarding the efficacy and safety of deferring PCI based on FFR assessment among patients with acute coronary syndrome (ACS). In the FAME trial, there was a trend to lower risk of MACE with FFR guidance at 2 years, with no subgroup difference among those with stable angina (absolute risk reduction [ARR] 3.7%) or non-ST elevation ACS (ARR 5.1%) [23, 25]. Conversely, the FUTURE (FUncTional Testing Underlying coronary REvascularization) trial, which included 49% of patients with ACS, aimed to evaluate FFR- versus angiography guidance in patients with multivessel CAD. The study was prematurely halted due to a signal of higher mortality in the FFR-guided group, despite no observed difference in major adverse cardiac/ cerebrovascular events between study groups [31]. The FUTURE trial had several unique features to keep in context when interpreting its results. First, unlike other RCTs, PCI eligibility was not among inclusion criteria in that trial. Second, more than 20% of FFR-negative patients underwent revascularization at operators' discretion. Third, the FUTURE comprised more complex patients with \approx 12% left main coronary disease, and $>$ 50% patients with \geq 3 vessel disease.

Few RCTs evaluated FFR-guided revascularization among patients exclusively presenting with ACS [32–35]. Both the COMPARE-ACUTE and DANAMI-3-PRIMULTI trials demonstrated that among patients with STEMI, FFR-guided

revascularization reduced clinical adverse events compared with culprit-only approach, an effect which was driven by fewer ischemia-driven repeat revascularization [34, 35]. In the FAMOUS-NSTEMI trial, 350 patients with NSTEMI were randomized into FFR-guided versus angiographic-guided management [32]. The proportion of patients initially treated by medical therapy was higher in the FFR group (22.2 vs. 13.2%, $p = 0.02$). However, FFR-guided management did not reduce MACE at 12 months (8.0 vs. 8.6%, $p = 0.89$). In the FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction) trial, patients with STEMI and multivessel disease were randomized to FFR-guided versus angiographic-guided PCI of non-culprit lesions [33]. FFR-guided management did not reduce the composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization at 1 year. In both FAMOUS-NSTEMI and FLOWER-MI trials, the proportion of patients receiving non-culprit PCI was reduced with FFR guidance as well as the mean number of stents per patient. The results of the FLOWER-MI and FAMOUS-NSTEMI studies were supported by data from non-randomized studies, with even some showing harm from deferral of PCI based on FFR assessment in patients with ACS [36, 37]. In a meta-analysis of nine studies (randomized and observational), Liou et al. showed a higher event rate with FFR-guided revascularization among those with ACS versus stable angina [38].

The discrepancy in clinical benefits with FFR among presentations with ACS compared with stable ischemic heart disease is probably related to several factors. The physiological milieu in cases with ACS commonly encompasses variable degrees of coronary microcirculatory dysfunction, myocardial dysfunction, and elevated left ventricular filling pressures, which results from abnormal metabolic and neurohormonal functions in cases of myocardial ischemia [39, 40]. These changes could alter coronary flow dynamics regardless of the severity of epicardial stenosis. Furthermore, microcirculatory dysfunction would preclude maximal microvascular dilatation, which is required for

recording reliable FFR values and might result in underestimation of lesion severity [39]. Furthermore, while FFR assess functional significance, the PROSPECT trial reported that adverse clinical events from non-culprit lesions were related to certain plaque characteristics detected on intravascular ultrasound (IVUS) imaging; including large plaque burden, the presence of thin cap-fibroatheromas, or minimal luminal area of $\leq 4\text{mm}^2$ [41].

Collectively, the use of FFR in evaluating non-culprit lesions among patients with STEMI is feasible and would reduce adverse events compared with the culprit-only approach. However, there are currently no data to support superior outcomes with FFR guidance versus angiography guidance among patients with STEMI or non-ST elevation ACS. Furthermore, abnormalities in coronary flow and microvascular resistance should be kept in consideration while interrogating coronary physiology among patients with ACS. Further studies should investigate the basis behind such unsatisfactory results with FFR guidance among patients with ACS, and whether a combined physiological/anatomical assessment would be more optimal among this group of patients.

The use of resting physiological indices, such as iFR, has been explored among patients with ACS. The use of resting indices will avoid the need for maximal hyperemia, which might not be achievable in cases with ACS secondary to microvascular dysfunction. In one small study evaluating FFR and iFR in patients with STEMI at the time of presentation and at 1 month demonstrated no significant difference in iFR between time points but lower FFR at 1 month (albeit the mean difference was small at 0.02) [42]. In the iFR-SWEDEHEART and DEFINE-FLAIR, 38 and 19% of patients included presented with ACS, respectively. A pooled analysis of both trials showed that there was no significant difference in 1-year MACE between iFR and FFR, although numerically lower with iFR (5.41 vs. 6.42%) [43]. While the adverse events rates were higher among those with SIHD versus ACS, subgroup analysis including the iFR group only showed no significant difference between SIHD versus ACS (HR 0.74; 95% CI 0.38–1.42) [43]. Taken together with data for complete

revascularization in acute coronary syndrome, particularly in STEMI, suggests there is no hard outcomes benefit of adding physiological testing with iFR or FFR when attempting non-culprit vessel PCI but that complete revascularization is better than culprit-only PCI (Table 1).

Post-PCI FFR

A knowledge gap still exists regarding strategies to optimize post-PCI clinical outcomes. Evaluating coronary physiology, via post-PCI FFR, has been proposed to optimize post-PCI outcomes. High residual FFR gradients after routine PCI commonly exist, even among cases with apparent angiographic success [44, 45]. The proportion of patients who had ≥ 1 lesion with post-PCI FFR ≤ 0.90 was 56% and 68.1% in the FFR-SEARCH and TARGET-FFR prospective studies [44, 45], while those with ≥ 1 lesion with post-PCI FFR ≤ 0.80 was 11% in FFR-SEARCH and 17.8% in another retrospective registry [44, 46].

A post-PCI FFR cutoff of ≤ 0.90 predicted adverse events in several studies [47–49]. In their meta-analysis, Johnson et al. demonstrated that post-PCI FFR showed an inverse relationship with MACE on continuous assessment (HR 0.86, CI 0.80–0.93) at a median follow-up duration of 16 months [50].

Importantly, a post-PCI FFR-guided optimization approach could facilitate improving post-revascularization FFR gradients [45]. The TARGET-FFR trial compared a post-PCI physiology-guided optimization strategy versus standard angiography guidance among 260 patients undergoing routine PCI [45]. Investigators adopted a protocol of physiology-guided incremental optimization strategy among patients with post-PCI FFR < 0.90 , which included measuring the hyperemic trans-stent gradient. Among patients with a hyperemic trans-stent gradient ≥ 0.05 , the protocol recommended high-pressure post-dilation using a non-compliant balloon. Repeat pullback was then performed, and in cases with residual focal FFR increase ≥ 0.05 in an unstented segment, additional stenting was recommended. However, in non-focal diffuse disease, no further intervention was recommended [45]. Almost one-third

Table 1 Studies on the role of FFR in acute coronary syndrome

Study	Year	Design	Patients (n)	Study groups	ACS (%)	FFR cutoff	Definition of primary outcome	Follow-up period	Outcomes
COMPARE-ACUTE	2017	Prospective, multicenter, randomized control trial	885	FFR-guided complete revascularization versus culprit-only approach	100% STEMI	≤ 0.80	MACCE: Composite of all-cause mortality, MI, cerebrovascular accident and repeat ischemia-driven revascularization	1 year	Lower MACE in FFR-guided group (HR 0.35; 95% CI 0.22–0.55)
DANAMI-3-PRIMULTI	2015	Prospective, multicenter, randomized control trial	627	FFR-guided complete revascularization versus culprit-only approach	100% STEMI	≤ 0.80	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	27 months	Lower MACE in FFR-guided group (HR 0.56; 95% CI 0.38–0.83)
FAME	2015	Prospective, multicenter, randomized control trial	1005	Angiography-guided versus FFR-guided revascularization	32.6% patients had NSTEMI (CK < 1000 U/l) or Unstable angina	≤ 0.80	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	5-year	2-year: Trend to lower risk of MACE with FFR guidance (RR 0.80; 95% CI 0.62–1.02) + no subgroup difference between SIHD [ARR 3.7%] or ACS [ARR 5.1%]. 5-year no difference in MACE (RR 0.91; 95% CI 0.75–1.10) + no subgroup difference between SIHD and ACS (pinteraction = 0.97)

Table 1 continued

Study	Year	Design	Patients (n)	Study groups	ACS (%)	FFR cutoff	Definition of primary outcome	Follow-up period	Outcomes
FUTURE	2021	Prospective, multicenter, randomized control trial	927	Angiography-guided versus FFR-guided revascularization	45% with ACS	≤ 0.80	MACCE: Composite of all-cause mortality, MI, cerebrovascular accident and repeat ischemia-driven revascularization	1 year	No difference in MACCE (HR 0.97; 95% CI 0.69–1.36). No subgroup difference between ACS (HR 1.03; 95% CI 0.61–1.73) and SA (HR 0.96; 95% CI 0.60–1.54)
FAMOUS NSTEMI	2015	Prospective, multicenter, randomized control trial	350	Angiography-guided versus FFR-guided revascularization	100% NSTEMI	≤ 0.80	MACCE: Composite of all-cause mortality, MI, cerebrovascular accident and repeat ischemia-driven revascularization	1 year	No difference in MACCE (risk difference – 1.8%; 95% CI: – 7.9, 4.2%)
FLOWER MI	2021	Prospective, multicenter, randomized control trial	1163	Angiography-guided versus FFR-guided revascularization	100% STEMI	≤ 0.80	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	1 year	No difference in MACE (HR 1.32; 95% CI 0.78–2.23)
PRIME FFR	2008–2013	Prospective, international multicenter registry	1983	Single arm for FFR-guided revascularization	27% ACS	≤ 0.80	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	1 year	Among ACS group, MACE after FFR-guided reclassification of management was similar to non-reclassified patients (8.0 vs. 11.6%; <i>p</i> = 0.20)

Table 1 continued

Study	Year	Design	Patients (n)	Study groups	ACS (%)	FFR cutoff	Definition of primary outcome	Follow-up period	Outcomes
POTVIN et al.	2002–2004	Prospective single-center study	201	Single arm for FFR-guided revascularization	62% ACS	≤ 0.75	MACE: Composite of cardiovascular mortality, MI, and repeat ischemia-driven revascularization	11-month	No difference in MACE among ACS vs. SIHD (9 vs. 13%, <i>p</i> = 0.44) and among patients with and without lesions associated with positive noninvasive test results (9 vs. 10%, <i>p</i> = 1.00)
Fischer et al.	2002–2004	Single-center retrospective observational	111	Single arm for FFR-guided revascularization	32%	≤ 0.75	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	1 year	No difference in MACE among ACS vs. SIHD (28.6 vs. 17.1%, <i>p</i> = 0.21)
Mehra et al.	2002–2010	Single-center retrospective observational	674	Patients with deferred revascularization based on FFR in the setting of ACS versus non-ACS	49.60%	≤ 0.80	MACE: Composite of cardiovascular mortality, MI, and repeat ischemia-driven revascularization in deferred lesions	4.5 years	Among ACS patients with deferred revascularization, every 0.01 decrease in FFR was associated with higher MACE (HR 1.08; 95% CR 1.03–1.12)
Hakeem et al.	2009–2014	Single-center retrospective observational	576	Patients with deferred revascularization based on FFR in the setting of ACS versus non-ACS	35.80%	≤ 0.75	Composite of MI or target vessel failure	3.4 years	Among patients with deferred revascularization, MACE was higher in ACS vs. SIHD (25 vs. 12%; <i>p</i> < 0.001)

Table 1 continued

Study	Year	Design	Patients (n)	Study groups	ACS (%)	FFR cutoff	Definition of primary outcome	Follow-up period	Outcomes
Lee et al.	2003–2011	Multicenter, prospective, registry	1596	Patients with deferred revascularization based on FFR in the setting of NSTEACS versus SIHD	18.9% NSTEACS	≤ 0.80	MACE: Composite of cardiovascular mortality, MI, and repeat ischemia-driven revascularization	2-year	Among patients with deferred revascularization, MACE was higher in ACS vs. SIHD (HR 3.0; 95% CI 1.23–7.17)

FFR fractional flow reserve, iFR instantaneous wave-free ratio, STEMI ST-segment elevation myocardial infarction, NSTEACS non ST-segment elevation acute coronary syndrome, SIHD stable ischemic heart disease

of patients allocated to the physiology-guided optimization arm underwent further intervention. The primary outcome of post-PCI FFR ≥ 0.90 was not different between both groups; however, the proportion of patients with final FFR ≤ 0.80 was reduced in the physiology-guided optimization group (– 11%) [45]. Similarly, residual ischemia using post-PCI iFR was demonstrated to be common in the DEFINE PCI (The Physiologic Assessment of Coronary Stenosis Following PCI) where residual ischemia (iFR < 0.90) was present after angiographic success in 24.0% of 500 patients [51]. At 1 year, post-PCI iFR ≥ 0.95 was associated with lower risk of MACE, compared with iFR < 0.95 (1.8 vs. 5.7%, $p = 0.04$) [52].

Another utility for physiology assessment post-PCI is in cases of bifurcation PCI, in which assessment of jailed side branch after main vessel stenting poses a clinical conundrum. Among jailed side branch lesions with $> 50\%$ stenosis by angiographic assessment, only 28.4% and 27.3% were functionally significant [53, 54]. In a single-center analysis, Lee et al. evaluated patients who underwent LM to left anterior descending (LAD) simple crossover stenting who had FFR measurements in the left circumflex (LCx) coronary artery. Their results showed no correlation between angiographic percent diameter stenosis of jailed LCx and FFR ≤ 0.80 [55]. At 5 years, patients with LCx FFR ≤ 0.80 had higher rates of target lesion failure than those with high FFR values (33.4 vs. 10.7%) [55]. In the DKCRUSH-VI (Double Kissing Crush Versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions VI) trial, FFR-guided side branch treatment reduced the rate of side branch stenting (25.9 vs. 38.1%, $p = 0.01$), and achieved similar 1-year adverse clinical events compared with angiography guidance (Table 2) [56].

Role of FFR in serial lesions

Serial coronary lesions are common and identification of the culprit lesion that causes ischemia using FFR can be challenging. The presence of one stenosis decreases the hyperemic flow across the other and, thus, the apparent FFR of each stenosis is higher than the true FFR. This leads to an underestimation of

Table 2 Studies on the role of FFR post-PCI

Study	Year	Design	Patients (<i>n</i>)	Study groups	Definition of primary outcome	Follow-up period	Outcomes
Pijls et al.	2002	Retrospective multicenter registry	750	Patients undergoing routine PCI who had post-PCI FFR measurements	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	6 months	Post-PCI FFR most significant independent variable correlating with MACE
Nam et al.	2011	Retrospective single-center registry	80	Patients undergoing routine PCI who had post-PCI FFR measurements	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	12 months	MACE correlated with post-PCI FFR < 0.9 (AUC: 0.69)
Leesar et al.	2011	Retrospective single-center registry	66	Among patients who underwent PCI for baseline FFR < 0.75, post- PCI FFR was measured	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	24 months	MACE-free survival lower in patients with final FFR < 0.96 (72 vs. 94%; <i>p</i> = 0.02)
Ito et al.	2014	Retrospective single-center registry	97	Patients undergoing routine PCI who had post-PCI FFR measurements	MACE: Composite of cardiovascular mortality, MI, stent thrombosis and target vessel revascularization	17.8 months	MACE correlated with post-PCI FFR < 0.9 (AUC: 0.82)
Reith et al.	2015	Prospective single-center analysis	66	Patients undergoing PCI for de novo lesions, underwent post-PCI FFR and OCT assessment	MACE: Composite of all-cause mortality, MI, and repeat ischemia-driven revascularization	15.11 months	MACE correlated with post-PCI FFR < 0.9 (AUC: 0.77)
DK- CRUSH VI	2015	Prospective, multicenter, randomized control trial	320	Angiography-guided versus FFR-guided revascularization for patients with single true coronary bifurcation lesion	MACE: Composite of cardiovascular mortality, MI, and repeat ischemia-driven revascularization	12 months	No difference in MACE (HR 0.91; 95% CI 0.48–1.88)
Agarwal et al.	2016	Retrospective single-center registry	574	Patients undergoing routine PCI, who had post-PCI FFR measurements	MACE: Composite of all-cause mortality, MI, and target vessel revascularization	31 months	MACE correlated with post-PCI FFR < 0.86

Table 2 continued

Study	Year	Design	Patients (<i>n</i>)	Study groups	Definition of primary outcome	Follow-up period	Outcomes
DK-CRUSH VII	2017	Prospective multicenter analysis	1476	Among patients who underwent PCI for baseline FFR < 0.80, post-PCI FFR was measured	Target vessel failure: cardiac mortality, target vessel-related MI, and TVR	36 months	Post-PCI FFR ≤ 0.88 was the only predictor of TVF (≤ 0.91 for LAD)
Piroth et al.	2017	Retrospective analysis from prospective multicenter clinical trials	639	All patients of FAME 1 and FAME 2 who had post-PCI FFR measurement were included	Vessel-related cardiovascular mortality, vessel-related spontaneous MI, and ischemia-driven target vessel revascularization	24 months	Post-PCI FFR of 0.92 had highest diagnostic accuracy for predicting adverse events; but with low specificity (43%) and sensitivity (75%)
Azzalini et al.	2019	Prospective single-center analysis	95	Among patients who underwent PCI for baseline FFR < 0.80, post-PCI FFR was measured	MACE: Composite of cardiovascular mortality, MI, readmission for angina and repeat ischemia-driven revascularization	12 months	MACE higher in patients with final FFR < 0.90 (31.6 vs. 9.1%; <i>p</i> = .047)
Hwang et al.	2019	Prospective multicenter registry	835	Patients undergoing PCI with DES, who had post-PCI FFR measurements	Target vessel failure: cardiac mortality, target vessel-related MI, and TVR	24 months	Post-PCI FFR predicted TVF, with cutoff of 0.82 and 0.88 in the LAD and non-LAD

Table 2 continued

Study	Year	Design	Patients (n)	Study groups	Definition of primary outcome	Follow-up period	Outcomes
FFR-SEARCH	2020	Prospective multicenter analysis	959	Among patients who underwent PCI, post-PCI FFR was measured at the end of the procedure	MACE: Composite of cardiovascular mortality, MI, and repeat ischemia-driven revascularization	24 months	Patient-level analysis showed no association between MACE and post-PCI FFR. Vessel-level analysis showed higher TVR with FFR < 0.90
TARGET-FFR	2021	Prospective, single-center, randomized control trial	260	After angiographically guided PCI, patients were randomized to receive a physiology-guided incremental optimization strategy or a blinded coronary physiology assessment (control group)	Proportion of patients with a final post-PCI FFR > 0.90	In-hospital	No difference in primary outcome; but FFR-guided optimization reduced the proportion of patients with a final FFR < 0.80 (− 11.2%, 95% CI − 21.87 to − 0.35, <i>p</i> = 0.045)

FFR fractional flow reserve, *iFR* instantaneous wave-free ratio, *AUC* area under the curve, *OCT* optical coherence tomography, *TVF* target vessel failure, *LAD* left anterior descending

the lesion severity (for both the proximal and distal lesions), the so-called “crosstalk phenomenon” [57–60]. Several solutions have been suggested to overcome this limitation. Pijls et al. proposed a formula that incorporates coronary occlusive wedge pressure but this is limited by requiring balloon inflation in patients who may not need intervention [59, 60]. Modi et al. proposed a new equation that does not require coronary wedge pressure to predict the true FFR [58, 61]. However, none of these are practically available widely. A more practical solution to assess the severity of serial

lesions is FFR measurement using pullback pressure recording. FFR pullback helps in determining the lesion with the largest pressure step-up (i.e., primary lesion) that warrants revascularization. Three phenotypes of FFR pullback curves in serial coronary lesions are described: (1) diffuse disease without FFR pressure step-ups, (2) FFR pullback with one step-up (i.e., one drop) and (3) FFR pullback with more than one step-up. Studies showed that in both proximal and distal lesions, there was an increase in the pressure step-up after treating the primary lesion [57, 59, 60]. Kim et al.

conducted FFR measurements for 131 patients with serial intermediate stenosis [57]. Among vessels with $FFR < 0.8$, pullback pressure recording was performed, and the stenosis that caused the largest pressure step-up was treated first then a repeat FFR measurement was done to determine the functional significance of the other stenoses. As a result of this strategy, revascularization was deferred in 61% of lesions, none of them were associated with adverse clinical events during follow-up. A major limitation of FFR pullback method is the requirement to use intravenous adenosine (as opposed to intracoronary boluses) (Table 3).

Serial Lesions Involving Left Main Coronary Artery Disease

A unique example of serial lesions includes those involving an intermediate lesion in the LMCA and significant lesion in downstream epicardial vessel, i.e., LAD or LCx. In such a clinical scenario, FFR assessment of LMCA by positioning the pressure wire in that diseased downstream vessel would be affected because the distal LAD stenosis would falsely decrease the trans-lesion gradient across LMCA stenosis [62]. Conversely, it is feasible to perform FFR assessment of LMCA stenosis by positioning the pressure wire in the non-diseased downstream vessel (e.g., LCx if stenosis exists in LAD and vice versa). In vitro studies suggested that downstream disease in LAD or LCx would not significantly affect FFR assessment of LMCA by positioning wire in the non-diseased vessel, unless FFR of diseased vessel was severely reduced (≤ 0.45) [63]. Fearon et al. evaluated 25 patients undergoing PCI of LAD or LCx, in whom an intermediate stenosis was created in the LMCA by a deflated balloon catheter. The authors measured FFR in LAD and LCx vessels before and after inflating an angioplasty balloon within the newly placed stent to create downstream stenosis. FFR of the LMCA measured in non-diseased vessel in absence of stenosis in the other vessel (i.e., FFR_{true}) was compared with $FFR_{apparent}$ of the LMCA, measured after balloon inflation in diseased downstream vessel. Results showed that FFR_{true} was numerically lower than

the $FFR_{apparent}$ (0.81 ± 0.08 vs. 0.83 ± 0.08 , $p < 0.001$), but without a clinically meaningful difference. The authors concluded that in most cases with intermediate LMCA lesion and significant downstream disease, FFR assessment of LMCA could be reliably obtained through the non-diseased vessel. Only in cases with FFR values of 0.80–0.85 and severely reduced FFR of the diseased vessel (≤ 0.45), it is possible that true FFR of LMCA would be ≤ 0.80 after revascularization of downstream stenosis.

Given the concerns regarding crosstalk phenomenon when evaluating physiology of serial stenoses under hyperemic conditions, more interest has been directed towards resting physiological indices, particularly iFR pullback. Bench studies suggest that hemodynamic interference of serial stenoses has a negligible impact on iFR measurement; unlike FFR, where serial stenoses could lead to variable errors in FFR measurements [64]. Moreover, few clinical studies have suggested that iFR pullback is more reliable in physiologically mapping coronary vessels and predicting post-PCI physiological outcomes. Nevertheless, further large-scale studies are still warranted to better characterize the role of these modalities on clinical outcomes of patients with serial stenosis [4, 64, 65].

Role of FFR in Aortic Stenosis

In severe aortic stenosis (AS), the systolic coronary flow is reduced and coronary microvascular resistance is commonly reduced; hence, adequacy of physiologic testing might be questionable in such cases [66]. Studies examining the FFR measurements before and immediately after TAVR suggested that hyperemic coronary indices are influenced by AS treatment [67, 68]. Pesarini et al. conducted FFR assessment of 133 lesions in 54 patients undergoing TAVR. They showed that positive FFR values (≤ 0.8) at baseline were significantly decreased after TAVR (0.71 ± 0.11 vs. 0.66 ± 0.14), while negative FFR values (> 0.8) at baseline improved after the procedure (0.92 ± 0.06 vs. 0.93 ± 0.07) [68]. Similarly, Ahmed et al. showed that FFR values for intermediate coronary stenoses decreased immediately post TAVR [69]. However, accuracy of hemodynamic assessment immediately after TAVR has been challenged in several reports.

Table 3 Studies on the role of FFR in serial lesions

Study	Year	Design	Study group(s)	Patients (n)	Lesions (n)	FFR cutoff (%)	ACS (%)	MVD (%)	Stents implanted (n)	Deferred lesions (%)	Follow-up period (days)	MACE definition	Study outcomes
Candrea et al.	2021	Prospective multicenter study	One group: FFR was measured using motorized pullback pressure recordings in patients who had serial intermediate coronary stenoses	23	51	0.8	NR	73.9	NR	NR	None	NR	Three patterns of FFR pullback curves were identified; no step up, 1 step up, and 2 step ups
Modi et al.	2020	Prospective	One group: apparent FFR, true FFR, Pd/Pa and iFR were measured in patients with serial lesions using manual pullback. Additionally, the predicted FFR was calculated using a novel equation	54	NR	0.8	NR	NR	NR	NR	None	NR	Stenosis misclassification rates based on FFR 0.80, iFR 0.89, and Pd/Pa 0.91 thresholds were not significantly different (17, 24, and 20%, respectively) but were higher than predicted FFR (11%, $p < 0.001$)
Kim et al.	2012	Prospective multicenter study	One group: FFR measurements with pullback pressure recordings in patients who had serial intermediate coronary stenoses	131	298	0.8	22.1	66.1	116	61.1	501 ± 311	Cardiac death, target vessel-related MI, and TVR	TLR of stented lesion: 1, TLR of deferred lesion: 0 Cardiac death: 0 Target vessel related MI: 0, nontarget vessel related MI: 1

Table 3 continued

Study	Year	Design	Study group(s)	Patients (n)	Lesions (n)	FFR cutoff	ACS (%)	MVD (%)	Stents implanted (n)	Deferred lesions (%)	Follow-up period (days)	MACE definition	Study outcomes
Pijls et al.	2000	Prospective	One group: apparent FFR, predicted FFR and true FFR were measured in patients undergoing PTCA and had ≥ 2 serial stenoses	32	64	NR	NR	NR	36	43.75	None	NR	Compared with true FFR, the percent differences were $4 \pm 0\%$ for predicted FFR and $11 \pm 12\%$ for apparent FFR. The differences between apparent FFR and true FFR were larger for the proximal stenosis than for distal stenosis ($14 \pm 16\%$ versus $9 \pm 8\%$, respectively; $p < 0.01$)

FFR fractional flow reserve, iFFR instantaneous flow reserve, MACE major adverse cardiovascular events, ACS acute coronary syndrome, MVD multivessel disease, NR not reported, Pd/Pa resting ratio of distal aortic coronary pressure, MI myocardial infarction, TLR target vessel revascularization, TLR target lesion revascularization, PTCA percutaneous transluminal coronary angioplasty

Moreover, a study evaluating FFR values before and 6–8 weeks after TAVR showed no significant difference in FFR values (0.77 ± 0.04 vs. 0.76 ± 0.08 ; $p = 0.11$) [67]. Others have compared the diagnostic accuracy for FFR versus perfusion scintigraphy-identified myocardial ischemia among patients with intermediate coronary stenosis and severe AS, and showed good correlation between both testing modalities in identifying myocardial ischemia [70]. In a study of 318 patients with moderate or severe AS and concomitant intermediate stenosis, FFR-guided revascularization was associated with similar clinical outcomes compared with angiography-guided revascularization at 5 years [71].

Resting physiological indices might carry an advantage among patients with severe AS who might not tolerate vasodilators challenge. Among patients with intermediate coronary stenosis and severe AS, there was a good correlation between iFR and FFR measurements ($R = 0.854$) [70]. In a study of iFR among 55 patients with intermediate coronary stenosis undergoing TAVR, there was no change in iFR values pre- and post-TAVR. However, they also demonstrated an increase in microvascular resistance after TAVR, which was independent of the severity of underlying CAD. When contrasting these results to a control group of patients undergoing PCI (with available pre- and post-PCI iFR), the authors concluded that TAVR results in hemodynamic improvement for moderate coronary lesions, similar to the hemodynamic benefit of stenting coronary stenoses with iFR values < 0.74 (Table 4) [66].

Overall, determining functionally significant coronary lesions might be challenging among patients with severe AS. Changes in coronary blood flow and microvascular resistance might be attributed to the valvular disorder and not epicardial coronary disease among patients with AS, a statement particularly relevant among patients with borderline physiological testing results. Studies suggest that iFR may be a better tool given the more stable results shown in pre- and post-TAVR patients, and the ability to avoid use of adenosine. In the use of FFR, a value ≤ 0.75 definitely indicates a flow-limiting lesion, and $\text{FFR} \geq 0.85$ a physiologically non-

significant lesion. FFR values in between those values can be more difficult to interpret.

Role of FFR in Heart Failure

Several theoretical concerns exist regarding the utility of FFR among patients with heart failure who were not represented in the major FFR clinical trials [8, 23]. The current simplified FFR calculation ($\text{FFR} = P_a/P_d$) does not take into account P_v values. The elevated left ventricular end diastolic pressure (LVEDP) and decreased viable myocardial mass among patients with heart failure could affect coronary flow and the accuracy of FFR measurements. Small-sized reports suggested that the simplified FFR led to misclassification of lesions as insignificant when P_v was ignored [72, 73]. On the contrary, Toth et al. examined the differences between simplified FFR and FFR_{myo} in 1675 stenoses from 1235 patients [74]. The median difference between FFR and FFR_{myo} was 0.01 (IQR 0.00–0.01). Out of 1146 stenoses with an $\text{FFR} > 0.80$, only 110 (9%) stenoses had $\text{FFR}_{\text{myo}} \leq 0.80$ with a median difference of 0.02 (IQR 0.02–0.03). Additionally, when applying a fixed P_v values model (5, 10, and 20 mmHg), in the 5- and 10-mmHg groups, values of $\text{FFR} > 0.80$ never yielded an $\text{FFR}_{\text{myo}} \leq 0.75$; whereas in the 20-mmHg group, only 4% of the cases had an $\text{FFR}_{\text{myo}} \leq 0.75$ [74]. Di Gioia et al. conducted a retrospective analysis of 433 patients with reduced LVEF ($\leq 50\%$) who underwent FFR-guided revascularization and were matched to a contemporary cohort of patients who underwent angiography-guided revascularization [75]. Patients with reduced LVEF who underwent FFR-guided revascularization had lower 5-year mortality and MACCE compared with the angiography-guided group [75].

Minimal data exist regarding the use of resting physiological indices among patients with heart failure. A study of 103 patients showed that iFR was negatively correlated with doppler-derived E/e' , while there was no correlation between FFR and E/e' [76]. Another study showed significant discordance between FFR and iFR values among patients with elevated LVEDP, which was not present among those with normal LVEDP. This likely suggests that resting diastolic indices such as iFR are likely

Table 4 Studies on the role of FFR in aortic stenosis

Study	Year	Design	Patients (n)	Study group(s)	FFR cut off	Method of adenosine administration	Degree of AS	Treatment of AS	Follow-up period	MACE definition	Outcomes
Strundl et al.	2020	Prospective study	246	<i>One group:</i> FFR measured before TAVR and 6–8 weeks after TAVR. FFR-positive intermediate lesions were left untreated in the first instance; 6–8 weeks following TAVR, both the coronary angiography and the FFR measurement were repeated. Revascularization was then performed according to the FFR values after successful TAVR	0.8	IV infusion	Severe	TAVR	1 year	NR	No significant difference between FFR pre and post TAVR (0.77 ± 0.04 vs. 0.76 ± 0.08 ; $p = 0.11$) 1-year all-cause mortality 8.5%, stroke 1.6%, MI 0%
Scarsini et al.	2019	Retrospective study	268	Patient with AS who underwent FFR assessment ($n = 137$) vs. those without AS ($n = 154$)	0.8	IV infusion or IC boluses	Moderate and Severe	NR	NR	NR	In propensity-matched analysis, no difference in FFR between severe AS vs. mod AS vs. no AS (0.81 ± 0.11 vs. 0.81 ± 0.08 vs. 0.80 ± 0.1 , $p = 0.72$)
Ahmad et al.	2018	Prospective study	28	<i>One group:</i> FFR/iFR measurements were done before and immediately after TAVR	NR	IC boluses	Severe	TAVR	NR	NR	FFR decreased post TAVR (0.87 ± 0.08 pre-TAVR vs. 0.85 ± 0.09 post-TAVR; $p < 0.01$) iFR did not change post TAVR (0.88 ± 0.09 pre-TAVR vs. 0.88 ± 0.09 post-TAVR; $p = 0.73$)

Table 4 continued

Study	Year	Design	Patients (n)	Study group(s)	FFR cut off	Method of adenosine administration	Degree of AS	Treatment of AS	Follow-up period	MACE definition	Outcomes
Scarsini et al.	2017	Retrospective study	252	FFR/iFR measured in patients with severe AS (n = 85) vs. in those without AS (n = 167)	0.8	IC boluses	Severe	TAVR	NR	NR	Using the 0.89 iFR cut-off, the diagnostic accuracy of iFR was significantly lower in AS vs. no AS (76.3 vs. 86.1%, p < 0.01)
Gioia et al.	2016	Retrospective study	318	Patients with AS who underwent FFR-guided revascularization n = 106 vs. who underwent angio-guided revascularization (n = 212)	0.8	NR	Moderate and Severe	SAVR	5 years	All-cause mortality, MI, and repeat revascularization	Best iFR cut-off in predicting FFR < 0.80 in patients with AS was 0.83 No differences were found between both groups in terms of MACE (38 vs. 39%, p = 0.98) and other study outcomes (mortality, MI, revascularization, AVR)
Pesarini et al.	2016	Prospective study	54	One group: FFR measured before and immediately after TAVR	0.8	IC boluses	Severe	TAVR	30 days	All-cause mortality, MI, stroke, angina, rehospitalization due to angina at rest or heart failure	Overall, FFR did not change post TAVR (0.89 ± 0.10 pre versus 0.89 ± 0.13 post; p = 0.73) Positive FFR values worsened after TAVR (0.71 ± 0.11 versus 0.66 ± 0.14) Conversely, negative FFR values improved after TAVR (0.92 ± 0.06 versus 0.93 ± 0.07) No MACE during follow-up

TAVR transcatheter aortic valve replacement, IV intravenous, IC intracoronary, AS aortic stenosis, SAVR surgical aortic valve replacement

Table 5 Studies on the role of FFR in heart failure

Study	Year	Design	Patients (<i>n</i>)	Study group(s)	FFR cut off	Follow- up period	Mean Pra	Outcomes
Digioia et al.	2020	Retrospective single- center analysis	1299	FFR-guided revascularization in patients with LVEF < 50% vs. matched group undergoing angiography-guided revascularization	0.8	60 months	NR	MACCE was lower at 5-year in FFR- guided versus angiography-guided groups (HR 0.81; 95% CI 0.67–0.97)
Toth et al.	2016	Prospective, single-arm study	1235	<i>One group:</i> FFR was measured with and without Pra in patients who underwent LHC/RHC with FFR measurement in at least one coronary stenosis	NR	None	7 (median)	The median difference between FFR and FFRmyo was 0.01 (IQR: 0.01–0.02) Out of 1146 stenoses with an FFR > 0.80, none had an FFRmyo < 0.75, and 110 (9%) stenoses had an FFRmyo < 0.80
Layland et al.	2013	Prospective, single-arm study	42	<i>One group:</i> FFR was measured with and without Pra in patients undergoing elective PCI	0.8	None	9.1	The mean FFR was significantly lower when Pra was included in the calculation (FFRmyo 0.77 ± 0.19 vs. FFR 0.80 ± 0.16, <i>p</i> < 0.001) An additional nine patients (21%) would have been reclassified as having an FFR ≤ 0.8 if Pra was incorporated into FFR calculation before PCI
Perera et al.	2004	Prospective, single-arm study	66	<i>One group:</i> FFR was measured with and without Pra	0.75	None	5.5	12 functionally significant stenoses (14% of all lesions) were misclassified as insignificant when Pra was ignored The sensitivity of FFR for detecting significant coronary lesions was reduced to 64% when Pra was ignored

LVEF left ventricular ejection fraction, *Pra* right atrial pressure, *HR* hazard ratio, *CI* confidence interval, *LHC* left heart catheterization, *RHC* right heart catheterization, *FFRmyo* myocardial FFR, *IQR* interquartile range, *PCI* percutaneous coronary intervention

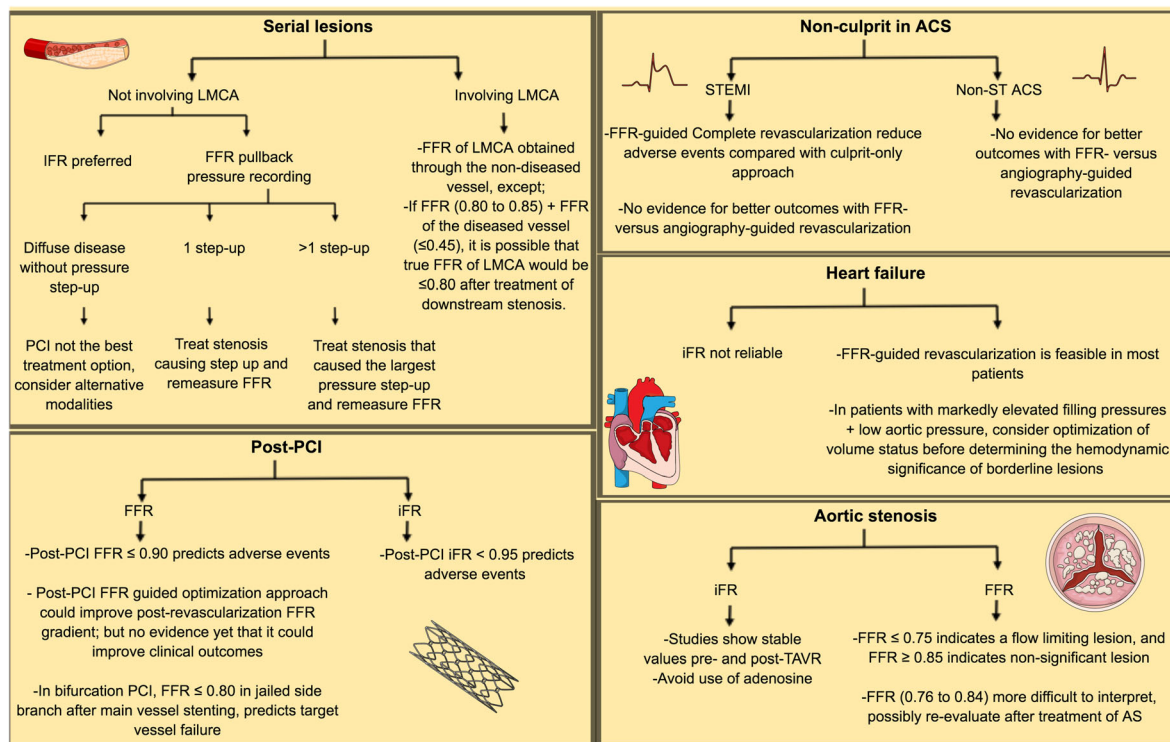


Fig. 1 Summary for use of FFR/iFR in special patients subgroups

influenced by LVEDP, independent of epicardial stenosis (Table 5).

Based on the above data, FFR-guided revascularization is feasible among patients with heart failure, except for patients with markedly elevated P_v and low aortic pressure, i.e., patients with severe heart failure or cardiogenic shock. In this particular group of patients, optimization of volume status before PCI may be more important than determining the hemodynamic significance of borderline lesions.

CONCLUSIONS

The assessment of coronary physiology might be more challenging among the presented patients’ subsets in this review. We outlined an evidence-based approach for utilizing FFR or iFR among these patients’ subsets. However, in virtually all the presented patients’ subsets in this review, coronary flow hemodynamics might be altered due to other cardiac causes beyond the interrogated epicardial stenosis. As such, a

comprehensive assessment of coronary physiology, including CFR, is encouraged whenever feasible, and decision-making for these patients should take into account clinical presentation and results of non-invasive testing.

Future Directions

Despite the big body of evidence supporting the use of FFR in numerous clinical scenarios (Fig. 1), FFR remains significantly underutilized. However, recent reports suggested a slow but steady rise in the utilization of FFR in the United States in recent years [77]. With further adoption of appropriate use criteria for PCI, coronary physiology evaluation via FFR would be expected to continue to rise in contemporary PCI [77]. Moreover, ongoing clinical trials will help in improving patient selection for FFR by providing more insight into the use of FFR in specific subgroups of patients, including those with aortic stenosis, ACS, and post-PCI evaluation. Notably, further long-term safety data are warranted regarding iFR-guided

revascularization, in light of the signal for harm noted in the 5-year data from the DEFINE-FLAIR trial [29].

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