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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve

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ABSTRACT

In this review, the authors reflect upon the role of coronary physiology in the modern management of coronary artery disease. They critically appraise the scientific background of the instantaneous wave-free ratio (iFR) and fractional flow reserve (FFR), from early experimental studies to validation studies against indexes of ischemia, to clinical trials assessing outcome. At this important juncture for the field, the authors make predictions for the future of physiological stenosis assessment, outlining developments for both iFR and FFR in new clinical domains beyond the confines of stable angina. With a focus on the evolving future of iFR and FFR, the authors describe how physiological assessment with iFR may advance its application from simply justifying to guiding revascularization. (J Am Coll Cardiol 2017;70:1379–402)

Since the introduction of fractional flow reserve (FFR) more than 20 years ago (1), physiology-guided revascularization has become an established practice in the modern, evidence-based management of patients with coronary artery disease. The central premise of coronary physiology is that it permits identification of myocardial ischemia on a per-vessel basis, measurable at the time of clinical decision making. This aids the selection of stenoses (and therefore patients) likely to benefit from revascularization.

FFR carries a Class 1a recommendation for guiding revascularization in angiographically intermediate coronary stenoses in patients with stable angina (**Table 1**) (2,3). However, despite this, uptake of FFR in coronary catheter laboratories worldwide has remained low (**Figure 1**). Potential reasons for the low adoption rate of coronary physiology despite demonstrated clinical benefit of its use may include time consumption to perform FFR measurements, costs associated with adenosine, or in certain countries, no availability of adenosine, patient-related discomfort, contraindications, or lack of reimbursement. Recently, there has been renewed interest and development in the field of coronary physiology, driven by the introduction of a new, nonhyperemic

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AUC = area under the curve

CABG = coronary artery bypass grafting

CFR = coronary flow reserve

CI = confidence interval

FFR = fractional flow reserve

FFRmyo = myocardial fractional flow reserve

HR = hazard ratio

HSR = hyperemic stenosis resistance

iFR = instantaneous wave-free ratio

MACE = major adverse cardiac events

MI = myocardial infarction

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

PET = positron emission tomography

STEMI = ST-segment elevation myocardial infarction

WFP = wave-free period

WIA = wave intensity analysis

pressure-based index of stenosis severity: the instantaneous wave-free ratio (iFR) (4).

Five years after its initial introduction, 2 large, prospective, randomized trials have concordantly reported noninferiority of iFR when compared with FFR for guiding revascularization (5,6). More importantly, the data yielded from these studies have provided a marked expansion of the patient outcome data available for coronary physiology as a whole. At this important juncture for the field, we pause to critically review how far the techniques and scientific testing for physiological stenosis assessment have progressed, and look forward to the techniques and applications that will define the future of coronary physiology. Specifically, we address the evolving future of iFR and FFR for physiological stenosis assessment.

CORONARY PHYSIOLOGY IN THE PRE-FFR ERA

The purpose-built pressure wires currently used to make coronary physiology measurements are the result of years of development and miniaturization of pressure sensor technology. However, in the pioneering procedures of Andreas Grüntzig in the late 1970s, such high-fidelity equipment was not available. Nevertheless, the importance of quantifying the hemodynamic impact of a coronary stenosis (and the resultant response to balloon angioplasty) led Grüntzig et al. (7) to measure and report the trans-stenotic pressure gradient through the fluid-filled guiding catheter. However, owing to the significant impediment to antegrade flow imposed by the catheters themselves, trans-stenotic pressure recordings failed to gain acceptance after it was demonstrated that the measurement was not always reliable (8).

In the early 1990s, as intracoronary pressure and flow velocity sensor-tipped guidewires became sufficiently miniaturized, a host of additional coronary physiology measurements were proposed (**Table 2**) (9). Furthermore, the notion of performing measurements during hyperemia emerged. In the early days of coronary physiology, efforts to quantify the hemodynamic impact of a stenosis focused mainly upon the measurement of coronary flow, rather than pressure. Instead, the pressure component of combined coronary pressure and flow indexes were considered merely supportive of why flow may not increase or increase abnormally in response to an impaired distal hyperemic response (9).

FFR: INTRODUCTION AND EXPERIMENTAL VALIDATION

In 1993, Pijls et al. (1) published work on FFR. Unlike preceding approaches to coronary physiological assessment, FFR specifically sought to determine coronary flow assessment by using pressure-only-based assessments during hyperemia. By expanding upon the earlier work of Gould (10), who had described the coronary circulation as an electrical circuit of variable serial resistances, with the stenosis of the epicardial artery being one component, Pijls applied Ohm's Law ($V = IR$, where V is the voltage difference, I is the current, and R is the resistance) to rationalize that when coronary resistance was stable and minimal (as occurred during maximal arterial dilation) (11,12), a direct relation between coronary pressure and flow could be presumed.

FFR is defined as the ratio of the pressure distal to a stenosis (Pd) relative to the pressure proximal to the stenosis (Pa) during hyperemia induced by a vasodilating agent. Accordingly, an FFR value of 0.80 represents a 20% pressure loss across the stenosis. This theory was tested experimentally in 5 anesthetized dogs in whom pressure-derived FFR was compared with Doppler-derived fractional coronary artery flow reserve in surgically dissected, balloon-ligated proximal circumflex arteries during intracoronary administration of papaverine (1). Despite the inherent differences between human and animal models, in these early experiments, Pijls et al. (1) demonstrated that FFR could theoretically be used under idealized experimental conditions to determine the flow-limiting potential of a coronary artery stenosis. Although the calculated values of FFR correlated closely with those directly measured by a Doppler velocity meter, replotting the data as a Bland-Altman plot shows that the pressure- and flow-derived FFR values are less tightly associated, as may be suggested by the correlations (**Figure 2**).

Nowadays, only a simplified version of FFR is used clinically, whereby the right atrial pressure measurement is omitted. However, the description of FFR to individually quantify myocardial (FFRmyo), coronary, and collateral components of the coronary circulation (**Table 3**) helped validate the concept and engender continued research in humans.

FFR: FROM THE ANIMAL TO THE HUMAN MODEL

Early studies of FFR in the human model focused on establishing FFR cutoff values for the detection of inducible ischemia, defined by a variety of

TABLE 1 Guideline Recommendations for the Use of FFR

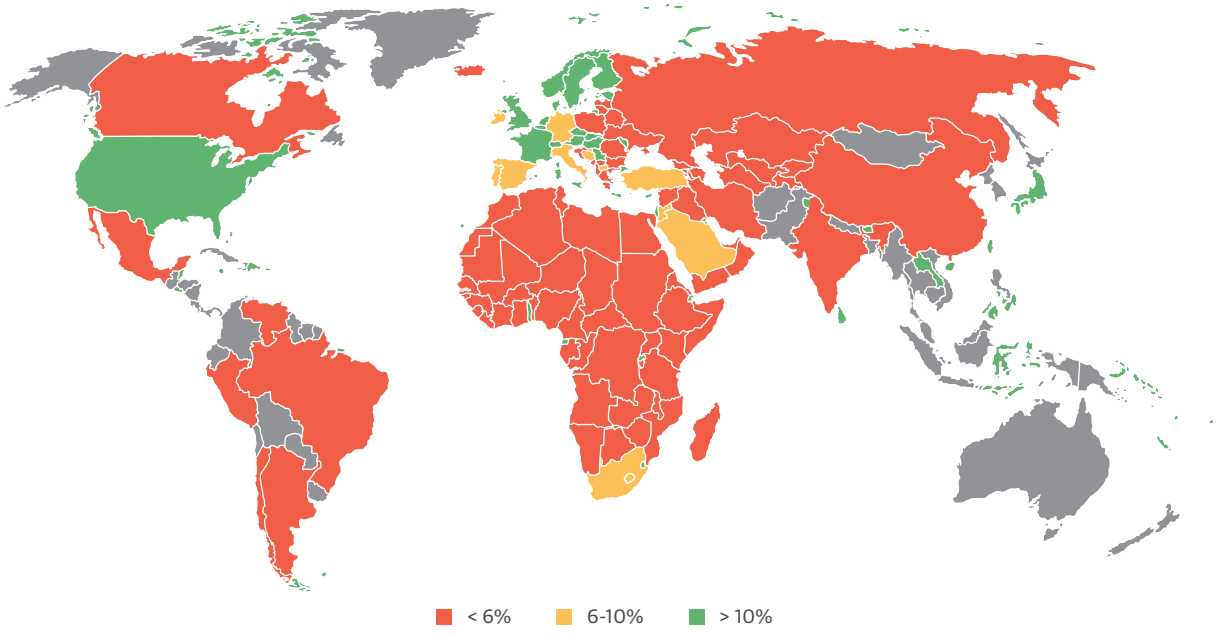
Organization(s)	Guideline Title	Year of Publication	Recommendation	Class	Level of Evidence
European Society of Cardiology and the European Association for Cardio-Thoracic Surgery	Guidelines on myocardial revascularization	2014	FFR to identify hemodynamically relevant coronary lesion(s) in stable patients when evidence of ischemia is not available (3)	1	A
American College of Cardiology/American Heart Association, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons	Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	2012	For recommendations about revascularization, coronary stenoses with FFR ≤0.80 can also be considered to be significant (2)	NA	NA
American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons	Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease	2017	If no stress test performed or, if performed, results are indeterminate, FFR ≤0.80 can be used to determine appropriateness of revascularization (35)	NA	NA

FFR = fractional flow reserve; NA = not applicable.

noninvasive tests. The first of these studies used exercise treadmill testing pre- and post-percutaneous transluminal coronary angioplasty in a total of 60 patients with single-vessel disease and normal left ventricular function (13).

The key findings of this first-in-man study demonstrated that a cutoff value of FFRmyo <0.75 accurately discriminated between lesions associated with inducible ischemia and those not, as defined by exercise treadmill testing. Moreover, the hypothesis

FIGURE 1 Global Adoption of Coronary Physiology to Guide Revascularization Decision Making in 2016



Despite clinical guideline recommendations for its use, the uptake of fractional flow reserve in coronary catheter laboratories worldwide remains low. Reproduced with permission from Philips Volcano, market research report by Decision Resources Group.

TABLE 2 Pre-FFR-Era Coronary Physiology Indexes

Index	Physiological Parameter	Advantages	Disadvantages
Trans-stenotic gradient at rest	Pressure	Provides a quantifiable measure of the acute hemodynamic change after coronary intervention Hyperemia not required	Systematic overestimation of physiological severity due to partial obstruction of antegrade flow by measuring catheter (9)
Trans-stenotic gradient during hyperemia	Pressure	Provides a quantifiable measure of the acute hemodynamic change after coronary intervention Hyperemia magnifies the pressure gradient signal, facilitating easier quantification	Absence of a significant hyperemic trans-stenotic pressure gradient is physiologically ambiguous: values can be related to the absence of a flow-limiting stenosis or to the presence an impaired distal vasodilator response to hyperemia Hyperemia required
CFR	Flow	Well validated for the detection of a lesion of increasing severity Measurement of flow (rather than pressure) is physiologically more intuitive for the identification of ischemia	Lack of a definitive normal value CFR values can be influenced by hemodynamics, loading conditions and contractility (57) An abnormal CFR does not delineate between epicardial and microvascular disease Similar CFR values may be obtained at different levels of resting and hyperemic flow Hyperemia required
Maximal hyperemic coronary flow velocity	Flow	Indicative of the increase in coronary conductance achieved with balloon angioplasty	Abnormal maximal hyperemic coronary flow velocity does not delineate between epicardial and microvascular disease Hyperemia required
Slope of the relation between mean gradient and coronary flow	Pressure and flow	The slope of this relation is inversely correlated with the resistance of the stenotic lesion	Use of mean gradient and flow velocities at baseline and maximal hyperemia oversimplifies coronary pressure/flow relationships (9) Hyperemia required
Slope of the instantaneous hyperemic flow velocity/pressure relation	Pressure and flow	Provides a more comprehensive interpretation of the fluid dynamics across the stenotic lesion, as well as of the myocardial capillary circulation	Offline calculation limits clinical applicability and prevents use in unselected patients Hyperemia required

CFR = coronary flow reserve; FFR = fractional flow reserve.

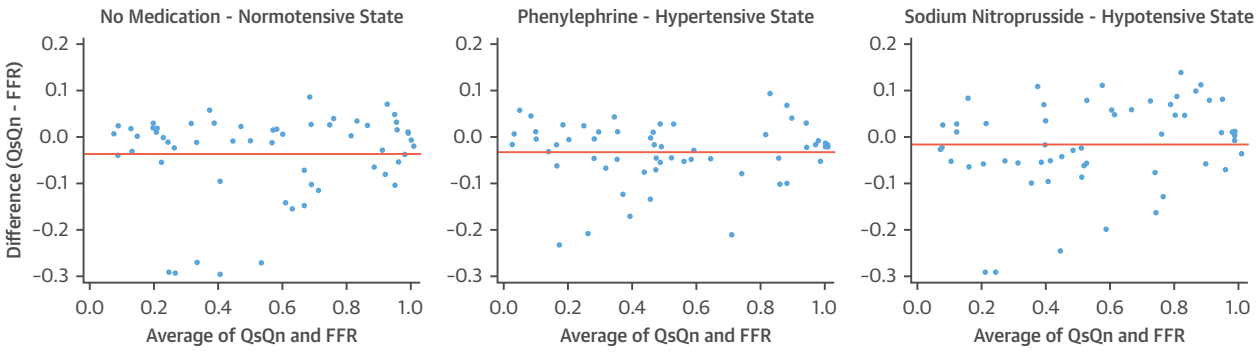
that FFRmyo of angiographically normal stenoses should equal ~1.0 was supported by the subgroup of 5 patients (18 unobstructed vessels) who had a mean FFRmyo value of 0.98 ± 0.03.

Multiple comparisons have since been made between FFR and a range of noninvasive ischemia tests spanning a variety of clinical settings and using a spectrum of pharmacological vasodilator agents (Table 4). Important findings across this more disparate dataset transpired. Firstly, the so-called FFR gray zone emerged as a concept following the observation that the specificity of FFR for the identification of ischemia compared with noninvasive testing decreased in the FFR 0.76 to 0.80 range. Secondly, the overall diagnostic accuracy of FFR (i.e., classification agreement between FFR and noninvasive tests) for the detection of ischemia was approximately 80%. This fair, but imperfect, level of agreement between FFR and other ischemic indexes reflects the lack of a true gold standard test for ischemia, with the limitations of each modality effectively ever preventing a perfect test for ischemia detection. Although FFR is often regarded as representing such a gold standard, it must be remembered that the validation of FFR for ischemia detection is derived from small studies in study patients with severe disease using noninvasive comparators contemporaneous in the early 1990s. Additionally, although measurement reproducibility with FFR is excellent, because most clinical populations cluster close to the clinical cutpoints, it means that it is difficult to attain levels of diagnostic accuracy in excess of 80%, even when FFR is compared against itself (Figure 3).

FFR AND CLINICAL OUTCOME STUDIES

The early FFR ischemia detection studies provided important foundations for the design of subsequent FFR patient outcome studies. Of particular importance were the establishment of a single FFR "ischemic" cutoff value and the observation that

FIGURE 2 Bland-Altman Analysis of Pressure-Derived FFR and Doppler-Derived Fractional Coronary Artery Flow Reserve



The original validation work for FFR measured a true FFR by directly measuring flow velocity in the presence and absence of an artificially introduced stenosis (Qs/Qn). Replotting the data as a Bland-Altman plot shows that the Qs/Qn values are less tightly associated as may be suggested by linear correlations. Reproduced with permission from Nijjer et al. (54). FFR = fractional flow reserve; Qn = flow velocity in the absence of a stenosis; Qs = flow velocity in the presence of a stenosis.

deferral of revascularization according to the FFR >0.75 cutoff value appeared to be safe.

THE DEFER STUDY. To help define the potential role of FFR as a generalizable tool for clinical decision making, the prospective, randomized the DEFER (Deferral Versus Performance of PTCA [percutaneous transluminal coronary angioplasty] in Patients Without Documented Ischemia) study was conducted (14). In this study, a total of 325 patients with stable coronary disease and intermediate lesions referred for PTCA underwent FFR and subsequent randomization to 1 of 3 groups. If the FFR were >0.75, patients were randomly assigned to deferral (deferral group: n = 91) or performance (performance group: n = 90) of PTCA. If the FFR were <0.75, PTCA was performed as planned (reference group: n = 144). The primary endpoint was the absence of adverse cardiac events during 24 months of follow-up. Subsequent to this originally reported endpoint, longer-term follow-up of the DEFER cohort is now available at 5 years (15) and 15 years (16). Across this broad timespan, the core messages that, in patients with stable coronary disease, deferral of stenoses with FFR >0.75 is comparatively safe and that revascularization of stenoses with FFR >0.75 confers no additional therapeutic benefit has remained.

THE FAME STUDY. With data from the DEFER study supporting that medical therapy alone was likely as effective as revascularization in nonischemic coronary stenoses, the FAME (Fractional Flow Reserve versus Angiography for Multi vessel Evaluation) study was performed to assess the clinical effectiveness of an FFR-guided versus angiography-guided approach to revascularization in patients with multivessel coronary artery disease (17). In this prospective, multicenter trial, 1,005 patients with at least 50% stenosis of the vessel diameter in at least 2 of the 3 major epicardial coronary arteries were randomly assigned to undergo percutaneous coronary intervention (PCI) with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements. A notable difference from any of the previous FFR studies (1,18,19) was the upward adjustment of the FFR cutoff for hemodynamic significance from <0.75 (referred to as the ischemic cutpoint) to ≤0.80 (referred to as the clinical cutoff value). The rationale for this was that FFR >0.80 had

TABLE 3 Calculations of Myocardial, Coronary, and Collateral FFR

Component of Coronary Circulation	FFR Derivative	Equation	Considerations
Myocardium	FFRmyo	Pd − Pv Pa − Pv	Requires measurement of mean right atrial pressure. Is dependent on the health of the microcirculation.
Epicardial coronary artery	FFRcor	Pd − Pw Pa − Pw	Requires measurement of mean coronary wedge pressure or distal coronary pressure during balloon inflation. Is dependent on the health of the microcirculation.
Collateral supply	Collateral FFR	FFRmyo − FFRcor	Requires measurement of mean coronary wedge pressure or distal coronary pressure during balloon inflation. Is dependent on the health of the microcirculation.

FFR = fractional flow reserve; FFRcor = coronary fractional flow reserve; FFRmyo = myocardial fractional flow reserve; Pa = aortic pressure; Pd = distal coronary pressure; Pv = right atrial pressure; Pw = coronary wedge pressure.

TABLE 4 Studies of FFR Compared With Noninvasive Stress Testing to Assess Myocardial Ischemia

First Author, Year (Ref. #)	Number of Patients (Lesions)	Ischemic Test	Best Cutoff Value	Accuracy (%)	Clinical Setting
Intravenous adenosine infusion (140 μg/kg/min)					
Pijls et al., 1995 (18)	60 (60)	X-ECG	0.74	97	SVD
Pijls et al., 1996 (19)	45 (45)	X-ECG, MPS, DSE	0.75	93	SVD
Jimenez-Navarro et al., 2001 (58)	21 (21)	DSE	0.75	90	SVD
Rieber et al., 2004 (59)	48 (48)	MPS, DSE	0.75	76–81	MVD
Erhard et al., 2005 (60)	47 (47)	MPS, DSE	0.75	77	MVD
Hacker et al., 2005 (61)	50 (50)	MPS	0.75	86	SVD
Total or average (as applicable)	271 (271)	NA	0.75	87	NA
Intracoronary adenosine bolus (maximum 40–60 μg)					
Tron et al., 1995 (62)	62 (70)	MPS	0.69	67	1, 2, and 3-VD
Bartunek et al., 1997 (63)	37 (37)	DSE	0.67	90	SVD
Caymaz et al., 2000 (64)	30 (40)	MPS	0.75	95	SVD
Fearon et al., 2000 (65)	10 (10)	MPS	0.75	95	SVD
Chamuleau et al., 2001 (66)	127 (161)	MPS	0.74	77	MVD
Seo et al., 2002 (67)	25 (25)	MPS	0.75	60	Previous MI
Krüger et al., 2005 (68)	42 (42)	MPS	0.75	88	ISR
Samady et al., 2006 (69)	48 (48)	MPS, DSE	0.78	92	Previous MI
van de Hoef et al., 2012 (70)	232 (299)	MPS	0.76	74	MVD
Total or average (as applicable)	613 (732)	NA	0.74	83	NA
Other method of vasodilation					
De Bruyne et al., 1995 (intracoronary papaverine or adenosine) (13)	60 (60)	X-ECG, MPS	0.66	87	SVD
Bartunek et al., 1997 (intracoronary papaverine or adenosine) (63)	75 (75)	DSE	0.75	81	SVD
Abe et al., 2000 (intravenous ATP) (71)	46 (46)	MPS	0.75	91	SVD
De Bruyne et al., 2001 (intravenous or intracoronary adenosine, or intravenous ATP) (72)	57 (57)	MPS	0.78	85	Previous MI
Yanagisawa et al., 2002 (intracoronary papaverine) (39)	165 (194)	MPS	0.75	76	Previous MI
Ziaee et al., 2004 (intravenous or intracoronary adenosine) (73)	55 (55)	MPS, X-ECG, DSE	0.75	88	Ostial
Morishima et al., 2004 (intracoronary papaverine) (74)	20 (20)	MPS	0.75	85	SVD
Kobori et al., 2005 (intracoronary papaverine) (75)	147 (155)	MPS	0.75	70	Restenosis
Ragosta et al., 2007 (intracoronary adenosine, 30–40 μg in the RCA, 80–100 μg in the LMCA) (76)	36 (36)	MPS	0.75	69	MVD
Total or average (as applicable)	661 (698)	NA	0.74	81	NA
Total or average (as applicable) for all studies	1,545 (1,701)	NA	0.74	83	NA

Adapted with permission from van de Hoef et al. (79).

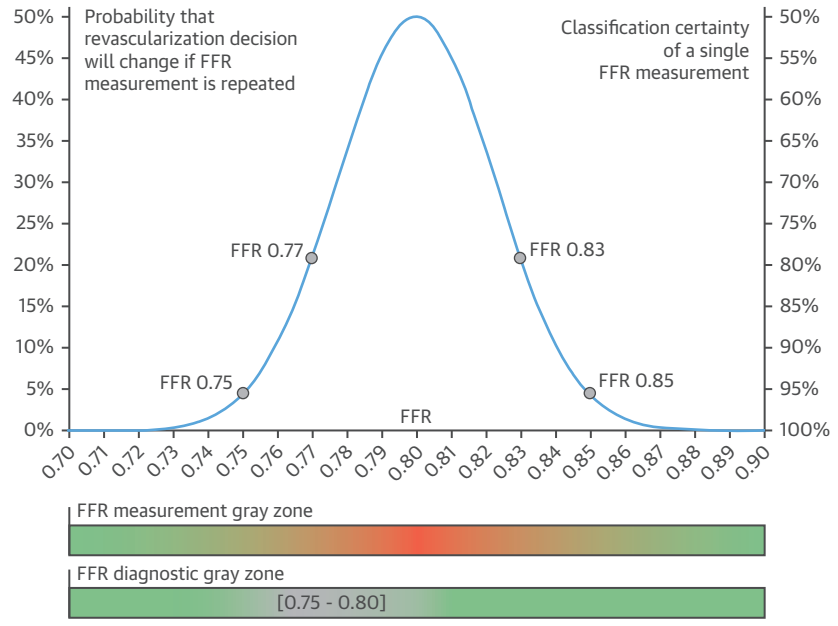
ATP = adenosine triphosphate; DSE = dobutamine stress echocardiogram; ISR = in-stent restenosis; LMCA = left main coronary artery; MI = myocardial infarction; MPS = myocardial perfusion scan; MVD = multivessel disease; NA = not applicable; RCA = right coronary artery; SVD = single-vessel disease; VD = vessel disease; X-ECG = exercise electrocardiogram.

been demonstrated to exclude ischemia in 90% of cases (from data from 45 patients) (20) and that, by accepting the upper limit of the gray zone, the potential number of ischemic lesions left untreated was decreased (17).

The primary endpoint for the FAME study was the rate of death, nonfatal myocardial infarction (MI), and repeat revascularization at 1 year. If randomized to angiography guidance, the protocol mandated that all visually estimated >50% stenoses underwent PCI at the operator's discretion, versus only stenoses with FFR ≤0.80 if randomized to FFR. The headline result of the FAME study was a significant reduction in major adverse cardiac events (MACE) at 1 year in the FFR versus angiography-alone group (13.2% vs. 18.3%; relative risk 0.72; 95% confidence interval [CI]: 0.54 to 0.96, respectively; p = 0.02).

THE FAME 2 STUDY. Both the DEFER and FAME studies supported the evolving strategy of revascularization of ischemic lesions and medical treatment of nonischemic lesions. Having already highlighted the inadequacies of coronary angiography alone to guide revascularization, the 2009 FAME 2 (Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease) study tested the hypothesis that FFR-guided PCI plus optimal medical therapy (OMT) would be superior to OMT alone (21). The study

FIGURE 3 Diagnostic Accuracy of Repeated FFR Measurements



The classification certainty of a single FFR measurement is presented for FFR values from 0.70 to 0.90 (right vertical axis). Outside the 0.75 to 0.85 range, measurement certainty is >95%. However, closer to its cutpoint, this certainty falls, reaching a nadir of approximately 50% around 0.80. Adapted with permission from Petraco et al. (55). FFR = fractional flow reserve.

population consisted of patients with multivessel coronary artery disease already on OMT and who had PCI being considered. FFR was first performed in all indicated stenoses. If at least 1 stenosis was FFR ≤0.80, patients were randomly assigned to receive either PCI in addition to OMT or OMT alone. If all stenoses were FFR >0.80, patients continued on OMT. The primary endpoint was a composite of death, MI, or urgent revascularization.

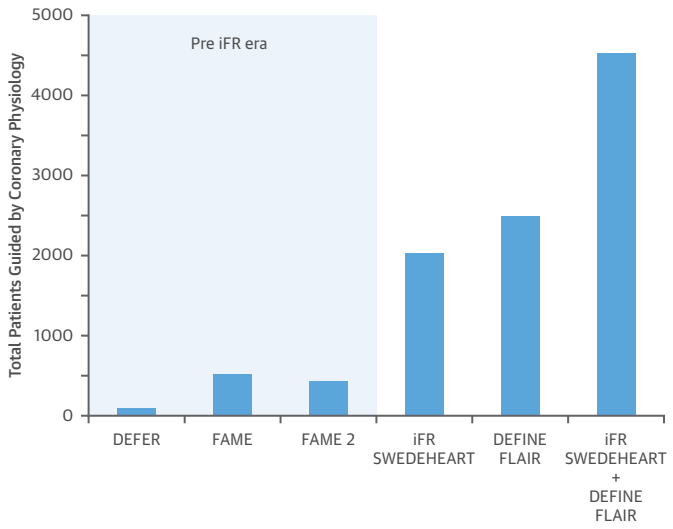
The study was halted prematurely (mean follow-up 7 months) after a significant reduction in the composite primary endpoint emerged in the PCI versus OMT group (hazard ratio [HR]: 0.32; 95% CI: 0.19 to 0.53; $p < 0.001$). However, this composite endpoint was driven by significantly fewer urgent revascularizations in the PCI arm (HR: 0.13; 95% CI: 0.06 to 0.30; $p < 0.001$), rather than by any signal for decreased mortality or MI. The premature

TABLE 5 Summary Characteristics of Patient Outcome FFR Trials

Trial (Ref. #)	Year	Patients Guided by Physiology	FFR Cutpoint for Functional Significance	Mean FFR	Treatment
DEFER (14)	2001	91	<0.75	Defer: 0.87 ± 0.07 Perform: 0.87 ± 0.06 Registry: 0.56 ± 0.16	PCI/BMS vs. FFR-guided deferral
FAME (17)	2009	509	≤0.80	Overall cohort: 0.71 ± 0.18 Ischemic lesions: 0.60 ± 0.14 Nonischemic lesions: 0.88 ± 0.05	Angiography-guided vs. FFR-guided PCI (DES)
FAME 2 (21)	2012	447	≤0.80	In lesions with FFR ≤0.80: 0.64 ± 0.13 (range: 0.19–0.80) FFR-guided PCI + OMT group: 0.68 ± 0.10 OMT alone: 0.68 ± 0.15	FFR-guided PCI (DES) + OMT vs. OMT alone

BMS = bare-metal stent; DEFER = Deferral Versus Performance of PTCA (percutaneous transluminal coronary angioplasty) in Patients Without Documented Ischemia; DES = drug-eluting stent; FAME = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FAME 2 = Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; OMT = optimal medical therapy.

FIGURE 4 Study Population Sizes From Coronary Physiology Outcome Trials



The heights of the bars represent the total number of patients guided by coronary physiology. DEFER = Deferral Versus Performance of PTCA (Percutaneous Transluminal Coronary Angioplasty) in Patients Without Documented Ischemia; DEFINE FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; FAME = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FAME 2 = Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease; iFR = instantaneous wave-free ratio; iFR SWEDEHEART = Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome.

termination of the study in this fashion obliged the FAME 2 investigators to limit their conclusions to FFR-guided PCI plus OMT leading to a decreased need for urgent revascularization, as compared with OMT alone (21). Additionally, the study received much criticism about the absence of blinding of patients and investigators.

FROM EVIDENCE TO GUIDELINE: THE DEFER, FAME, AND FAME 2 STUDIES IN CONTEXT. In 2013, FFR received a Level 1A recommendation by the European Society of Cardiology to guide revascularization in patients with stable angina, intermediate coronary stenosis, and no prior ischemia test. Without detracting from the importance of the landmark FFR patient outcome trials, a number of critical observations can be levied at the transferability of the findings to modern-day FFR practice, especially as framed within current clinical guidelines.

First, the number of patients guided by FFR was relatively small by modern patient outcome trial standards. In the DEFER, FAME, and FAME 2 studies, respective totals of 91, 509, and 447 patients were assigned to FFR-guided therapy (Table 5). This compares with a combined total of ~4,500 patients assigned to coronary physiology-guided therapy in recently reported coronary physiology trials (Figure 4) (5,6).

Second, the absence of the FFR gray zone from revascularization guidelines means that interpretation of FFR values between 0.75 to 0.80 frequently pose a challenge for operators in daily clinical practice. FFR values that lie within this range must be interpreted in the context of the individual patient. For example, if an FFR gray zone measurement relates to a complex lesion, in a patient without severe angina, or with other clinical factors, such as impeding surgery or high bleeding risk, such a stenosis may be appropriately deferred. This practice is supported by the data from the DEFER trial (which adopted the initial FFR 0.75 cutoff) and respects the fundamental principle that ischemia is a continuum of disease, and not simply a dichotomous status.

Third, similar to the early validation studies comparing FFR with noninvasive ischemic tests (13,19), in the FFR outcome studies, physiologically positive and negative groups were characterized by markedly severe and normal mean FFR values (Table 5). This bimodal distribution of FFR values denotes a different disease population than real-world clinical populations where unimodal distributions of FFR values (Figure 5) are observed, with values tightly clustered around the 0.80 cutoff (5,6,22).

Last, the DEFER, FAME, and FAME 2 studies were notable for their omission of measurement of right atrial pressure in the determination of the FFR value. Although undoubtedly simpler for the practicing physician, this deviation from the validated FFRmyo in both animal and human models has been associated with a systematic underestimation of FFR values, with resultant implications on revascularization decision made in accordance with the FFR 0.80 cutoff value (Table 6) (23,24).

FUNDAMENTALS OF iFR

Since the early work of Gould et al. (25) in the canine model, it has long been appreciated that resting coronary flow remains stable across a wide range of stenosis severities (until near occlusion). In contrast, hyperemic flow declines significantly beyond approximately 50% reduction in lumen diameter (25). The stable flow conditions that exist in the resting state provide an ideal environment for the application of a pressure-based index of stenosis severity. However, the confounding influences of myocardial contraction and relaxation on flow initially proved insurmountable for early attempts at applying resting

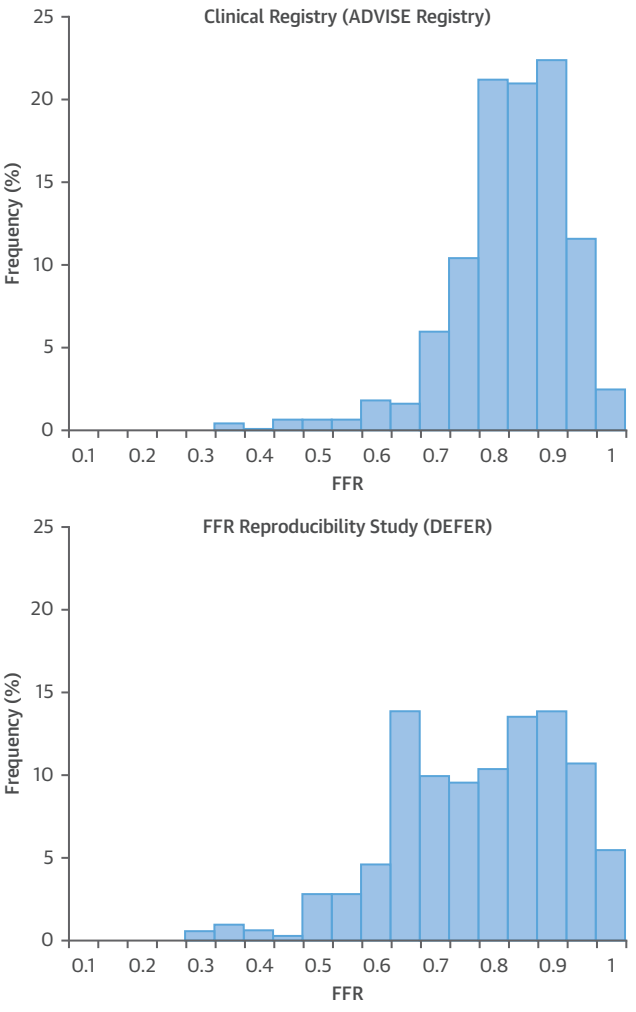
pressure-based indexes (26). In order to understand why iFR is now capable of determining physiological stenosis severity in the resting state, a basic understanding of the mechanisms of cardiac mechanics is required. Using wave intensity analysis (WIA), it is possible to perform quantifiable measurements in humans to elucidate such mechanisms.

Derived from combined coronary pressure and flow data, WIA permits the separation of waves (a disturbance that spreads directionally with time) according to their origin and direction of travel. This makes WIA an ideal tool to interrogate the coronary circulation, given that both proximal and distal vascular beds (aortic and microcirculatory originating) of the coronary artery contribute energy to the system. By classifying waves by their origin (proximal or distal) and influence on blood flow (expansion or compression), a total of 6 waves can be identified in the human coronary circulation (27). The wave-free period (WFP) occurs in diastole, where it was observed that the generation of new waves is absent, and competing waves that affect coronary blood flow are quiescent (**Figure 6**) (4). The defining features of the WFP of diastole are: 1) flow velocity is approximately 30% higher than whole-cycle resting flow velocity; 2) intracoronary pressure and flow decline together in a linear fashion; and 3) microvascular resistance is significantly more stable and lower than that over the rest of the cardiac cycle (4). From a physiological standpoint, these features make the WFP a suitable window within the cardiac cycle during which a pressure-only assessment of the hemodynamic significance of coronary stenoses can be made, without the need for maximal pharmacological vasodilation. Furthermore, because the WFP exists as a proportion of diastole changing with alterations of the R-R interval, iFR can also be calculated dynamically on a beat-by-beat basis without requiring several beats to be averaged at a time (4).

WHAT DOES iFR ACTUALLY MEASURE?

Although the WFP provided the theoretical framework for iFR, it did not sufficiently explain exactly what iFR was measuring. Unlike FFR, which was defined from first principles as the maximum achievable myocardial blood flow in the presence of a coronary artery stenosis as a percentage of the maximum blood flow in the hypothetical case of a completely normal artery (1), the definition of iFR was initially less clear, opting instead for a technical description of the ratio of distal coronary to aortic pressure during the WFP of diastole (4).

FIGURE 5 Differing Distribution of FFR Values in Clinical and Nonclinical Datasets



(Top) A unimodal distribution of FFR values clustered around the 0.80 cutoff value is demonstrated in the clinical ADVISE Registry study population. **(Bottom)** A bimodal distribution of FFR values is demonstrated in the FFR reproducibly study (DEFER). Adapted with permission from Petraco et al. (22). FFR = fractional flow reserve. ADVISE = Adenosine Vasodilator Independent Stenosis Evaluation; other abbreviations as in **Figures 2 and 4**.

Subsequent study of the coronary pressure-flow relationship in humans with and without angiographic evidence of obstructive atherosclerosis, under resting and hyperemic conditions, provided the necessary insight to determine physiologically what iFR actually measures. By replicating the earlier animal studies in humans, the IDEAL (Iberian-Dutch-English) study (28) demonstrated that trans-stenotic pressure gradients at rest were predominantly determined by compensatory vasodilator changes in

TABLE 6 Considerations for the Omission of Right Atrial Pressure From the Calculation of FFR

Consideration	For	Against
Physiological reasoning regarding FFR	Right atrial pressure is assumed negligible relative to aortic pressure (77)	Right atrial pressure values vary individually amongst patients Right atrial pressure is a key component of the original FFRmyo equation that was validated against ischemia testing (1,19) Omission of right atrial pressure systematically underestimates FFRmyo values (23)
Revascularization decision making	FAME and FAME 2 clinical outcome trials omitted right atrial pressure from the FFR calculation Initially deferred stenoses do not cross the FFR 0.75 threshold when right atrial pressure is subsequently included in the FFR calculation (24)	FAME and FAME 2 clinical outcome trials are not representative of intermediate disease clinical populations (22) Approximately 10% of initially deferred stenoses cross the FFR 0.80 threshold when right atrial pressure is subsequently included in the FFR calculation (24)

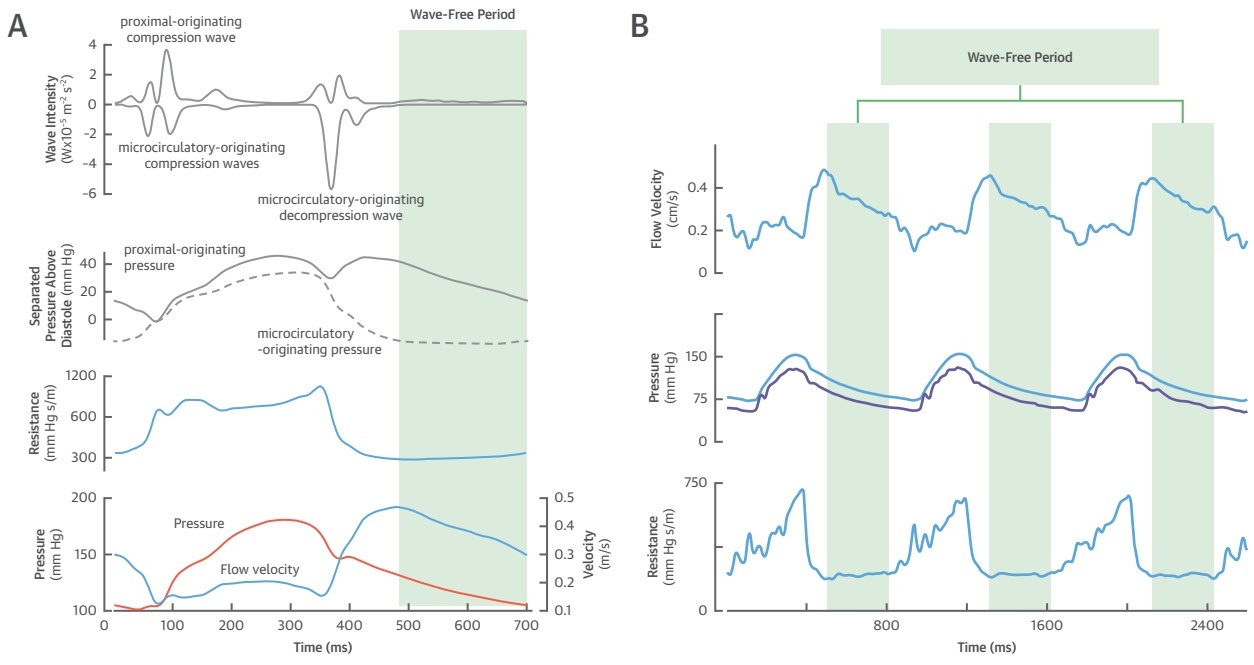
Abbreviations as in Tables 3 and 5.

microvascular resistance (Figure 7). Therefore, according to the homeostatic principles of coronary autoregulation, for a stenosis to have a meaningful physiological impact upon the flow of blood to the myocardium, it should have a gradient that is detectible at rest (28). In simpler terms, by means of the distal pressure value obtained during the WFP of diastole, iFR measures the physiological impact of a coronary stenosis on the distal coronary bed (Figure 7).

CAN RESTING WHOLE-CYCLE Pd/Pa BE USED AS AN ALTERNATIVE TO iFR?

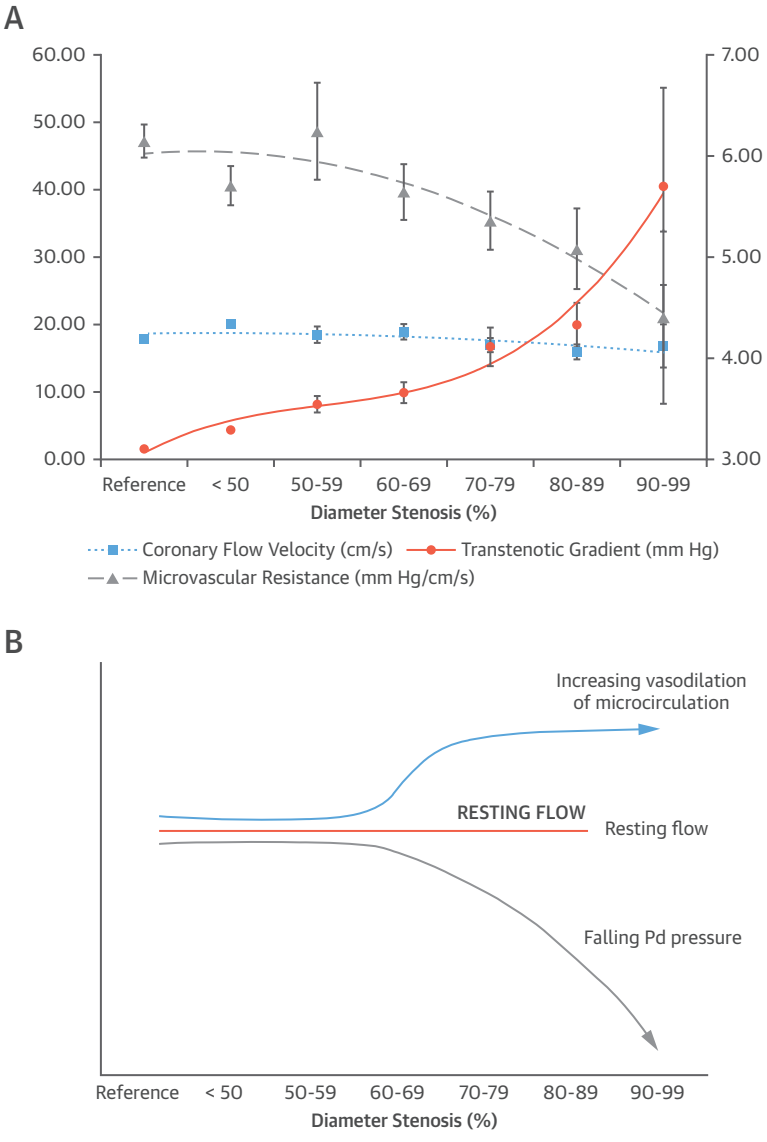
The notion that resting whole-cycle averaged measurements (Pd/Pa) could be used as an alternative to FFR was always fiercely opposed as physiologically implausible by the inventors of FFR. However, with the renewed focus on resting pressure measurements that iFR has engendered, comparisons have now been drawn between iFR and resting whole-cycle Pd/Pa. In the RESOLVE study (A Multicenter Study Evaluating the Diagnostic Accuracy of iFR Compared to FFR) (29), a strong linear correlation between iFR and Pd/Pa values was demonstrated. Although Bland-Altman analysis revealed that substantial variation between iFR and Pd/Pa existed, some observers commented that both indexes had similar correlation to FFR, and were

FIGURE 6 Schematic Diagram Illustrating the Wave-Free Period of Diastole and Associated Hemodynamic Characteristics



(A) The **green shading** highlights the wave-free period of diastole where the multiple different waves propagating from the proximal and distal ends of the vessel are quiescent. Coronary pressure **(orange)** and flow **(blue)** are linearly related during the wave-free period. **(B)** Flow velocity **(top trace)**, proximal **(light blue)**, and distal **(purple)** pressure traces and instantaneous resistance **(bottom trace)** demonstrate the stability of the wave-free period beat to beat. Reprinted with permission from Nijjer et al. (54).

FIGURE 7 Coronary Autoregulation as a Means of Quantifying Physiological Stenosis Severity Under Resting Conditions



(A) With increasing stenosis severity, resting coronary flow velocity **(dotted line)** is maintained at a stable level by progressive compensatory reduction of microvascular resistance **(dashed line)**. **(B)** Schematic representation of the behavior of resting coronary physiology in the face of increasing stenosis severity. The physiological impact of a coronary stenosis on the distal coronary bed can be quantified by a falling distal coronary pressure (Pd) in the resting state. Adapted with permission from Nijjer et al. (28).

thus essentially the same and may be used interchangeably (30).

To challenge that statement scientifically requires revision of the physiological differences between Pd/Pa and iFR (**Table 7**). The most significant of these is that Pd/Pa is a whole-cycle measure, whereas iFR is measured in the WFP of diastole only. Given that the majority of coronary blood flow occurs during diastole, from an engineering standpoint, where the signal-to-noise ratio defines the utility of a tool, systole can be considered primarily as "noise." Therefore, by limiting interrogation of the trans-stenotic pressure ratio to the period of greatest flow (i.e., signal) without the confounding influences of

TABLE 7 Comparisons Between FFR, iFR, and Pd/Pa Pressure-Based Indexes of Stenosis Severity

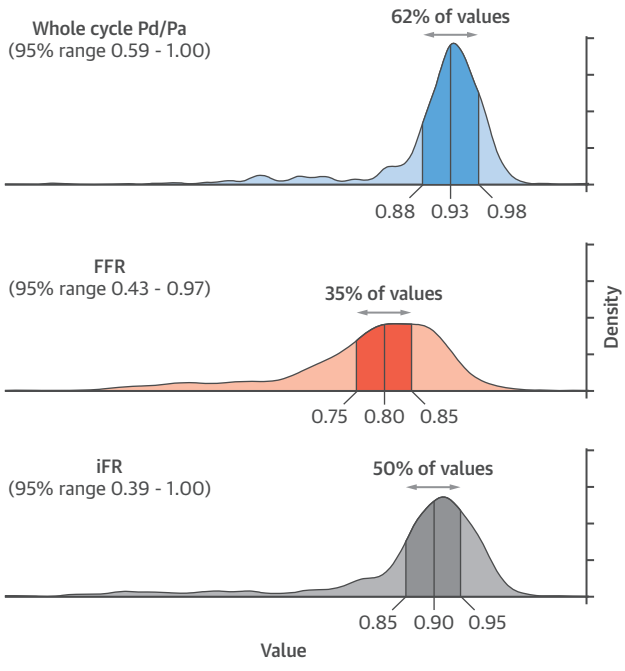
Index	Conditions for Measurement	Sampling Window	Acquisition	Coronary Flow	Outcome-Derived Cutoff Value for Hemodynamic Significance	Gray Zone Range	Dynamic Range	Independently Assess Tandem Stenoses	Resilience to Pressure Wire Drift
FFR	Hyperemia	Whole cardiac cycle	Averaged (~5 beats)	++	≤0.80	0.75–0.80	Wide	No	Resilient
iFR	Baseline	Wave-free period of diastole	Beat-by-beat	+	≤0.89	NA	Wide	Yes	Resilient
Pd/Pa	Baseline	Whole cardiac cycle	Averaged (~5 beats)	~	NA	NA	Narrow	No	Susceptible

iFR = instantaneous wave-free ratio; other abbreviations as in Tables 1 and 3.

myocardial contraction on flow (i.e., noise), iFR enjoys a superior signal-to-noise ratio than that of whole-cycle Pd/Pa (31).

This enhanced quality of iFR equips it with important advantages over Pd/Pa for the pressure-based assessment of physiological stenosis severity. Because the range of values for any given population is decreased with Pd/Pa as compared with iFR, Pd/Pa has a lower diagnostic resolution to distinguish hemodynamically important lesions (**Figure 8**) (32). The tight clustering of Pd/Pa values (coupled with the need to average measurements over ~3 to 5 beats) means that Pd/Pa has a much lower fidelity for the pullback assessment of serial lesions or diffuse disease, as compared with iFR (4). Lastly, iFR has been demonstrated to be significantly more robust to clinically accepted levels of pressure wire drift than whole-cycle Pd/Pa (33). Therefore, aside from the lack of a well-defined cutoff value for Pd/Pa, validation against ischemia testing for Pd/Pa, and patient outcome data for Pd/Pa, the differences in clinical applicability between iFR and Pd/Pa can be

FIGURE 8 The Distribution of Values for FFR, iFR, and Whole-Cycle Pd/Pa



Solid black lines indicate the cutpoint value. The **highlighted regions** indicate values within ±0.05 U of the cutpoint; 155 (34.6%), 224 (50.1%), and 278 (62.2%) values lay within ±0.05 U of the cutpoint for FFR, iFR, and whole-cycle Pd/Pa, respectively. Reprinted with permission from Cook et al. (33). Pa = aortic pressure; Pd = distal coronary pressure; other abbreviations as in Figures 3 and 4.

TABLE 8 Recommendations for Best Practices to Avoid Measurement Error With FFR/iFR

Cause of FFR/iFR Measurement Error	Mechanism of FFR/iFR Measurement Error	Recommendation for Best Practice
Variability of the aortic pressure transducer height	Varying the transducer height can alter hydrostatic forces and influence the Pa	Ensure that the transducer is fixed to the table at a reference height at the level of the aortic root (5 cm below the sternum)
Debris on the pressure wire connector	Any blood or saline remnants on the connector may interfere with the Pd recording	Ensure the connector is kept dry and free from debris, especially during the unpacking and flushing process before calibration
Inappropriate pressure wire calibration	Inappropriate calibration establishes an incorrect 0 Pd	Ensure the pressure wire tubing is adequately filled with saline and wait ~60 s to have the wire completely and stably wet. Calibration (establishing zero pressure) can then be performed at this stage
Using guide catheters with side holes	Pressure proximal to the stenosis is a composite of coronary pressure and aortic pressure (through the side holes)	Avoid side-hole catheters in the first instance. If side-hole catheter must be used, ensure the catheter is disengaged from the ostium, while leaving the pressure wire in the distal vessel during the measurement
Contrast medium in the catheter	Contrast medium can cause damping of the aortic pressure waveform	Ensure the guiding catheter is adequately flushed with saline before equalization
Not removing the needle guidewire introducer prior to FFR/iFR measurement	The space around the wire within the introducer may introduce leak and decrease aortic pressure (Pa) by 0–5 mm Hg	Ensure the needle guidewire introducer is removed and the O-ring tightly closed before all measurements, including normalization, FFR, and iFR measurements, and the verification for pressure wire drift at the end of a procedure
Excessive intubation of the guide catheter in the coronary ostium (particularly if ostial disease is present)	Wedging of the guide catheter can damp the proximal aortic pressure signal	Ensure the aortic pressure trace is not damped and optimize and stabilize guide catheter position if possible. Alternatively, disengage from the ostium and leave the pressure wire in the distal vessel during the measurement (particularly if hyperemia is used)
Failure to check for pressure wire drift	Pressure wire drift artifactually alters the Pd value	Always check for (and document) the presence of pressure wire drift at the end of any FFR/iFR measurement. If drift > ±2 mm Hg is identified, repeat the equalization and FFR/iFR measurement.

Abbreviations as in Tables 3 and 7.

rationalized according to fundamental physiological principles.

Regardless of the index used for coronary physiological assessment, in real-world clinical populations where intermediate severity lesions predominate, physiological values tend to cluster around the cut-point (**Figure 8**). Because reproducibility of repeated FFR and iFR measurements for the same lesion is excellent (34), this elevates the responsibility to avoid potential measurement errors by adhering to best clinical practice at all times (**Table 8**).

iFR VALIDATION

The path of iFR into contemporary clinical guidelines (35) paralleled that of FFR. Following the initial description of the iFR concept, a series of comparative studies with other tests of myocardial ischemia were performed. The ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) and ADVISE Registry studies were the first to assess the diagnostic accuracy of iFR against FFR as the ischemic reference standard (4,22). Following these initial comparisons of iFR to FFR, a series of further comparison studies between iFR, FFR, and third-party arbiters of ischemia were conducted (**Table 9**).

The CLARIFY study (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study) compared iFR and FFR to the hyperemic stenosis resistance (HSR) index (36). The HSR is a combined pressure and flow-velocity index that essentially calculates the gradient of the pressure-flow curve (37), as originally described by Gould (26). In the CLARIFY study, iFR, FFR and iFR with adenosine had equal diagnostic efficiency to match an ischemic classification with HSR (both 92%, with no significant difference between the 2 tests and no

TABLE 9 FFR and iFR Ischemic Comparisons

Comparator (Ref. #)	N	FFR Diagnostic Accuracy (%) or AUC	iFR Diagnostic Accuracy (iFR) or AUC	p Value
HSR (36)	51	92	92	NS
HSR (78)	120	82	89	<0.01
MPS (38)	85	63	62	NS
PET (40)	49	76	76	NS
CFR (42)	216	67	74	<0.01
PET (41)	115	70%	74	NS

AUC = area under the curve; CFR = coronary flow reserve; HSR = hyperemic stenosis resistance; NS = not significant; PET = positron emission tomography; other abbreviations as in Tables 1, 4, and 7.

TABLE 10 Summary Characteristics of Patient Outcome iFR Trials

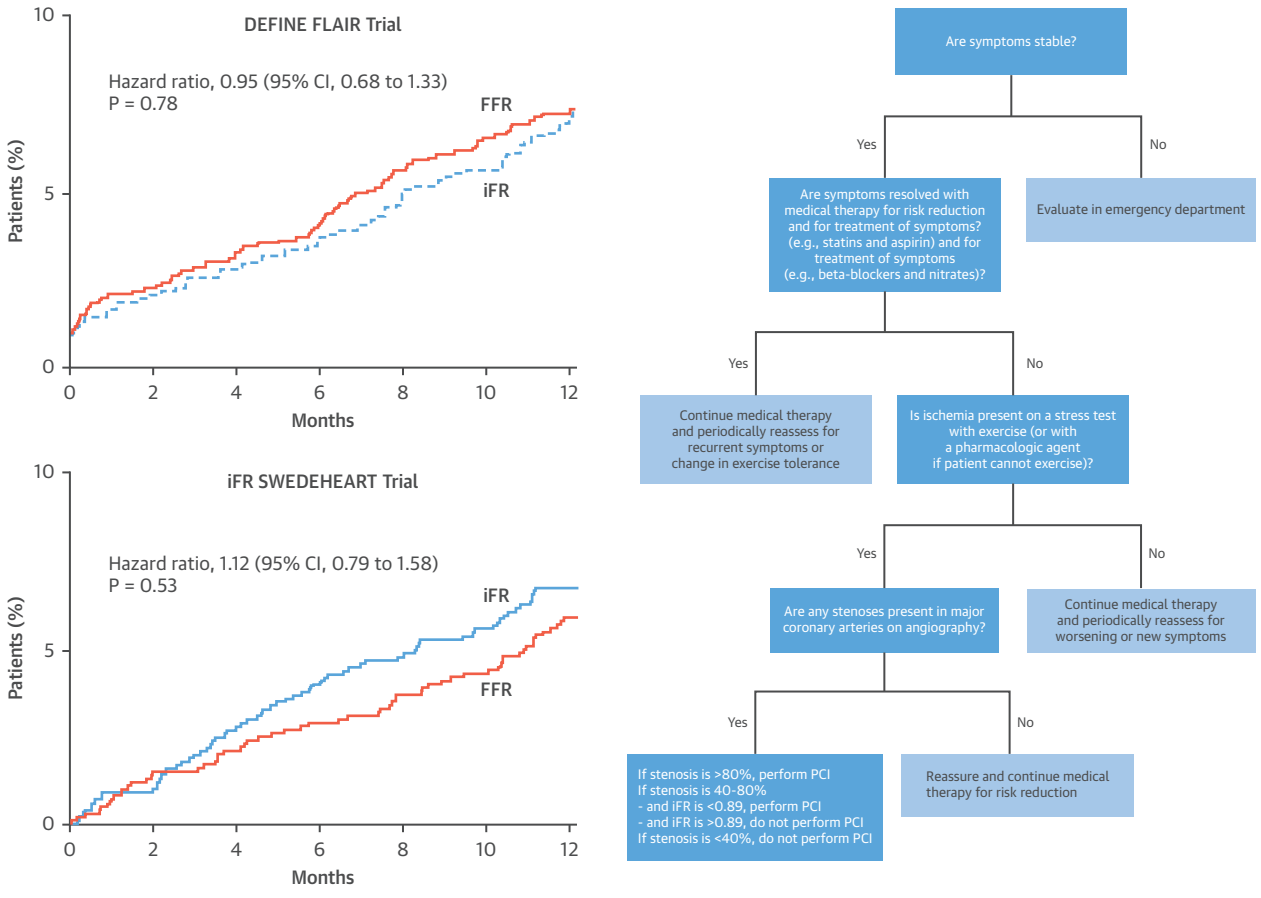
Trial (Ref. #)	Total Study Population	Randomized to FFR	Randomized to iFR	FFR Value	iFR Value	Stable Angina	ACS	Functionally Significant Lesions by FFR, n (% of Total Vessels Evaluated)	Functionally Significant Lesions by iFR, n (% of Total Vessels Evaluated)
DEFINE-FLAIR (5)	2,492	1,250	1,242	0.83 ± 0.09	0.91 ± 0.09	1,998 (80.2)	370 (14.9)	557 (34.6)	451 (28.6)
iFR SWEDEHEART (6)	2,037	1,019	1,018	0.82 ± 0.10	0.91 ± 0.10	1,264 (62.1)	773 (19.0)	528 (36.8)	457 (29.1)

Values are mean ± SD or n (%) unless otherwise indicated.

ACS = acute coronary syndrome; DEFINE-FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; iFR SWEDEHEART = Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome; other abbreviations as in Tables 1 and 7.

diagnostic advantage demonstrated with the administration of adenosine) (36). A second, larger study similarly assessed iFR and FFR against HSR in 120 stenoses. In that study, iFR was found to have a significantly higher classification match than FFR (89% vs. 82%; $p < 0.01$) (10). A third study assessed iFR and FFR against a comprehensive combined ischemic reference of myocardial perfusion scintigraphy and HSR (38). No significant difference was found between each index (38), and the results were consistent with other nonselective cohorts using myocardial perfusion scintigraphy (39). A fourth study compared iFR and FFR against positron emission tomography (PET), which is recognized as the

FIGURE 9 Revascularization Decision Making Using iFR



(Left) Kaplan-Meier curves demonstrating noninferiority of iFR versus FFR for major adverse cardiac events at 12 months in the DEFINE-FLAIR **(top)** and iFR SWEDEHEART **(bottom)** clinical outcome trials. **(Right)** Proposed clinical decision-making flow chart for the evaluation of stable coronary artery disease. Adapted with permission from Bhatt et al. (45). CI = confidence interval; PCI = percutaneous coronary intervention; other abbreviations as in Figures 3 and 4.

gold standard for quantifying myocardial blood flow (40). de Waard et al. (40) performed (H215O) PET imaging in 34 patients with 49 intermediate coronary stenoses, followed by invasive pressure-wire assessment. Both iFR and FFR had a 76% classification agreement with PET, and both had similar areas under the curve (AUC) for receiver-operating characteristic analysis (0.85 for FFR and 0.86 for iFR; $p = 0.71$) (40). Notably, both iFR and FFR had an identical pattern of agreement and disagreement with PET myocardial blood flow. A second, larger (13H3) PET study has more recently been performed and demonstrated similar classification agreement between iFR and FFR compared with PET-derived coronary flow reserve (CFR) (74% for iFR and 70% for FFR; $p = 0.36$) across 115 left anterior descending coronary artery stenoses (41). Finally, iFR and FFR have been compared with invasive CFR (42). When iFR, FFR, and CFR were measured in 216 stenoses, iFR had closer agreement with CFR than with FFR, with a statistically significant higher AUC (iFR 0.82 vs. FFR 0.72; $p < 0.001$) (42). Even when constrained to the physiological range of 0.60 to 0.90, iFR maintained a stronger association with CFR than with FFR (AUC: 0.78 vs. 0.59; $p < 0.001$) (42). Importantly, the findings of this study suggest iFR has a closer association than FFR with both hyperemic flow velocity and CFR.

EARLY INTEGRATION OF iFR INTO CLINICAL PRACTICE: THE HYBRID STRATEGY

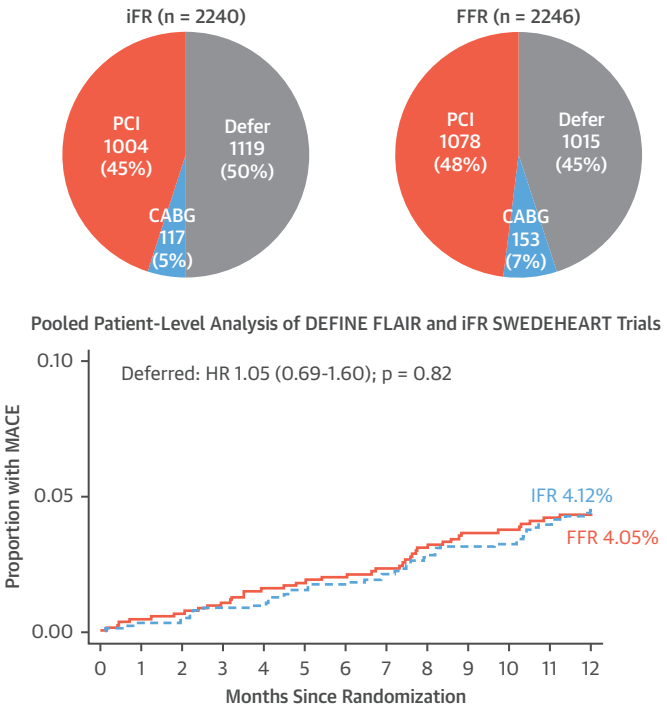
According to the hybrid strategy, iFR is measured in all patients; if the iFR value is between 0.86 and 0.93, then adenosine is administered to calculate FFR. This method was noted to spare 60% to 70% of patients from unnecessary adenosine administration (43,44). When the iFR hybrid approach was first proposed, it represented a practical solution to integrate the iFR into clinical practice although lacking outcome data. However, with multiple validation trials and 2 large randomized clinical trials now demonstrating that iFR is as at least as good as FFR to detect ischemia, and with a noninferior outcome, there is no contemporary need for the iFR hybrid strategy.

iFR AND PATIENT OUTCOME DATA

The recently reported DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) (5) and iFR SWEDEHEART (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome) (6) trials addressed whether an iFR-only guided approach using a single cutoff to guide to revascularization was a safe and feasible alternative to FFR. The rationale for such studies was clear; namely, that an iFR-only approach would permit the avoidance of adenosine, a potential improvement in procedural time and costs, and a reduction in adverse patient side effects. Although the primary study objectives were to establish noninferiority of iFR to FFR for the invasive assessment of stenoses of ambiguous hemodynamic severity, the ultimate goal was to provide a further catalyst to the generally low adoption of coronary physiology techniques in clinical decision making.

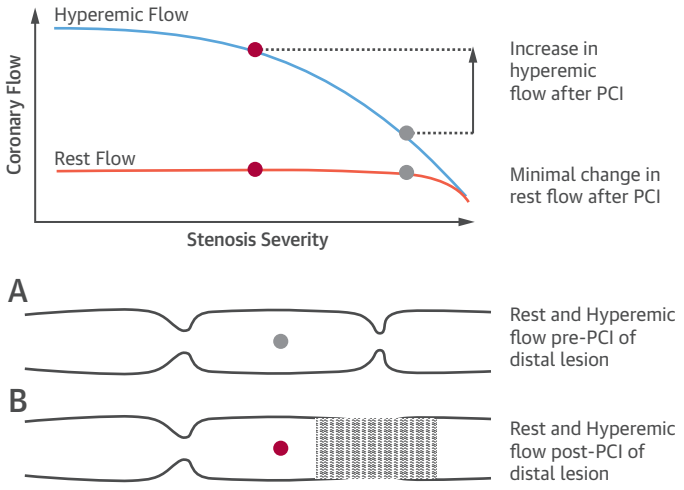
The DEFINE-FLAIR study was a conventional prospective, multicenter international, double-blinded patient strategy study design (5). By contrast, the iFR SWEDEHEART study adopted an open-label registry based randomized clinical trial design using SCAR (the Swedish Coronary Angiography and Angioplasty Registry) for enrollment (6). In both trials, patients with intermediate severity coronary artery disease were randomly allocated in a 1:1 ratio to undergo either iFR-guided or FFR-guided coronary revascularization. Both stable patients and those

FIGURE 10 Deferral of Revascularization According to iFR and FFR



(Top) Significantly less revascularization was performed based on iFR versus FFR interrogation in the pooled analysis of the DEFINE-FLAIR and iFR SWEDEHEART trials. **(Bottom)** Outcomes in deferred ACS patients are similar for both iFR and FFR arms. ACS = acute coronary syndrome; CABG = coronary artery bypass graft; HR = hazard ratio; MACE = major adverse cardiac events; other abbreviations as in **Figures 3, 4, and 9**.

FIGURE 11 The Expected Behavior of Hyperemic and Resting Flow After Removal of Stenosis



(Top) Resting flow is preserved until critical stenosis develops. Conversely, hyperemic flow reduces as stenosis severity exceeds ~40% to 50%. **(Bottom)** In tandem stenoses **(A)**, a measurement of flow at the **gray dot** will elicit a flow value as denoted by the **gray dot on the upper panel**. In **B**, the distal stenosis has been stented. Under hyperemic conditions, flow will have increased significantly **(red dot)**; however, under resting conditions, there is minimal change expected. Reprinted with permission from Nijjer et al. (56). PCI = percutaneous coronary intervention.

with acute coronary syndrome (ACS) and nonculprit vessels with intermediate disease were included (Table 10). The primary endpoint across both trials was harmonized as the 1-year risk of MACE, as a composite of death from any cause, nonfatal MI, or unplanned revascularization. The DEFINE-FLAIR and iFR SWEDEHEART trials were designed to show the noninferiority of iFR to FFR, with respective noninferiority margins of 3.4% and 3.2% for the difference in risk. These margins were more conservative than the criteria typically set in the evaluation of medical devices (45).

THE DEFINE-FLAIR TRIAL. The DEFINE-FLAIR trial demonstrated that coronary revascularization guided by iFR was noninferior to revascularization guided by FFR with respect to the risk of MACE at 1 year. Among a total study population of 2,492 patients, the primary endpoint occurred in 78 of 1,148 patients (6.8%) in the iFR group and in 83 of 1,182 patients (7.0%) in the FFR group (difference in risk −0.2 percentage points; 95% CI: −2.3 to 1.8; $p < 0.001$ for noninferiority; HR: 0.95; 95% CI: 0.68 to 1.33; $p = 0.78$) (Figure 9).

Important secondary findings that favored iFR over FFR were also elucidated. The number of patients who had adverse procedural symptoms and clinical signs was significantly lower in the iFR group than in the FFR group (39 patients [3.1%] vs. 385 patients [30.8%]; $p < 0.001$), and the median procedural time was significantly shorter (40.5 min vs. 45.0 min; $p = 0.001$).

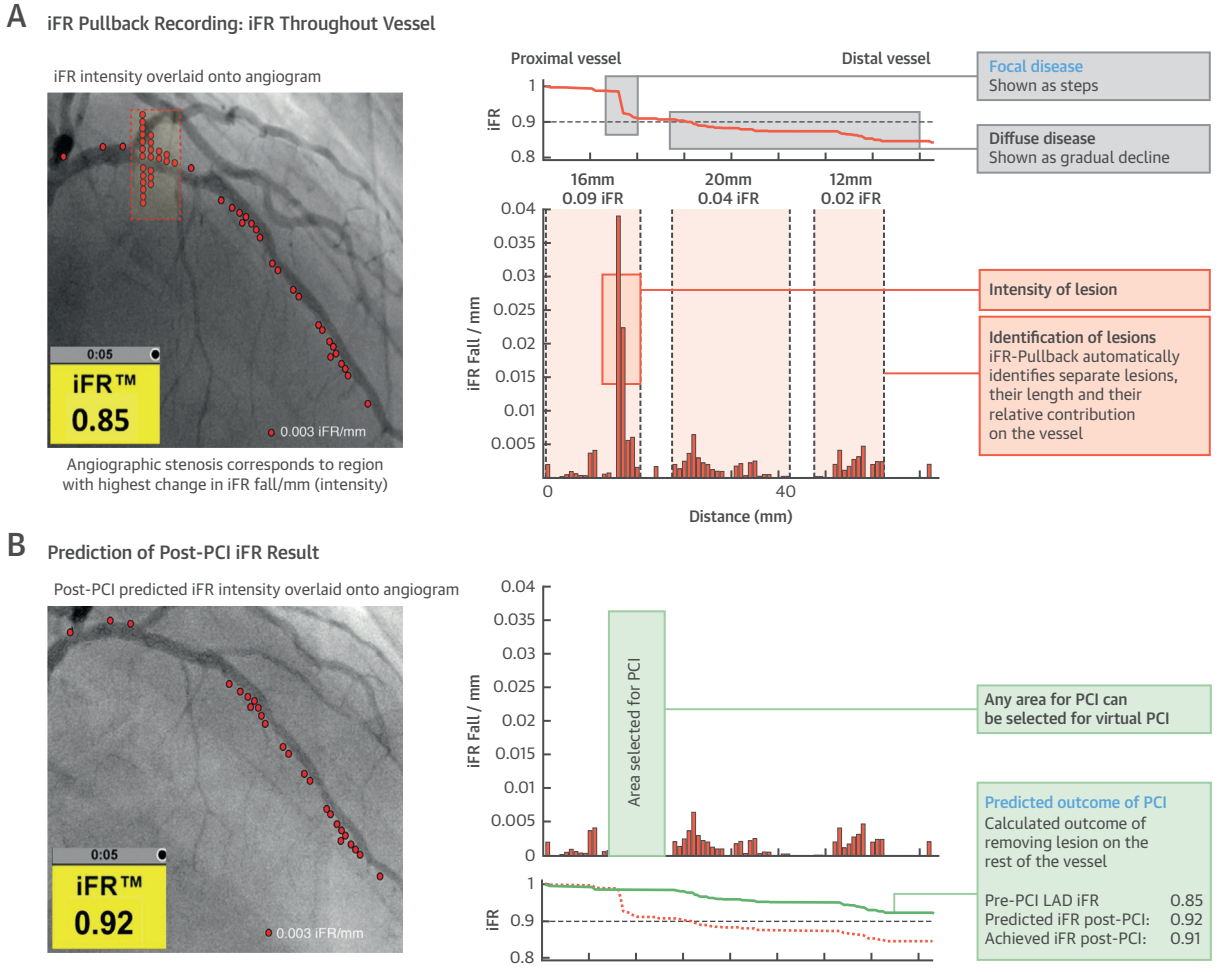
THE iFR SWEDEHEART TRIAL. The results of the iFR SWEDEHEART trial were concordant with those of the DEFINE-FLAIR trial. Namely, among patients with stable angina or an ACS, an iFR-guided revascularization strategy was noninferior to an FFR-guided revascularization strategy with respect to the rate of MACE at 1 year. Among 2,037 patients randomized to undergo revascularization guided by either iFR or FFR, the primary endpoint event occurred in 68 of 1,012 patients (6.7%) in the iFR group and in 61 of 1007 (6.1%) in the FFR group (difference in event rates 0.7%; 95% CI: −1.5 to 2.8%; $p = 0.007$ for noninferiority; HR: 1.12; 95% CI: 0.79 to 1.58; $p = 0.53$) (Figure 9). Similar findings regarding adverse procedural symptoms related to FFR measurement were also reported, with chest discomfort during the procedure reported by 3.0% of the patients in the iFR group and by 68.3% of the patients in the FFR group ($p < 0.001$).

POOLED PATIENT-LEVEL META-ANALYSIS OF THE DEFINE-FLAIR AND iFR SWEDEHEART STUDIES. Combined analysis of the DEFINE-FLAIR and iFR SWEDEHEART trials provided outcome data for 4,529 patients with intermediate-severity coronary lesions guided by coronary physiology in contemporary clinical practice (46). The mean FFR value from the combined datasets was 0.83 ± 0.10. This was in contrast to the study populations of the DEFER and FAME studies, which were characterized by mean FFR values of 0.71 and 0.75, respectively.

Aside from the demonstrated noninferiority of iFR- versus FFR-guided revascularization (HR: 1.03; 95% CI: 0.81 to 1.31; $p = 0.81$), of particular importance was the additional finding that deferral of myocardial revascularization on the basis of pressure guidewire interrogation was more frequently performed when iFR was used, compared with FFR. Deferral from revascularization occurred in 1,119 of 2,240 patients (50.0%) in the pooled iFR group and in 1,015 of 2,246 (45.0%) in the pooled FFR group ($p < 0.01$). Crucially, similarly low MACE rates at 1 year were demonstrated regardless of iFR- or FFR-based deferral, indicating that despite less frequent revascularization with iFR, patient outcomes remained the same (Figure 10).

The lower deferral rate of revascularization with FFR may, in part, reflect the use of the clinically accepted 0.80 cutoff, rather than the 0.75 ischemic cutoff or any value within the FFR gray zone.

FIGURE 12 Illustrative Case From the iFR Pullback Pilot Study



(A) Post hoc coregistration of the iFR pullback trace with the coronary angiogram identifies pressure loss along the length of the vessel and distinguishes focal from diffuse disease. **(B)** Virtual PCI calculates the expected post-PCI iFR result for the area selected for PCI. Reprinted with permission from Nijjer et al. (48). LAD = left anterior descending coronary artery; other abbreviations as in Figures 4 and 9.

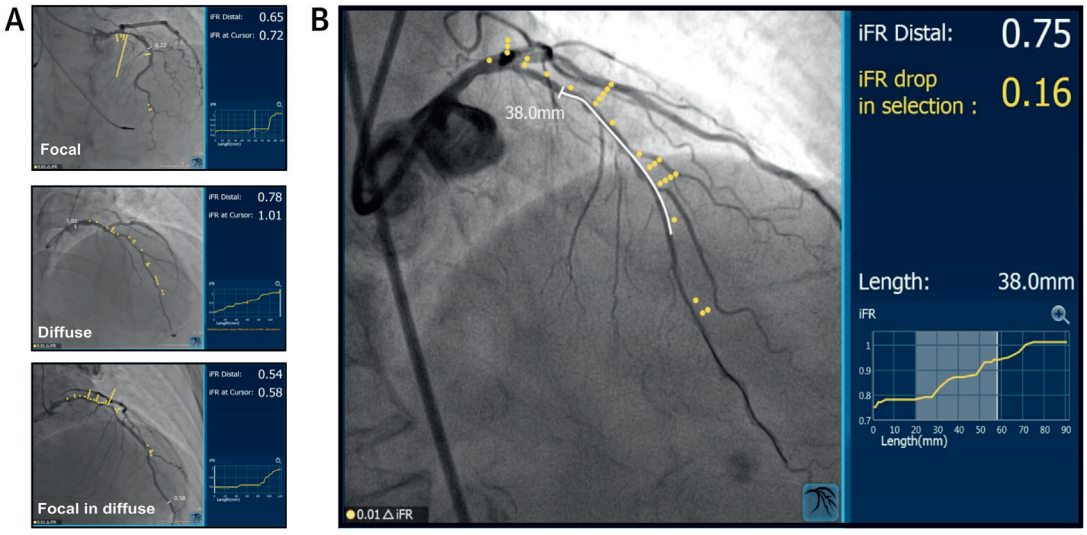
However, uncertainties regarding the optimal FFR cutoff value do not address the underlying physiological differences between iFR and FFR, namely the closer relationship between iFR and flow than between FFR and flow (42).

In summary, the results of the DEFINE-FLAIR and iFR SWEDEHEART trials contribute significantly to the field of coronary physiology. The data have led thought leaders in the field of cardiology, themselves removed from any potential biases, to conclude that iFR may be the new evidence-based standard for invasive evaluation of intermediate-severity coronary lesions (**Figure 9**) (45). Furthermore, imperative for the continued development of iFR-based physiological applications, the trials also validated the use of a single iFR 0.89 cutoff value, without resorting to a diagnostic gray zone or hybrid approach.

THE FUTURE OF CORONARY PHYSIOLOGY: FROM JUSTIFICATION TO GUIDANCE

It is widely recognized that under hyperemic conditions, in the presence of tandem lesions or diffuse disease, interrogation of the physiological severity of an individual stenosis is not clinically possible (47). These difficulties arise due to the cross-communication between stenoses that exists under hyperemia: hyperemic flow through one stenosis is limited by the presence of another stenosis and vice versa.

FIGURE 13 iFR Coregistration



(A) Example hemodynamic phenotypes identified by iFR coregistration. Three distinct patterns of pressure loss are demonstrated. **(B)** Operators can plan their PCI approach with real-time calculation of expected post-PCI iFR results. Images courtesy of Dr. Hidetaka Nishina, Tsukuba Medical Center Hospital, Tsukuba, Japan. Abbreviations as in Figures 4 and 9.

Because resting flow is stable across almost the entire range of stenosis severities (28), resting pressure changes measured with iFR along the length of a vessel are more predictable. In combination with the ability to measure iFR on a beat-by-beat basis, a high-fidelity resting pressure pullback trace can be created where the hemodynamic significance of each individual stenosis can be accurately mapped and quantified. Furthermore, in contrast to hyperemic pressure measurements, removing a stenosis does not alter resting flow profiles, meaning the iFR pressure drops across any residual stenoses remain unchanged (Figure 11).

PILOT STUDY OF THE iFR PULLBACK STUDY AND VIRTUAL PCI TECHNOLOGY

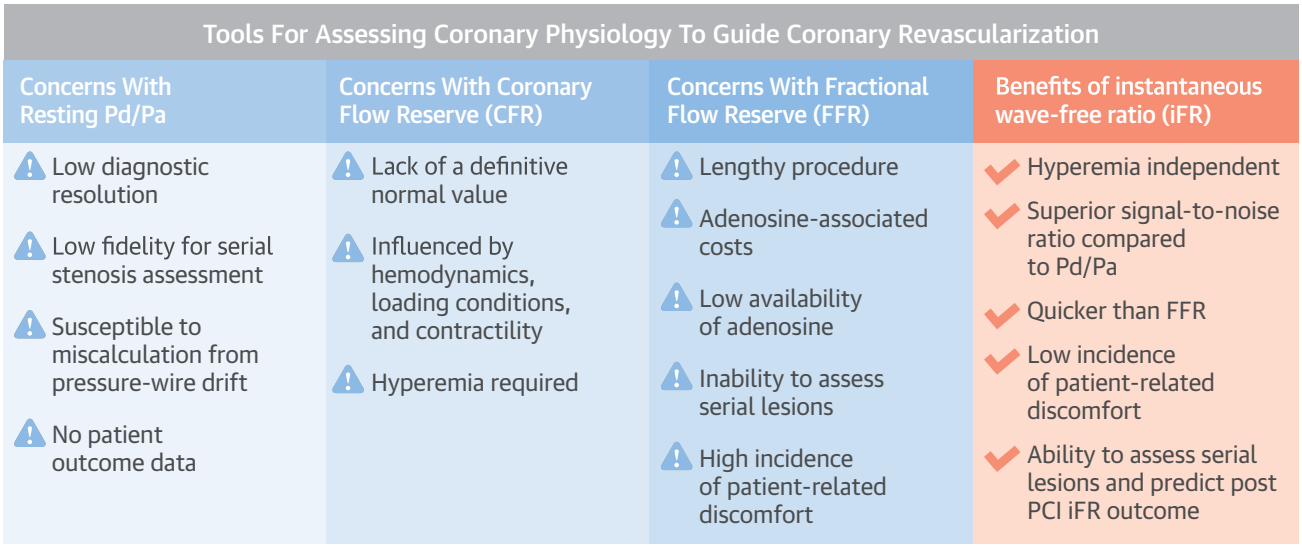
In 2014, Nijjer et al. (48) reported the results of the iFR Pullback study. This pilot study performed a motorized iFR pullback recording in 29 patients with tandem disease or diffuse atheroma. iFR pullback analysis was performed offline, using customized software to calculate the change or decrease in iFR for every millimeter of the vessel. These data were then plotted and overlaid onto a time-stamped fluoroscopic run of the pullback recording to create a coregistered physiological map of the vessel, highlighting the drop(s) in iFR across individual stenoses. "Virtual PCI" was then performed using computer-aided simulations to model the hemodynamic effect of removing a stenosis on the iFR Pullback trace to estimate a post-PCI iFR value (Figure 12). This first-in-man study of iFR-based virtual PCI demonstrated a high degree of accuracy for predicting post-PCI iFR values without a significant systematic bias (48). However, the need for offline analysis and motorized pressure-wire pullback limited application for real-world clinical practice.

iFR SCOUT: FULLY-INTEGRATED VIRTUAL PCI PLANNING

Following proof of the iFR Pullback concept, continued iFR algorithmic developments, combined with real-time computer tracking of pressure-wire movement, removed the remaining logistical barriers to full clinical integration. Accordingly, it is now possible to generate a fully integrated physiological map of any coronary vessel acquired under manual pullback that is coregistered with the angiogram in real time (Figure 13).

The development of such a system permits instant calculation of predicted post-PCI iFR values of any number of interventional approaches. Operators are able to evaluate the potential physiological benefit of multiple different virtual stenting strategies at the planning stage. Strategies that maximize the physiological gain with a minimum of stenting may be

CENTRAL ILLUSTRATION **Contemporary Considerations for Integrating Coronary Physiology Into Clinical Decision Making**



Götberg, M. et al. J Am Coll Cardiol. 2017;70(11):1379–402.

Schematic representation of the relative limitations of commonly used coronary physiological indexes. CFR = coronary flow reserve; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; Pa = aortic pressure; PCI = percutaneous coronary intervention; Pd = distal coronary pressure.

hypothesized to improve outcomes over more extensive stenting approaches. Conversely, the technology also identifies situations where greater numbers or longer stents are justified in order to achieve acceptable hemodynamic improvement. Importantly, angiographically diffuse disease can now be documented physiologically. In such instances, operators may be inclined to pursue alternative approaches to stenting, such as medical therapy or coronary artery bypass grafting (CABG). Taken together, fully integrated virtual PCI planning with iFR marks an exciting new domain for coronary physiology that heralds a shift away from simply the justification of PCI toward the guidance of PCI.

FURTHER NEW FRONTIERS FOR CORONARY PHYSIOLOGY

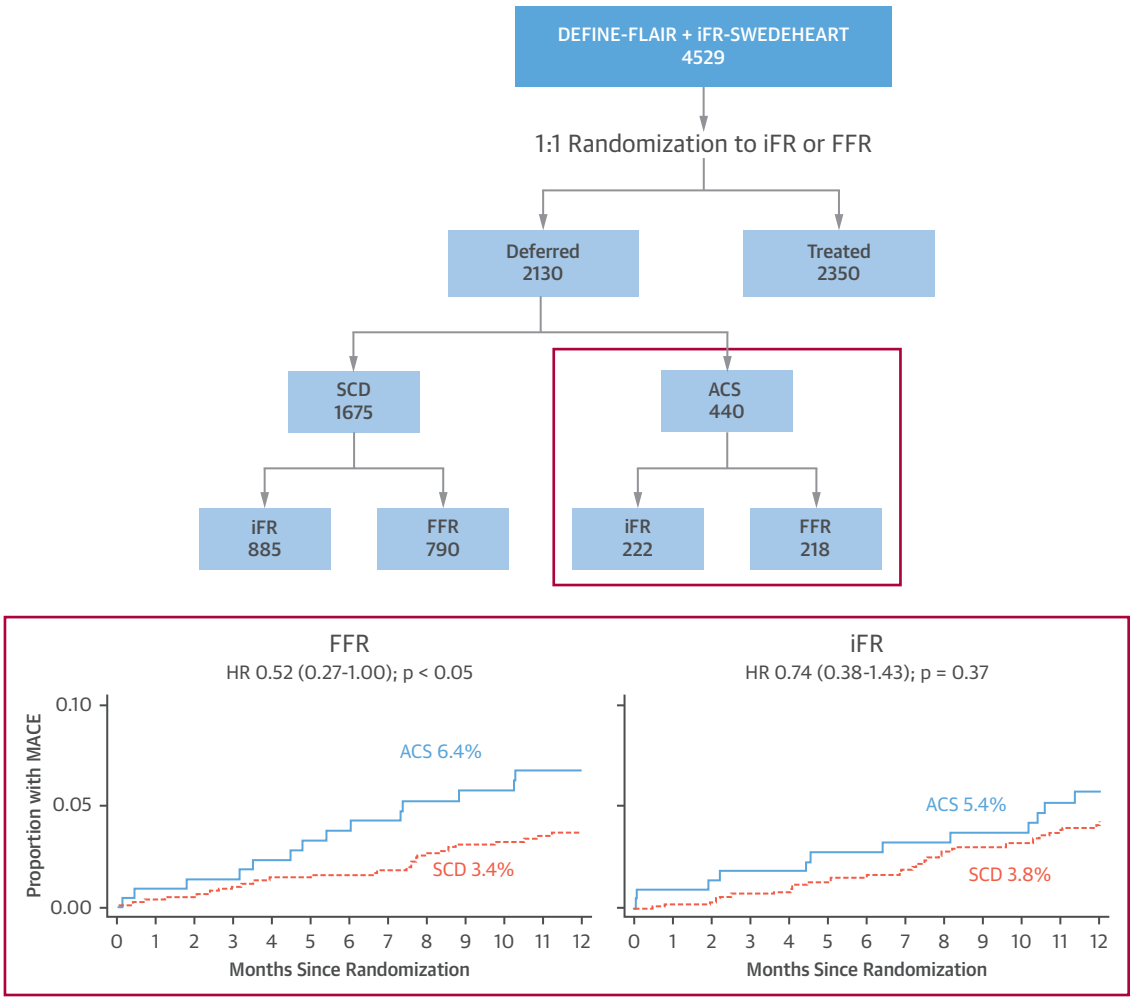
Aside from refinements of existing techniques to optimally integrate coronary physiology into clinical practice (**Central Illustration**), coronary physiology continues to expand into new areas of clinical decision making. In particular, the application of coronary physiology to define appropriate targets for bypass grafting during CABG and to guide revascularization of nonculprit vessels in ACS mark important new frontiers for both FFR and iFR.

CORONARY PHYSIOLOGY TO GUIDE CABG. Despite the wealth of physiological data to guide revascularization with PCI, the scientific body of evidence for using coronary physiology to guide CABG remains scarce. In 1 small study (164 patients), Botman et al. (49) demonstrated a significant increase in graft failure at 1 year in FFR functionally nonsignificant lesions compared with FFR functionally significant lesions. However, the clinical relevance of the primary study endpoint was negated by the fact that patients with patent or occluded bypass grafts on nonsignificant lesions did not experience an excess of angina or repeat interventions.

Data on the role of iFR to guide CABG are currently lacking. However, given the closer association between iFR and flow than between FFR and flow, and the detrimental effect of native vessel competitive flow on long-term graft patency, iFR may be particularly suited to identifying appropriate targets for bypass grafting. Prospective, randomized trials with hard clinical endpoints are warranted to address the relative merits of FFR- and/or iFR-guided CABG.

CORONARY PHYSIOLOGY IN ACS. The application of coronary physiology to bystander nonculprit disease in ST-segment elevation myocardial infarction

FIGURE 14 Safety of Coronary Revascularization Deferral Based on iFR and FFR Measurements in ACS



(Top) A total of 440 patients with ACS were deferred with iFR (n = 218) or FFR (n = 220) in the pooled analysis of DEFINE-FLAIR and iFR SWEDEHEART trials. **(Bottom)** FFR was associated with a significantly worse outcome compared with deferred patients with stable angina (HR: 0.52; 95% CI: 0.27 to 1.00; p < 0.05). iFR yielded a similar outcome among deferred patients, regardless of clinical indication (HR: 0.74; 95% CI: 0.38 to 1.43; p = 0.37). SCD = stable coronary disease; other abbreviations as in Figures 3, 4, and 10.

(STEMI) has been most studied with FFR. The open-label DANAMI-3 PRIMULTI trial (Third Danish Study of Optimal Acute Treatment of Patients With STEMI: Primary PCI in Multivessel Disease) (50) studied the clinical outcome of patients with STEMI treated with FFR-guided complete revascularization versus treatment of the infarct-related artery only. A total of 627 patients with ≥1 clinically significant coronary stenosis after successful recanalization of the infarct-related artery were randomized to either no further invasive treatment (n = 313) or complete FFR-guided revascularization (n = 314) before discharge (occurring at a median of 2 days [interquartile range: 2 to 4 days]) post-index procedure). Patients were followed up for a median of 27 months (interquartile range: 12 to 44 months) and observed for development of the composite primary study endpoint of all-cause mortality, nonfatal reinfarction, and ischemia-driven revascularization of lesions in non-infarct-related arteries. The primary endpoint was significantly reduced in the FFR complete revascularization arm, with a HR of 0.56; 95% CI: 0.38 to 0.83; p = 0.004. Similar to the open-label FAME 2 trial, the primary endpoint in the DANAMI-3 PRIMULTI trial was driven by a large reduction in the need for repeat revascularizations, with no difference between the

groups noted in all-cause mortality or nonfatal reinfarction.

The recently reported open-label COMPARE-ACUTE (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) trial (51) was similar in design to the DANAMI-3 PRIMULTI trial, except FFR measurements were performed at the time of the primary PCI procedure, rather than staged. Patients were randomized in a 1:2 fashion to undergo FFR-guided complete revascularization of non-infarct-related coronary arteries (n = 295) or no revascularization of non-infarct-related coronary arteries (n = 590). The primary study endpoint was a composite of death from any cause, nonfatal MI, revascularization, and cerebrovascular events at 12 months. FFR-guided complete revascularization at the time of the index procedure was associated with a significant reduction in the primary endpoint, with a hazard ratio of 0.35 (95% CI: 0.22 to 0.55; $p < 0.001$), driven primarily by a reduction in subsequent revascularizations. Although a net beneficial outcome was clearly demonstrated, it is important to note that the physiological assessment of non-infarct-related vessels is not a benign process. Serious adverse events occurred in 0.2% of the COMPARE-ACUTE study population, including the dissection of a coronary artery with subsequent vessel occlusion, MI, and death (51).

Both the DANAMI-3 PRIMULTI and COMPARE ACUTE trials demonstrated the applicability and general safety of FFR to guide complete revascularization in STEMI. However, due to the lack of a physiological comparator arm, the full potential of coronary physiology applied to ACS cannot be elucidated from these data. In contrast to stable angina, ACS can unpredictably upset the microvascular milieu by a variety of mechanisms, including intramyocardial hemorrhage and microvascular obstruction. These factors have been demonstrated to limit the attainment of "maximal" hyperemia (52). In such situations, the true hemodynamic significance of a stenosis may be underestimated by FFR. In accordance with this theory, in a study of the long-term prognosis of deferred ACS lesions based on non-ischemic FFR values, an upward revision of the FFR cutpoint from 0.75 to 0.84 was demonstrated to provide an almost 2-fold reduction in the annualized MACE rate (53).

Pooled analysis from the DEFINE-FLAIR and iFR SWEDEHEART studies provides the first data comparing the relative performance of FFR versus iFR in the physiological assessment of nonculprit vessels in 440 patients with ACS. Among patients with ACS, those deferred using FFR were associated with a significantly worse outcome compared with those deferred with stable angina (HR: 0.52; 95% CI: 0.27 to 1.00; $p < 0.05$). However, patients deferred using iFR yielded similar outcomes among deferred patients, regardless of clinical presentation (HR: 0.74; 95% CI: 0.38 to 1.43; $p = 0.37$) (**Figure 14**). These data are suggestive that FFR may be an inferior prognostic tool in comparison with iFR for deferring nonculprit lesions in patients with ACS.

CONCLUSIONS

Recently reported clinical trials increase the amount of coronary physiological data 4-fold, more than double the available patient outcome data for FFR, and provide the first study of decision making for iFR-guided revascularization. Currently, FFR remains the legacy coronary physiology index in common daily practice. However, the contemporary, largescale body of evidence that supports the use of iFR as an alternative to FFR challenges this legacy, particularly as iFR is quicker and spares the patient the unpleasant side effects of adenosine.

Importantly, emerging data support that iFR may be a superior prognostic tool in comparison with FFR for deferring nonculprit lesions in patients with ACS. In this new era of physiological lesion assessment, the patient regains the central focus of attention, as prior debates over ischemia detection are superseded by clinical events as the ultimate gold standard test against which iFR and FFR modalities are judged.

The evolving future of iFR involves a change in the mindset of what coronary physiology as a modality is capable of. Specifically, real-time coregistered iFR pressure mapping with virtual PCI capability heralds a new paradigm for functional lesion assessment, where physiology is used to both justify and guide optimal coronary intervention.

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