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STATE-OF-THE-ART REVIEW

The Impact of Coronary Physiology on Contemporary Clinical Decision Making

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ABSTRACT

Physiological assessment of coronary artery disease (CAD) has become one of the cornerstones of decision making for myocardial revascularization, with a large body of evidence supporting the benefits of using fractional flow reserve and other pressure-based indexes for functional assessment of coronary stenoses. Furthermore, physiology allows the identification of specific vascular dysfunction mechanisms in patients without obstructive CAD. Currently, more than 10 modalities of functional coronary assessment are available, although the overall adoption of these physiological tools, of either intracoronary or image-based nature, is still low. In this paper the authors review these modalities of functional coronary assessment according to their timing of use: outside the catheterization laboratory, in the catheterization laboratory prior to the percutaneous coronary intervention (PCI), and in the catheterization laboratory during or after PCI. The authors discuss how the information obtained can be used in setting the indication for PCI, in planning and guiding the procedure, and in documenting the final functional result of the intervention. The advantages and limitations of each modality in each setting are discussed. Furthermore, the key value of intracoronary physiology in diagnosing mechanisms of microcirculatory dysfunction, which account for the presence of ischemia in many patients without obstructive CAD, is revisited. On the basis of the opportunities generated by the multiplicity of diagnostic tools described, the authors propose an algorithmic approach to physiological coronary investigations in clinical practice, with the key aims of: 1) avoiding unneeded revascularization procedures; 2) improving procedural PCI and long-term outcomes in patients with obstructive CAD; and 3) diagnosing vascular dysfunction mechanisms that can be effectively treated in patients with NOCAD. The authors believe that such structured approach may also contribute to the wider adoption of available technologies for functional assessment of patients with CAD. (J Am Coll Cardiol Intv 2020;13:1617–38)

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ABBREVIATIONS AND ACRONYMS

3VD = 3-vessel disease

ACh = acetylcholine

ACS = acute coronary syndrome

AS = aortic stenosis

CAD = coronary artery disease

CCS = chronic coronary syndrome

CTA = computed tomographic angiography

CFR = coronary flow reserve

CMD = coronary microvascular disease

CT = computed tomography

FFR = fractional flow reserve

FFR_{CT} = fractional flow reserve derived from computed tomographic angiography

HMR = hyperemic microvascular resistance

ICA = invasive coronary angiography

iFR = instantaneous wave-free ratio

IMR = index of microvascular resistance

MVD = multivessel disease

NHPR = nonhyperemic pressure ratio

NOCAD = nonobstructive coronary artery disease

PCI = percutaneous coronary intervention

Pd = distal coronary pressure

PET = positron emission tomography

QFR = quantitative flow ratio

RCT = randomized controlled trial

RFR = resting full-cycle ratio

SPECT = single-photon emission computed tomography

STEMI = ST-segment elevation myocardial infarction

TAVR = transcatheter aortic valve replacement

Physiological assessment of coronary artery disease (CAD) has become one of the cornerstones of decision making for myocardial revascularization. To date, more than 10 modalities are available for coronary physiological assessment (**Central Illustration**), although the adoption of physiological assessment is still restricted and limited, for multiple reasons. In this review we classify these modalities according to their timing of use: outside the catheterization laboratory prior to the treatment decision, in the catheterization laboratory prior to percutaneous coronary intervention (PCI), and in the catheterization laboratory during or after PCI. We elaborated on the advantages and limitations of each modality. Of note, the majority of these modalities used in daily practice focus only on epicardial artery disease, but a substantial number of patients have combined epicardial and microvascular disease. Therefore, it is essential to always take into consideration the presence or absence of microvascular dysfunction and perform appropriate tests to identify the dominant endotype of coronary microvascular disease (CMD).

HIGHLIGHTS

- Since the introduction of FFR, 10 more novel modalities for the assessment of coronary physiology have emerged.
- Physiological modalities should be appropriately selected according to their timing of use: outside the catheterization laboratory prior to the treatment decision and in the catheterization laboratory before and after PCI.
- The next challenge is to integrate the evaluation of microvascular circulation as part of daily practice.
- In the near future, invasive and noninvasive modalities of assessing coronary physiology may be integrated to stratify patients with history of anginal symptoms.

CLINICAL SCENARIO 1: PRE-PROCEDURAL PHYSIOLOGICAL ASSESSMENT OF CORONARY STENOSES OUTSIDE THE CATHETERIZATION LABORATORY

Interventional cardiologists are becoming familiar with physiological assessment in the catheterization laboratory, such as fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR). Other noninvasive functional tests are recommended in current guidelines for patients with suspected CAD (1). In the MR-INFORM (MR Perfusion Imaging to Guide Management of Patients With Stable Coronary Artery Disease) trial, the cardiac magnetic resonance–guided PCI strategy demonstrated noninferiority to the FFR-guided PCI strategy in terms of a composite clinical outcome among patients with typical angina and cardiovascular risk factors (2). However, several studies have shown that noninvasive functional tests can be falsely negative or can underestimate the amount of ischemia, especially in patients with multivessel disease (MVD) (3). In this regard, computed tomography (CT)-derived FFR has been introduced as a noninvasive physiological assessment to identify ischemia-generating stenoses before the procedure.

DEVELOPMENT OF CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY (CTA) AS A NONINVASIVE ANATOMIC TEST. In SCOT-HEART (Scottish Computed Tomography of the Heart Trial), among patients with suspected CAD, additional coronary CTA on top of standard care demonstrated a lower incidence of a composite primary endpoint of death from coronary heart disease or nonfatal myocardial infarction (MI) at 5 years compared with standard care alone (4). It is important to notice, however, that the difference was driven by a significant reduction in nonfatal MI

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in the coronary CTA arm, but there was no difference in death from coronary heart disease, cardiovascular disease, and any cause. Furthermore, other clinically important outcomes, such as hospitalization for heart failure and atrial fibrillation or flutter, were not reported in this trial. These issues may be partially addressed in the ongoing randomized DISCHARGE (Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease; NCT02400229) trial, which is designed to investigate the comparative effectiveness of coronary CTA and invasive coronary angiography (ICA) in 3,546 patients with intermediate pre-test probability of CAD (10% to 60%) (5).

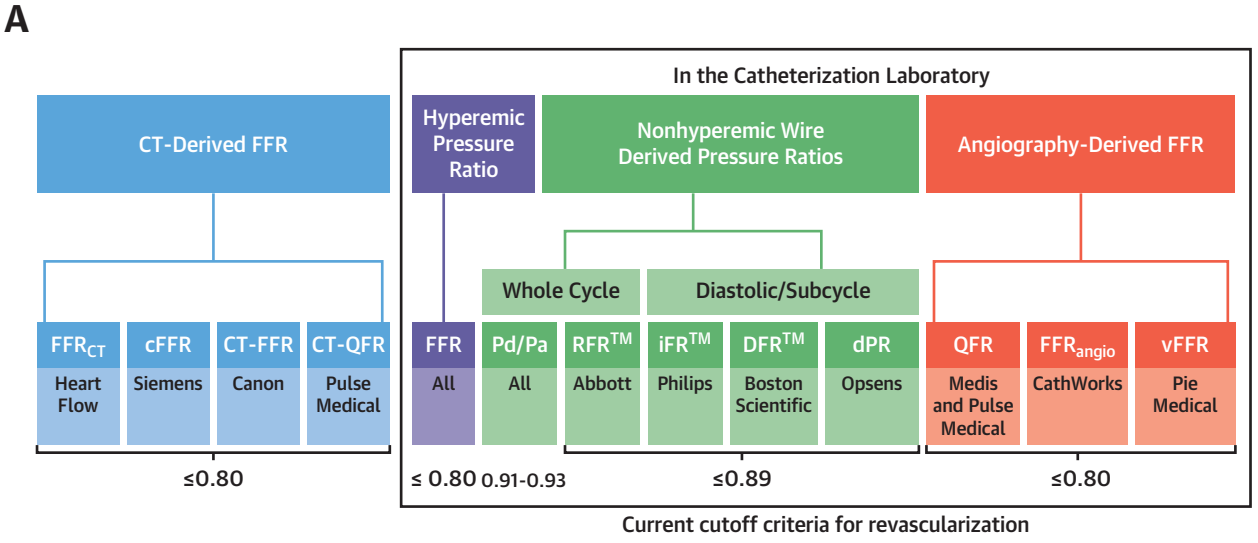
In terms of recommendations from international guidelines, the CE-MARC2 trial randomized patients with suspected angina to 3 arms: cardiac magnetic resonance-guided, single-photon emission CT (SPECT)-guided, or National Institute for Health and Care Excellence (NICE) 2010 guidelines-based management. The NICE 2010 guidelines recommended selecting the type of investigation according to CAD pre-test likelihood (10% to 29%, coronary CTA; 30% to 60%, SPECT; 61% to 90%, ICA). At 12 months, cardiac magnetic resonance-guided management resulted in a lower probability of unnecessary angiography than NICE 2010 guidelines-based management (6). Thereafter, the NICE guidelines were updated in November 2016 (7). The updated NICE guidelines were notable for the use of coronary CTA as the first-line investigation in all patients with atypical or typical angina symptoms or those who were asymptomatic with suggested electrocardiographic changes for ischemia. In current European Society of Cardiology (ESC) guidelines for chronic coronary syndrome (CCS), noninvasive functional imaging for myocardial ischemia or coronary CTA is also recommended as the initial test for diagnosing CAD in symptomatic patients with a Class I (Level of Evidence: B) recommendation (1). The same guidelines propose coronary CTA as preferentially considered if the pre-test likelihood of CAD is low and information on atherosclerosis desired. Therefore, symptoms and quality of life are as important as clinical outcomes on an individual patient basis. In the substudy of SCOT-HEART, additional coronary CTA did not alleviate symptoms and improve quality of life at 6 months compared with standard care, because of more detection of patients with undiagnosed nonobstructive CAD (NOCAD) in whom preventive therapies were initiated (8). Furthermore, physiological information is required for decision making in patients with undiagnosed NOCAD, as coronary CTA is only an anatomic test.

CT-DERIVED FFR. High sensitivity of coronary CTA is accompanied by moderate specificity and may result in an increase in unnecessary ICA (9). To address the moderate specificity of coronary CTA, CT-derived FFR was introduced in the field. FFR derived from CTA (FFR_{CT}) was developed using 3-dimensional reconstruction of the coronary arteries and computational fluid dynamics (10). Three major prospective trials demonstrated the feasibility and diagnostic performance of FFR_{CT} using invasive FFR ≤0.80 as a reference (**Table 1**) (11–13). The NXT (HeartFlowNXT—HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography) trial, in which best-practice guidelines for the acquisition of coronary CTA and the updated HeartFlow FFR_{CT} software (version 1.3) were used, demonstrated the superiority of FFR_{CT} over coronary CTA, with a higher area under the curve for FFR ≤0.80 (13). The specificity of FFR_{CT} for detecting invasive FFR ≤0.80 was acceptable and higher than that of coronary CTA (79% vs. 34%). In the PACIFIC (Comparison of Cardiac Imaging Techniques for Diagnosing Coronary Artery Disease) study, FFR_{CT} demonstrated higher diagnostic performance for invasive FFR ≤0.80 than coronary CTA, SPECT, and positron emission tomography (PET) in a per vessel analysis, whereas PET had favorable performance in per-patient and intention-to-diagnose analysis compared with coronary CTA, FFR_{CT}, and SPECT (14).

The PLATFORM (Prospective Longitudinal Trial of FFR_{ct}: Outcome and Resource Impacts) trial, which randomized patients with new-onset chest pain to either a coronary CTA/FFR_{CT} arm or a usual testing arm, demonstrated that coronary CTA/FFR_{CT} was a feasible and safe alternative to ICA and was associated with a significantly lower rate of ICA showing no obstructive CAD within 90 days (15). Furthermore, CTA/FFR_{CT}-guided care was associated with equivalent clinical outcomes and quality of life and lower costs (33% reduction) compared with usual care over 1-year follow-up (16). The ongoing FORECAST (Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain; NCT03187639) trial, which will randomize 1,400 patients with new-onset chest pain to either routine FFR_{CT} strategy or standard care according to updated NICE guidelines, is also investigating resource utilization.

In terms of clinical outcome, the 1-year results of the ADVANCE (Assessing Diagnostic Value of Non-Invasive FFR_{CT} in Coronary Care) registry, which prospectively enrolled 5,083 patients with suspected CAD, demonstrated that negative FFR_{CT} values

CENTRAL ILLUSTRATION **Currently Available Physiological Assessment**



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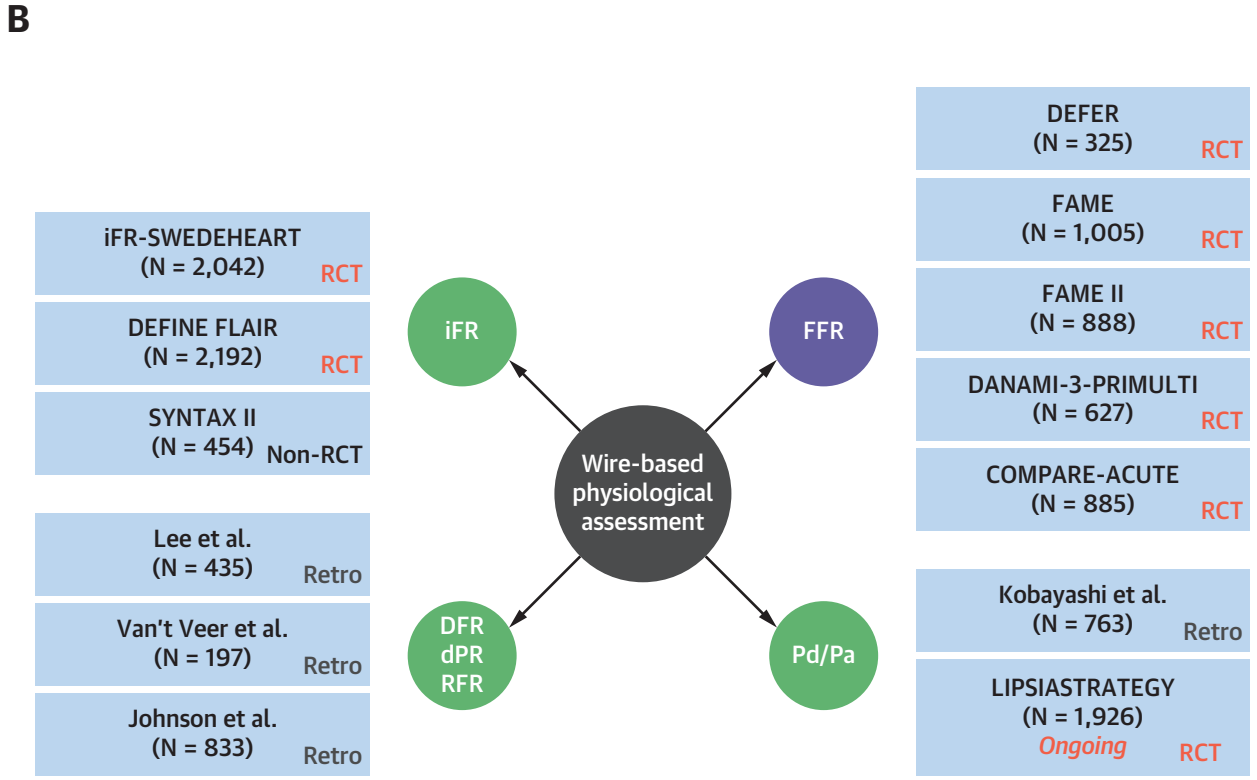
Overview is shown in **(A)**. Wire-based and imaging-derived physiological assessment with major trials are shown in **(B)** and **(C)**, respectively. ADVANCE = Assessing Diagnostic Value of Non-Invasive FFR_{CT} in Coronary Care; CT = computed tomography; DANAMI-3-PRIMULTI = Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction–Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization; DEFACTO = Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; DEFINE FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; DFR = diastolic hyperemia-free ratio; DISCOVER-FLOW = Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve; dPR = diastolic pressure ratio; FAME = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FAST = Fast Assessment of Stenosis Severity; FAST-FFR = FFR_{angio} Accuracy vs. Standard FFR; FAVOR II Europe-Japan = Diagnostic Accuracy of On-Line Quantitative Flow Ratio; FAVOR Pilot = Functional Assessment by Various Flow Reconstructions Pilot; FFR = fractional flow reserve; FORECAST = Fractional Flow Reserve Derived From Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain; iFR = instantaneous wave-free ratio; iFR-SWEDEHEART = Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome; LIPSIASTRATEGY = Comparison of Pd/Pa Versus FFR in Intermediate Coronary Stenoses; NXT = HeartFlowNXT—HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography; PACIFIC = Comparison of Cardiac Imaging Techniques for Diagnosing Coronary Artery Disease; PLATFORM = Prospective Longitudinal Trial of FFR_{ct}: Outcome and Resource Impacts; PRECISE = Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization; PROMISE = Prospective Multicenter Imaging Study for Evaluation of Chest Pain; QFR = quantitative flow ratio; RCT = randomized controlled trial; Retro = retrospective; RFR = resting full-cycle ratio; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; vFFR = vessel fractional flow reserve; WIFI II = Wire-Free Functional Imaging II.

Continued on the next page

(>0.80) were associated with favorable clinical outcomes compared with abnormal FFR_{CT} values (≤0.80) (17). Median 4.7-year follow-up of the NXT trial also showed an independent association of FFR_{CT} with major adverse cardiac event(s) (MACE) (18). However, more outcome data are needed, especially from randomized controlled trials (RCTs). The ongoing randomized PRECISE (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization; NCT03702244) trial will compare 1-year outcomes between usual care and coronary CTA/FFR_{CT}-guided therapy in 2,100 patients with suspected CAD.

Recently the potential of coronary CTA/FFR_{CT} to help inform revascularization decision making was investigated. In the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) II trial, calculation of the noninvasive functional SYNTAX score with coronary CTA/FFR_{CT} was feasible and yielded similar results to those obtained with invasive pressure-wire assessment in patients with 3-vessel disease (3VD) (19). Building on these findings, the hypothesis that combined noninvasive anatomy and physiology derived from coronary CTA plus FFR_{CT} may allow heart teams to plan complex coronary revascularization in patients with left main coronary artery (LMCA) disease or 3VD was proved in the SYNTAX III trial (20). FFR_{CT} changed the treatment decision in 7% of the patients. These findings suggest that the SYNTAX score III has emerged as a potentially useful tool combining information from physical comorbidities, coronary anatomy, and

CENTRAL ILLUSTRATION Continued



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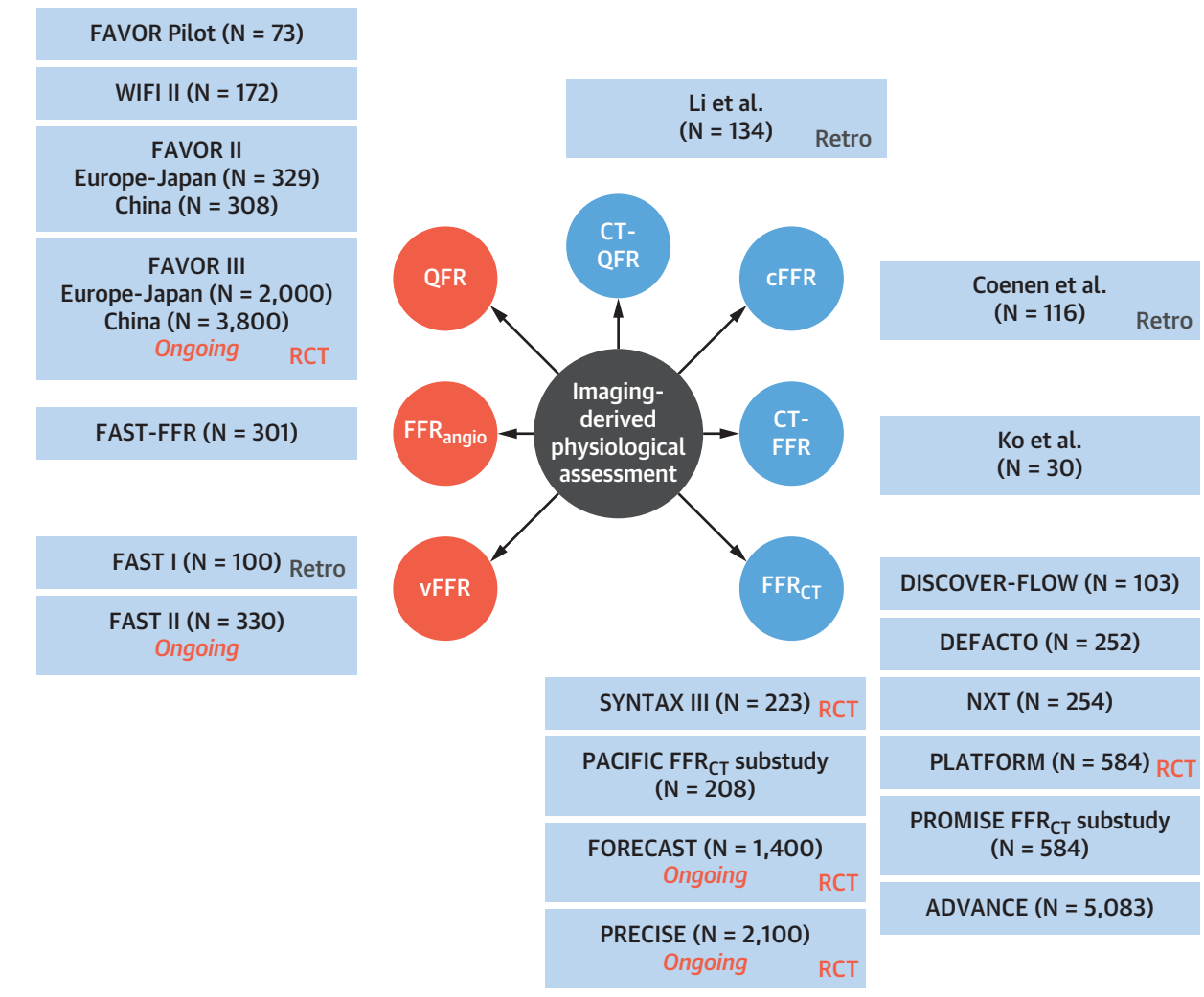
physiology derived from a single scan for decision making on the appropriate modality of revascularization (**Figure 1**).

A growing body of evidence suggests that the FFR_{CT} will be potentially a game changer in the diagnosis of patients with CCS. NICE (February 13, 2017) issued guidance for the use of FFR_{CT}, which recommends FFR_{CT} as the most cost-effective option when coronary CTA shows CAD with uncertain functional significance or is nondiagnostic (21).

However, several limitations and pitfalls of FFR_{CT} should be noted before privileging it as initial test. Suboptimal imaging quality of coronary CTA is among the major limitations of FFR_{CT}, which can be attributed to irregular heart rate, significant obesity, or inability to cooperate with breath-hold commands (1). The extra use of contrast media may also be a consequence. Despite optimizing image quality, severe and extensive coronary calcification remains challenging for coronary CTA as well as FFR_{CT}; however, among patients with high Agatston scores, FFR_{CT} provided high and superior diagnostic performance compared with coronary CTA alone using invasive FFR ≤0.80 as a reference (22). The rejection rate of FFR_{CT} ranged from 2.9% to 13%, as determined in prospective trials and a large clinical cohort (**Table 1**) (12,13,23). The main reason for the inability to perform FFR_{CT} was the presence of motion artifacts (23). Thinner CT slice thickness and lower patient heart rate may increase the analyzability of FFR_{CT}. Furthermore, a history of MI or the presence of a chronic total occlusion may be a limitation of FFR_{CT}. Indeed, a study comparing FFR_{CT} versus ICA using invasive FFR as reference for staged evaluation of nonculprit lesions in patients with ST-segment elevation MI (STEMI) showed similar but moderate diagnostic accuracy of FFR_{CT} compared with conventional ICA (accuracy 0.72 in both groups) (24). Of note, the use of FFR_{CT} is not validated in vessels previously revascularized. At the present time, FFR_{CT} analysis is feasible only in a central core laboratory (HeartFlow, Redwood City, California), limiting its real-time clinical use and necessitating telemedicine.

Thereafter, 3 CT-derived FFR software packages were developed to address longer computational time and inconvenience of off-site analysis. These

CENTRAL ILLUSTRATION Continued



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modalities demonstrated acceptable diagnostic accuracy for FFR ≤0.80 with shorter computational time, although none of them are commercially available (**Table 1**) (25–27).

According to current guidelines, coronary CTA is the first-line test in patients with suspected CAD, especially with low clinical likelihood (1). Additional CT-derived FFR will provide anatomic and lesion-specific physiological information as a "one-stop shop," which may facilitate speed of diagnosis with a substantial impact on quality of life and cost-effectiveness, despite somewhat lower specificity (about 80%) compared with physiological assessment in the catheterization laboratory with pressure wire.

CLINICAL SCENARIO 2: PHYSIOLOGICAL ASSESSMENT BEFORE THE PROCEDURE IN THE CATHETERIZATION LABORATORY

The second opportunity to perform physiological assessment is in the catheterization laboratory prior to revascularization, when localized ischemia is not documented and stenosis severity is between 50% and 90% diameter stenosis by visual estimation or MVD (1). Because fewer than one-half of all patients with stable CAD have documented ischemia by noninvasive testing within 90 days prior to elective PCI (28), a large number of patients are candidates to physiological assessment in the catheterization

TABLE 1 Diagnostic Performance of CT-Derived FFR Using FFR ≤0.80 as Reference

Trial/First Author (Ref. #)	No. of Patients or Vessels	Rejection Rate of CT-Derived FFR	AUC	Accuracy, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
FFR_{CT}								
DISCOVER-FLOW (11)	103 patients	NA	0.92	87	93	82	85	91
	159 vessels		0.90	84	88	82	74	92
DeFACTO (12)	252 patients	13%	0.81	73	90	54	67	84
	407 vessels		NA	NA	80	61	NA	NA
NXT (13)	254 patients	11%	0.90	81	86	79	65	93
	484 vessels		0.93	86	84	86	61	95
cFFR								
Coenen et al. (25)	116 patients	5%	NA	NA	NA	NA	NA	NA
	203 lesions		NA	75	88	65	66	87
CT-FFR								
Ko et al. (26)	30 patients	3%	0.88	NA	78	87	74	89
	58 vessels		0.77	84	79	74	60	88
CT-QFR								
Li et al. (27)	134 patients	13%	NA	87	90	85	83	91
	156 vessels		NA	87	88	87	83	91

AUC = area under the curve; CT = computed tomography; DeFACTO = Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography; DISCOVER-FLOW = Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve; FFR = fractional flow reserve; NA = not available; NPV = negative predictive value; NXT = HeartFlowNXT—HeartFlow Analysis of Coronary Blood Flow Using Coronary CT Angiography; PPV = positive predictive value; QFR = quantitative flow ratio.

laboratory. Furthermore, even when proof of myocardial ischemia is available, intracoronary interrogation may be required to identify which stenosis accounts for ischemia.

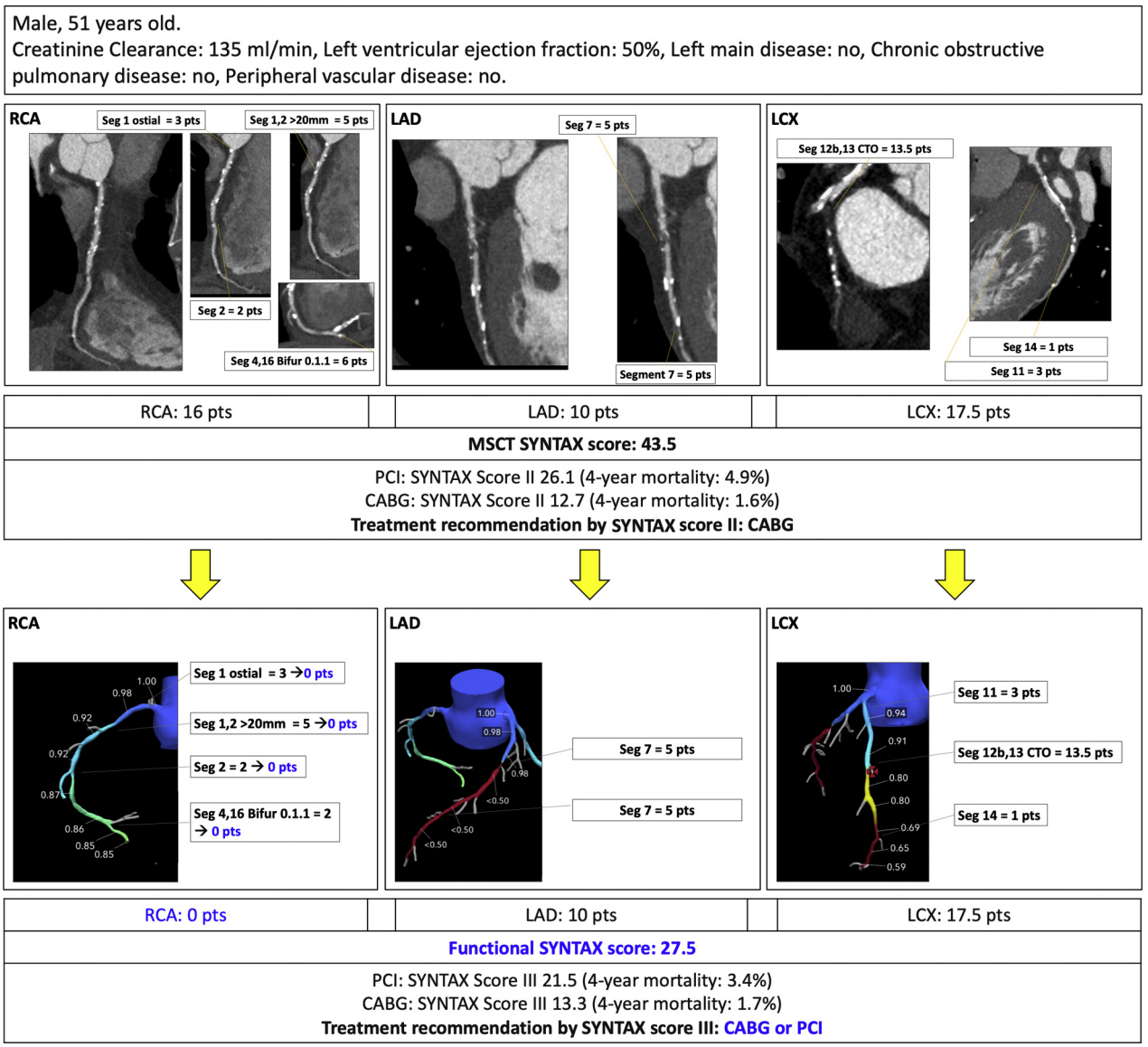
FFR. FFR is the best known index for physiological assessment in the catheterization laboratory. FFR is the mean ratio of distal coronary pressure to aortic pressure at maximum hyperemia. On the basis of the linear coronary pressure-flow relationship during maximal hyperemia, with a few assumptions incorporated into its theoretical framework, FFR expresses the percentage contribution of a coronary stenosis to myocardial flow impairment. The clinical significance of FFR ≤0.75 was first validated against noninvasive functional testing (29). The 2005 ESC guidelines recommended, for the first time, considering the existence of a gray zone of FFR values (between 0.75 and 0.80) in which the decision to perform revascularization should be left to the operator (30). Since then, the cutoff threshold value of FFR ≤0.80 has been used in most clinical studies.

In a meta-analysis of FFR-guided PCI versus medical therapy using individual patient data, a 28% of reduction in the composite endpoint of cardiac death or MI was observed with FFR-guided PCI compared with medical therapy (31). The difference between groups was driven by MI. These findings justify the recommendation of performing FFR to assess functional coronary relevance, whenever prior evidence of ischemia is not available, laid out in the 2018 ESC guidelines (Class I, Level of Evidence: A) (32). The first studies of FFR focused on setting the indication for PCI, thus avoiding unneeded revascularization of stenoses without functional relevance. The DEFER study demonstrated the very long term (15 years) safety and efficacy of deferral PCI in stenoses with FFR <0.75 (**Table 2**) (33).

The next large trial on FFR focused on its value in patients with MVD, a clinical scenario in which noninvasive functional testing does not always provide accurate information to decide which stenoses should be considered for revascularization (3). FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) I demonstrated the superiority of the FFR-guided PCI over angiography-guided PCI among patients with MVD in terms of a composite clinical endpoint at 1 year (34). Of note, the grounds of the recommendations of the 2005 ESC guidelines (30), the FAME study applied for the first time an FFR cutoff of ≤0.80 for decision making. The favorable results of the study were achieved with lower cost and without prolongation of the procedure time (35). Even after 5 years, differences persisted but lost statistical significance because of the smaller number of patients at risk (**Table 2**) (36).

Thereafter, FAME II demonstrated that the FFR-guided PCI with medical therapy is superior to medical therapy alone in clinical outcome in patients with at least 1 stenosis with FFR ≤0.80 (37). The 5-year follow-up clearly confirmed the initial results and extended these findings to a reduction in the

FIGURE 1 SYNTAX Score III Calculation by Coronary CTA and FFR_{CT}



A representative case for SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score III calculation using coronary computed tomographic angiography (CTA) and computed tomography–derived fractional flow reserve (FFR_{CT}). After incorporation of FFR_{CT}, the treatment recommendation was changed from coronary artery bypass grafting (CABG) to equipoise risk between CABG and percutaneous coronary intervention (PCI). CTO = chronic total occlusion; LCX = left circumflex coronary artery; LAD = left anterior descending coronary artery; MSCT = multislice computed tomography; pts = points; RCA = right coronary artery; Seg = segment.

composite of death and MI, driven mainly by a reduction in spontaneous MI with PCI compared with medical therapy (Table 2) (38).

Of note, the FAME II trial was launched in the aftermath of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (39), which demonstrated a lack of benefit of PCI over optimal medical therapy alone in terms of long-term death and MI rates. The results of COURAGE were criticized because of the inclusion of patients with mild myocardial ischemia. Recently, ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) showed that in patients with moderate or severe myocardial ischemia assessed by noninvasive testing, an invasive strategy with optimal medical

TABLE 2 Major Randomized Controlled Trials Using Wire-Based Physiological Assessment

Study Name	n	Follow-Up	Population	Comparison	Primary Endpoint	Result	p Value
DEFER	325	15 yrs	Patients with de novo stenosis (DS >50%)	Deferral with FFR ≥0.75 vs. performed PCI with FFR ≥0.75	MI	2.2% vs. 10.0%	0.033
FAME	1,005	5 yrs	Patients with multivessel disease	FFR-guided vs. angiography-guided PCI	Composite of death, MI, or revascularization	28.0% vs. 31.0%	0.31
FAME II	888	5 yrs	Patients with de novo stenosis with FFR ≤0.80	FFR-guided PCI plus OMT vs. OMT alone	Composite of death, MI, or urgent revascularization	13.9% vs. 27.0%	<0.001
DANAMI-3-PRIMULTI	627	1 yr	Patients with STEMI with ≥1 clinically significant stenosis in the non-infarct-related vessel	FFR-guided complete revascularization vs. no further invasive treatment (culprit only)	Composite of death, nonfatal MI, or ischemia-driven revascularization	13.0% vs. 22.0%	0.004
Compare-Acute	885	1 yr	Patients with STEMI with ≥1 clinically significant stenosis in the non-infarct-related vessel	FFR-guided complete revascularization vs. no further invasive treatment (culprit only)	Composite of death, nonfatal MI, revascularization, and cerebrovascular events	7.8% vs. 20.5%	<0.001
iFR SWEDEHEART	2037	2 yrs	Patients with de novo stenosis (DS 40%–70%)	FFR-guided vs. iFR-guided PCI	Composite of death, nonfatal MI, or unplanned revascularization	8.4% vs. 8.7%	0.93
DEFINE-FLAIR	2492	2 yrs	Patients with de novo stenosis (DS 40%–80%)	FFR-guided vs. iFR-guided PCI	Composite of death, nonfatal MI, or unplanned revascularization	10.5% vs. 11.8%	0.25

DANAMI-3-PRIMULTI = Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction–Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization; DEFINE-FLAIR = Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation; DS = diameter stenosis; FAME = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; iFR SWEDEHEART = Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; STEMI = ST segment elevated myocardial infarction.

therapy offers no clinical benefit compared with optimal medical therapy alone in terms of the composite primary endpoint at a median of 3.2 years (40). From the viewpoint of physiological assessment, whether physiology-guided invasive management might have led to different outcomes is unknown, as decisions during invasive management were predominantly angiography guided. FFR was used in only 20% of patients in the invasive arm, according to the protocol.

Another important subset of patients who might benefit from FFR interrogation are those presenting with STEMI and MVD. Several studies in this subset of patients have used FFR to ascertain the functional relevance of nonculprit coronary stenoses (**Table 2**). In the Compare-Acute and DANAMI-3-PRIMULTI (Danish Study of Optimal Acute Treatment of Patients With ST-Elevation Myocardial Infarction-Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization) trials, FFR-guided complete revascularization strategy significantly reduced the incidence of the composite clinical endpoint at 12 months compared with the culprit-only revascularization strategy in patients with STEMI and MVD (41,42). However, in the COMPLETE (Complete vs Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) trial, angiography-guided complete revascularization of lesions with diameter stenosis >70% clearly demonstrated superiority to a culprit-only revascularization strategy among 4,041 patients with STEMI and MVD in terms of the primary composite endpoint at 3 years (43). Further study is warranted to compare FFR-guided versus angiography-guided complete revascularization in patients with STEMI and MVD as far as outcomes and cost-effectiveness are concerned.

The growth of evidence supporting the clinical value of FFR was not mirrored by a substantial increase in its adoption in clinical practice (44). A number of potential causes for this (**Table 3**) include the following: 1) prolongation of procedural time; 2) additional cost for pressure wire and adenosine or other drugs; 3) discomfort or side effect from vasodilator drugs; 4) submaximal hyperemia; 5) precise acquisition of coronary pressure measurement for avoiding pressure drift, aortic pressure ventricularization, and aortic waveform distortion; and 6) suboptimal mechanical quality of pressure wire, which may result in difficult wire manipulation in complex anatomy and procedural complication.

INTRODUCTION OF A NONHYPEREMIC PRESSURE RATIO (NHPR): iFR. To avoid adenosine administration, NHPRs have been recently introduced, with iFR being the first index (45). iFR is measured as the mean ratio of instantaneous phasic distal coronary pressure

TABLE 3 Advantages and Limitations of Physiological Assessment in the Catheterization Laboratory

Wire-Based Physiological Assessment			
Hyperemic Index	**NHPR**		
FFR	**iFR**	**Novel NHPRs (DFR, dPR, RFR)**	**Pd/Pa**
Advantages			
• Evidence for outcomes up to 15 yrs (vs. angiography-guided PCI, OMT alone) • Well validated with noninvasive functional tests in various clinical settings • Cost-effectiveness was demonstrated against angiography-guided PCI • Available with all pressure wires	• Evidence for outcomes up to 2 yrs (vs. FFR-guided PCI) • Validated with noninvasive functional tests in several clinical settings • Well validated with FFR in various clinical settings • Hyperemia independent • Quicker than FFR • Ability with potential to assess serial lesions • Coregistration with angiography available	• Validated with FFR and iFR in limited clinical settings (retrospective) • Hyperemia independent • Quicker than FFR	• Validated with FFR and iFR in limited clinical settings • Hyperemia independent • Quicker than FFR • Available with all pressure wires
Limitations			
• Hyperemia required (additional cost and hyperemic agent-related side effect) • Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Prolonged procedure	• Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Proprietary and the software of specific vendor required	• No evidence for outcomes • Validation data with noninvasive functional tests are limited • Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Proprietary and the software of specific vendor required • No coregistration with angiography available	• No evidence for outcomes • Validation data with noninvasive functional tests are limited • Pressure wire required (additional cost and wire-related complication) • Precise acquisition of coronary pressure required • Susceptible to miscalculation from pressure-wire drift • No coregistration with angiography available

TABLE 3 Continued

Imaging-Based Physiological Assessment		
Angiography Derived		
QFR	**FFR_{angio}**	**vFFR**
Advantages		
• Validated with FFR in limited clinical settings • Hyperemia independent • Pressure wire free • Flow information (TIMI frame count) incorporated • Quicker than FFR	• Validated with FFR in limited clinical settings • Hyperemia independent • Pressure wire free	• Validated with FFR in limited clinical settings (retrospective) • Hyperemia independent • Pressure information (Pa) incorporated • Pressure wire free
Limitations		
• No evidence for outcomes (FAVOR III is ongoing) • Precise acquisition of angiography required • Specific software required • Manual correction required in some cases	• No evidence for outcomes • No validation data with noninvasive functional tests • Precise acquisition of angiography required • Specific software required • Manual correction required in some cases	• No evidence for outcomes • No validation data with noninvasive functional tests • Precise acquisition of angiography required • Specific software required • Manual correction required in some cases

DFR = diastolic hyperemia-free ratio; dPR = diastolic pressure ratio; IVUS = intravascular ultrasound; NHPR = nonhyperemic pressure ratio; Pa = aortic pressure; Pd = distal coronary pressure; QFR = quantitative flow ratio; RFR = resting full-cycle ratio; TIMI = Thrombolysis In Myocardial Infarction; vFFR = vessel fractional flow reserve; other abbreviations as in Table 2.

to aortic pressure during a diastolic window free of newly generated wave activity called the "wave-free period." Interrogation of the coronary circulation over the wave-free period has the advantage that microcirculatory resistance is considered to be stable and the lowest value over the whole cardiac cycle (45). The wave-free period was calculated beginning 25% of the way into diastole (identified from the dicrotic notch of pressure waveform) and ending 5 ms before the end of diastole (**Figure 2**).

The iFR concept has been tested in a number of validation studies with direct comparison with FFR (45,46). An iFR value of 0.89 was determined to be the best cutoff value to predict FFR of 0.80 (46) and has been widely used for decision making.

Subsequent studies were performed focusing on head-to-head comparisons of iFR and FFR against other independent standards used for the detection of ischemia. These studies found no difference between iFR and FFR in terms of the diagnostic

performance using as a reference PET (47,48) and SPECT (49).

Thereafter, 2 of the largest randomized trials in coronary physiology compared iFR with FFR, with clinical outcomes as an endpoint (2,042 patients in iFR SWEDEHEART [Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome], 2,492 patients in DEFINE-FLAIR [Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation]) and reached the same conclusion: iFR-guided PCI was noninferior to FFR-guided PCI in the selection of the vessels to be treated or deferred and in the resulting rates of MACE at 12 months (50,51) (**Table 2**). The incidence of MACE in both arms did not differ up to 2 years in both trials (52). Nevertheless, limitations of iFR pertain to the lack of long-term prognostic data as opposed to FFR (38). However, it should be noted that the FFR long-term data are predominately in very significant lesions, and the first data to support the use of coronary physiology, whether FFR or iFR, in intermediate lesions was generated in the iFR outcomes studies.

Following iFR SWEDEHEART and DEFINE-FLAIR, the ESC guidelines were revised and gave a Class I (Level of Evidence: A) recommendation for guiding PCI in both iFR and FFR (32). Of note, iFR coregistration with angiography allows physicians to identify the lesion and the length of the narrowing that must be treated (**Figure 3**) (44). Some advantages of iFR over FFR include shorter procedure time, less patient discomfort, and easy pull back, especially for evaluation of serial lesions (**Table 3**). iFR, but not FFR, can separately assess the severity of each individual stenosis within the same tandem lesion. This is because in nonhyperemic conditions coronary flow remains relatively constant and stable regardless of the severity of stenosis, because of the autoregulation of microvascular circulation, whereas during hyperemia coronary flow becomes unpredictable if it passes through stenosis with a dimeter stenosis ≥40% (53,54). In the iFR GRADIENT registry, iFR pull back predicted the physiological outcome of PCI with a difference of 0.011 ± 0.004 in tandem and diffuse coronary disease (55). In contrast, Modi et al. (56) reported that individual stenosis severity is significantly underestimated in the presence of serial disease, using both hyperemic and resting pressure-based indexes. An important limitation of iFR is that it cannot be measured without the software of a specific vendor (Philips/Volcano, Amsterdam, the Netherlands) (**Table 3**).

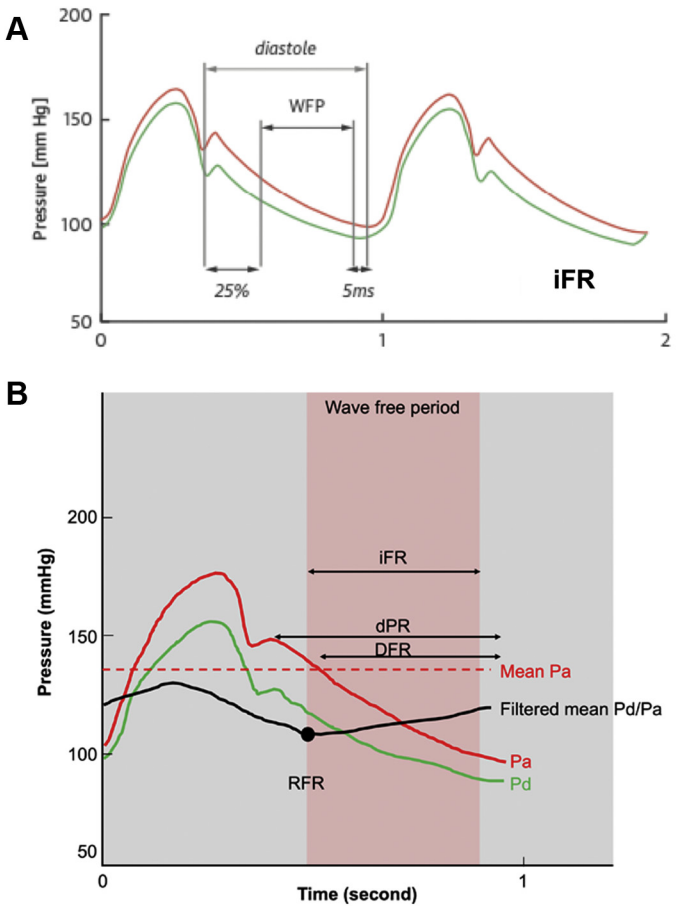
DISCORDANCE BETWEEN FFR AND iFR. Approximately 20% of cases show discrepancies between FFR with a threshold of 0.80 and iFR with a threshold of 0.89 (57). The cause of the discordance may be attributable to different thresholds, effects of hyperemia (e.g., 2 to 3 times larger pressure gradient at maximum hyperemia than at rest), and/or different responses to microvascular dysfunction. Interestingly, with regard to wire-based coronary flow reserve (CFR), iFR was found to have better diagnostic performance than FFR in 3 separate studies (58–60). This observation provided important clues on one of the main causes for discrepancy between FFR and iFR. Yet it should to be clarified that both FFR and iFR were unable to discriminate the impact of epicardial and microvascular disease.

The discordance between FFR and iFR would depend partially on lesion location and type. Kobayashi et al. (61) reported that at the LMCA or the proximal left anterior descending artery (LAD), iFR was less correlated with the reference of FFR compared with other lesion locations. In a substudy of the DEFINE-FLAIR trial, iFR-guided deferral for LAD lesions was associated with a lower rate of MACE at 1 year compared with FFR-guided deferral for LAD lesions (62). However, this result should be considered as a truly hypothesis generating because of the post hoc character of the analysis, with insufficient statistical power. Thus, a further confirmatory randomized trial will be needed to conclude whether FFR or iFR is better or if they are comparable for LAD lesions.

Of note, the methodology of the available studies investigating the discrepancy between FFR and iFR cannot rule out other important causes of this discrepancy. As an example, none of the reported trials checked for patient intake of coffee over the 24 h prior to FFR interrogation, which has been demonstrated to blunt the effect of adenosine-induced hyperemia and FFR values (63).

In contrast, available evidence suggests that overall, discordant FFR versus iFR results lack clinical relevance. Lee et al. (64) found that the presence of discordance between FFR and NHPRs including iFR was not an independent predictor of vessel-oriented composite outcomes. This lack of clinical translation of the discordance between indexes is most likely related to its occurrence in borderline stenosis with a low risk for hard clinical events. Although further research might be needed to clarify clinical relevance of discordance between indexes, it might be too challenging from a statistical standpoint. On the basis of some premises derived from iFR SWEDEHEART and DEFINE-FLAIR, it is hypothesized that a study would require a sample size of 290,000 patients to clarify the difference of predictive value for MACE between FFR and iFR (65). Therefore, it would be

FIGURE 2 Commercially Available Nonhyperemic Pressure Ratios



Instantaneous wave-free ratio (iFR) is defined as average Pd/Pa during the wave-free period (WFP) **(pink shaded area)**. The WFP was calculated beginning 25% of the way into diastole and ending 5 ms before the end of diastole **(A)**. Diastolic pressure ratio (dPR) is defined as average Pd/Pa during entire diastole **(B)**. Diastolic hyperemia-free ratio (DFR) is defined as average Pd/Pa during Pa less than mean Pa with negative slope **(B)**. Resting full-cycle ratio (RFR) is defined as the lowest filtered mean Pd/Pa during the entire cardiac cycle **(B)**. Adapted with permission from Van't Veer et al. (85).

necessary to discuss the appropriate clinical and lesion setting for the use of FFR or iFR rather than to debate whether one is superior to the other.

DIFFERENCES BETWEEN FFR AND iFR IN SOME SPECIFIC CLINICAL SETTINGS. LMCA disease. The importance of physiological assessment has been suggested even in the field of LMCA disease (66). The only dedicated study to date is the DEFINE LM registry, which included patients in whom LMCA stenosis was deferred (51.9%) or revascularized (48.1%) according to an iFR cutoff of 0.89 (67). The result suggests that decision making in LMCA disease on the basis of iFR is safe in terms of a composite clinical endpoint at 30 months. Ongoing research includes the iLITRO (Concordance Between FFR and iFR for the Assessment of Intermediate Lesions in the Left Main Coronary Artery: A Prospective Validation of a Default Value for iFR) study (NCT03767621), whose aim is to demonstrate the actual feasibility and efficacy of iFR compared with FFR in patients with intermediate LMCA disease.

Diffuse and focal lesions. The physiological pattern of lesions, such as focal or diffuse, obtained over iFR pull back curves has been reported as one of the factors of discordance between FFR and iFR. Warisawa et al. (68) demonstrated that a focal pattern was associated with discordance of FFR ≤0.80 and iFR >0.89, whereas a diffuse pattern was associated with discordance of FFR >0.80 and iFR ≤0.89. These discordances may stem from the higher turbulence-generating potential of focal stenosis, which under hyperemia may cause lower FFR, or from microvascular dysfunction, as diffuse disease is associated with the presence of microvascular dysfunction (69), and response to microvascular dysfunction is different between FFR and iFR, as previously described (59). Physiological pattern, which can be derived from FFR (e.g., pull back pressure gradient index) (70), may have the potential to determine the eligibility of revascularization for those lesions with discordance. The pull back pressure gradient index is a novel metric that is able to discriminate focal and diffuse functional CAD; further validation of this metric is still required. In the occasional cases in which the discordance between iFR and FFR related to the focal and diffuse pattern is deemed to be clinically relevant, other noninvasive functional tests may be considered.

MVD. The efficacy of FFR-guided PCI for patients with MVD has been demonstrated, as previously described. From a practical perspective, the ease of performing multiple measurements and pressure pull backs without inducing hyperemia makes iFR a very attractive alternative to FFR in patients with MVD. About 40% of patients included in the iFR SWEDEHEART and DEFINE-FLAIR trials had MVD (50,51), and a substudy of iFR SWEDEHEART demonstrated no significant difference between FFR- and iFR-guided revascularization in terms of MACE at 1 year in patients with MVD as well as single-vessel disease (71).

Recently, SYNTAX II, which prospectively enrolled patients with 3VD, demonstrated less repeat revascularization in deferred lesions on the basis of iFR value than in stented lesions between 1 and 2 years (72,73). The results support the safety of iFR-guided decision making for long-term results in patients

with 3VD. iFR-guided PCI for MVD seems promising, but more prospective data are required to reinforce the evidence.

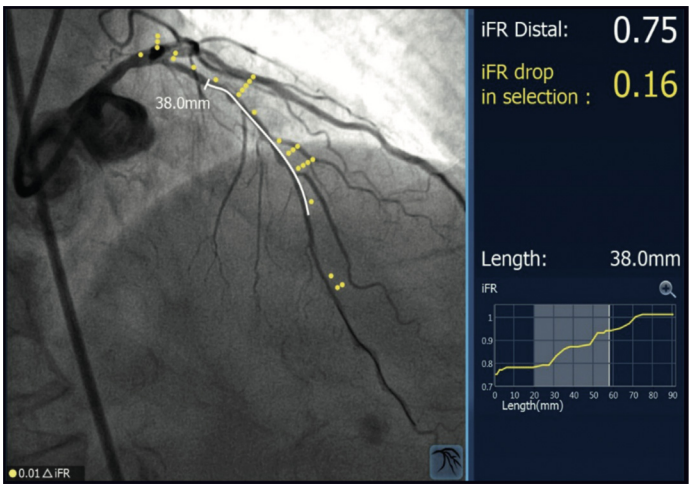
Non-infarct-related arteries in the early phase of acute coronary syndrome (ACS). The interest in using iFR in patients with ACS relates to circumventing the problem of blunted hyperemia associated to ACS and to the reluctance of many operators to use vasodilators during primary PCI. Several studies have fostered interest in iFR as a faster and potentially safer alternative to FFR for interrogation of nonculprit stenoses in ACS. A pooled analysis of DEFINE-FLAIR and iFR SWEDEHEART showed comparable clinical outcomes between iFR- and FFR-guided PCI, with more deferral in the iFR arm in patients presenting with ACS but not including STEMI (74). In non-infarct-related lesions in patients with STEMI, a substudy of the REDUCE-MVI (Reducing Micro Vascular Dysfunction in Revascularized STEMI Patients by Off-Target Properties of Ticagrelor) trial found lower iFR values in nonculprit vessels at the time of primary PCI than in the subacute STEMI phase, with 11% false-positive classification of nonculprit stenosis (75). False-positive measurements with iFR at the time of primary PCI might be a result of the documented increase in resting flow in nonculprit stenoses in patients with STEMI (76), potentially as a result of enhanced adrenergic drive during the acute STEMI phase.

In contrast, Choi et al. (77) reported that FFR and iFR values were not significantly different between non-infarct-related vessels in acute MI and target vessels in stable CAD across all percentage diameter stenosis groups, which contradicts the result of the previous report. Clarification of this will be provided by future research. Ongoing randomized trials such as iMODERN (iFR Guided Multi-Vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction; NCT03298659) and SAFE STEMI for Seniors (Study of Access Site for Enhancing PCI in STEMI for Seniors; NCT02939976) will provide key information on then reliability of iFR-guided intervention of nonculprit lesions during STEMI.

Severe aortic stenosis (AS). In patients with severe AS, simultaneous revascularization of severe coronary artery stenosis by visual estimation is recommended in the current guidelines (32). Some studies showed the feasibility and safety of wire-based physiological assessment, including administration of adenosine, in patients with severe AS (78), but it is unclear whether wire-based physiological assessment has clinical implications with respect to decision making in patients with severe AS. The specific pathophysiological characteristic of severe AS, including left ventricular hypertrophy, increased afterload, and microvascular dysfunction, make the interpretation of wire-based physiological measurement difficult (79). Adjusted cutoff criteria of FFR and iFR for patients with severe AS have been reported but not yet been firmly established (80).

Ahmad et al. (81) reported changes in coronary physiological status in intermediate lesions before and after transcatheter aortic valve replacement (TAVR). FFR was significantly reduced after TAVR (from 0.86 to 0.83), whereas iFR was unchanged (0.87 both before and after TAVR). This finding can be explained by the improvement in coronary microvascular circulation assessed using CFR after TAVR (from 1.56 to 1.74), suggesting that FFR may underestimate the severity of coronary stenosis in patients with severe AS. However, Pesarini et al. (78) showed that the FFR was unchanged before (0.89) and immediately after (0.89) TAVR, although iFR was not measured in that study. These inconsistent findings indicate that the data remain uncertain, and the robustness of previous analyses is debatable, mainly because of small sample sizes. The ongoing FORTUNA (Evaluation of Fractional Flow Reserve Calculated by Computed Tomography Coronary Angiography in Patients Undergoing TAVR; NCT03665389) and FAI-TAVI trial (Functional Assessment in TAVI;

FIGURE 3 iFR Coregistration



The result of coregistering instantaneous wave-free ratio (iFR) pull back data with angiography in the left anterior descending coronary artery with several irregularities. Each **yellow dot** represents a modification of 0.01 iFR units. Plot location of pressure loss on angiogram in its final interactive action allows the physician to identify the lesion and the length of the narrowing that must be treated. Adapted with permission from Gotberg et al. (44).

TABLE 4 Commercially Available Software for Angiography-Derived FFR

	QFR	FFR_{angio}	vFFR
Online computation	Available	Available	Available
Required angiography	2 projections 25° apart	≥2 projections	2 projections 30° apart
Process	Integrated mathematical approach	Rapid flow analysis	Integrated mathematical approach
Published clinical data	FAVOR Pilot (90), FAVOR II China (91) and FAVOR II Europe-Japan (92), WIFI II (93)	FAST-FFR (94)	FAST (95)
Incidence of nonanalyzable cases in each study	10%, 0.9%, 3.2%, and 5.9%, respectively	3.7%	49% (retrospective)
Predictive performance for predicting wire-derived FFR ≤0.80 (AUC)	0.92-0.96	0.94	0.93
Time to computation	5 min	NA*	NA

*An average processing time was reported as 2.7 min, but this processing time did not include the manual correction of the coronary reconstruction and lesion identification (94).

FAST = Fast Assessment of Stenosis Severity; FAST-FFR = FFRangio Accuracy vs. Standard FFR; FAVOR Pilot = Functional Assessment by Various Flow Reconstructions Pilot; FAVOR II Europe-Japan = Diagnostic Accuracy of On-Line Quantitative Flow Ratio; WIFI = Wire-Free Functional Imaging II; other abbreviations as in Tables 1 to 3.

NCT03360591) will provide new insights and evaluate coronary physiology in severe AS.

OTHER NHPRs. Since the success of iFR, other NHPRs have become commercially available, such as the diastolic hyperemia-free ratio (Boston Scientific, Marlborough, Massachusetts), diastolic pressure ratio (Opsens Medical, Quebec, Quebec, Canada), and resting full-cycle ratio (RFR) (Abbott, Abbott Park, Illinois) (**Central Illustration, Figure 2**). These novel NHPRs are also proprietary and can be used only with the software provided by the vendors. However, the fact that most of companies have their own pressure wires, wire-specific consoles, and NHPRs may ultimately result in wider adoption of physiology-guided PCI.

The ratio of distal coronary pressure (Pd) to aortic pressure (Pa) is the oldest and most straightforward NHPR. As early as 1985, the first clinical application of Pd/Pa in humans was reported (82). High correlation and excellent agreement between Pd/Pa and iFR were reported (83). However, from a practical perspective, the use of Pd/Pa is limited by a lower signal-to-noise ratio and significantly lower data spread than iFR and other NHPRs, contributing to higher influence of pressure drift on measurements (47,84).

Other NHPRs use phasic and beat-by-beat Pd/Pa during part of or the entire diastolic phase, except for RFR, as RFR uses the lowest filtered Pd/Pa over the entire cardiac cycle (**Figure 2**). Van't Veer et al. (85) evaluated 6 NHPRs and concluded that all diastolic resting indexes tested were identical to iFR, both numerically and with respect to their agreement with FFR. Several studies also retrospectively demonstrated excellent correlation and agreement of RFR, diastolic pressure ratio, and diastolic hyperemia-free ratio with iFR (86,87). However, the previous validation studies were retrospective comparisons using a "cleaned" pressure database in the core laboratory, and a prospective in vivo validation study using a commercially available system has not yet been performed. Furthermore, we must emphasize the fact that to date, no RCTs have evaluated the impact of NHPR-guided PCI on clinical outcomes compared with established PCI strategies. The commonly shared opinion of experts in the field is that if RCTs do take place, there is a great likelihood that they would lead to similar outcomes. Therefore, in addition to an in vivo validation study, large-scale RCTs with clinical outcomes may not necessarily be required, and single-arm prospective trials with objective performance criteria may be sufficient to demonstrate the noninferiority of non-iFR NHPRs to FFR- or iFR-guided PCI, which also may result in faster and wider adoption of physiological assessment in daily practice. At this point, according to the latest appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease (88), it seems reasonable to suggest that NHPR may be considered a substitute for FFR in most clinical scenarios.

ANGIOGRAPHY-DERIVED FFR. In the context of growing interest in functional assessment of coronary stenoses, advances in computational power and 3-dimensional coronary angiography have made possible the development of functional coronary angiography. Currently, 3 technologies are commercially available: quantitative flow ratio (QFR) (Medis

TABLE 5 Major Trials Investigating the Impact of Post-PCI Physiological Assessment on Clinical Outcomes

	Primary Endpoint	Cutoff Value of FFR (QFR) for Predicting Primary Endpoint (AUC)	Comparison of Low vs. High Post-PCI FFR (QFR) on Primary Endpoint	
Pressure wire–derived FFR				
FAME I and II (101): 838 vessels	2-yr VOCE (vessel-related cardiac death, vessel-related MI, ischemia-driven TVR)	FFR ≤0.92 (NA)	9.2% vs. 3.8% (lower [<0.88] vs. upper [>0.92] tercile)	p = 0.037
DK CRUSH VII (102): n = 1,476	1-yr TVF (cardiac death, target vessel MI, clinically driven TVR)	FFR ≤0.88 (0.83)	8.0% vs. 4.0%	p = 0.001
Agarwal et al. (98): n = 574	MACE (death, MI, TVR); mean follow-up 31 ± 16 months	FFR ≤0.86 (NA)	23% vs. 17%	p = 0.02
Angiography-derived FFR				
HAWKEYE (104): 751 vessels	2-yr VOCE (vessel-related cardiac death, vessel-related MI, ischemia-driven TVR)	QFR ≤0.89 (0.77)	25% vs. 3.5%	p < 0.001
SYNTAX II (105): 771 vessels	2-yr VOCE (vessel-related cardiac death, vessel-related MI, TVR)	QFR <0.91 (0.702)	12% vs. 3.7%	p < 0.001

HAWKEYE = Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation; MACE = major adverse cardiac events; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; TVF = target vessel failure; TVR = target vessel revascularization; VOCE = vessel-oriented composite endpoint; other abbreviations as in Tables 1 and 2.

Medical Imaging System, Leiden, the Netherlands, and Pulse Medical Imaging Technology, Shanghai, China), FFR_{angio} (CathWorks, Kefar Sava, Israel), and vessel FFR (Pie Medical Imaging, Maastricht, the Netherlands) (**Central Illustration, Table 4**). In general, a mathematical formula related to the Lance Gould equation has been used for the process of computation (89).

QFR has the most published data, including prospective multicenter trials (90–93). FFR_{angio} was validated in the prospective multicenter FAST-FFR (FFR_{angio} Accuracy vs. Standard FFR) study (94). Recently, retrospective clinical validation data on vessel FFR were reported (95). Overall, all 3 technologies show excellent areas under the curve for predicting FFR ≤0.80, with a low incidence of nonanalyzable cases (0.9% to 10%) except for the retrospective FAST (Fast Assessment of Stenosis Severity) study (**Table 4**). A systematic review and Bayesian meta-analysis demonstrated that there was no difference in diagnostic performance of angiography-derived FFR between methods for computation and online or offline analysis (96).

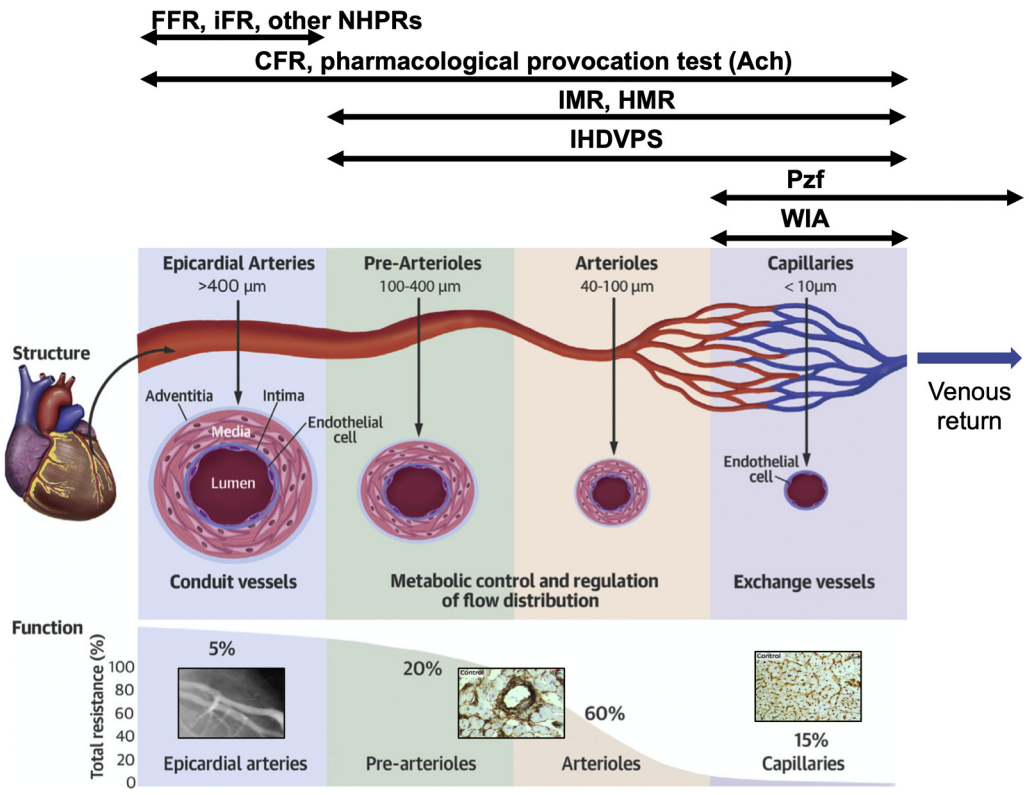
Time to computation is a major argument in favor of adopting this technology and is relevant for both patients and physicians. Only QFR was prospectively evaluated for "time to computation of the entire procedure" compared with FFR. In the FAVOR II Europe-Japan (Diagnostic Accuracy of On-Line Quantitative Flow Ratio) study, the median time for QFR computation was significantly shorter than for FFR (5.0 min vs. 7.0 min) (**Table 4**) (92). Whether these differences can be observed outside of a clinical trial environment remains to be established.

There are advantages and limitations of angiography-derived FFR compared with wire-based FFR (**Table 3**). Regarding the advantages, there is no requirement for wire and hyperemic agent, and this results in shorter procedure time, less patient discomfort, and elimination of erroneous coronary pressure measurement by pressure wire, which can occur in up to one-third of cases (97). Furthermore, both online and offline analyses can be performed, allowing review of available angiograms from a functional standpoint. The major limitation is of course the absence of a large RCT evaluating clinical outcomes compared with established PCI strategies. However, large RCTs to address this are ongoing: FAVOR III China (The FAVOR III China Study; NCT03656848) and FAVOR III EJ (Functional Assessment by Virtual Online Reconstruction: The FAVOR III Europe Japan Study; NCT03729739). Some specific lesion types, such as LMCA, bifurcation, and ostial lesions, are confounding because of differences in interpretation, and results may not be reliable in these lesion subsets for the time being. Furthermore, it is understood that the result depends strongly on the quality of acquisition in 2 or 3 angiographic views.

CLINICAL SCENARIO 3: PHYSIOLOGICAL ASSESSMENT AFTER THE PROCEDURE IN THE CATHETERIZATION LABORATORY

Post-PCI physiological assessment has 2 potential purposes in clinical practice. First, post-PCI physiological assessment can be used for the optimization of PCI result. Agarwal et al. (98) reported that in patients with satisfactory angiographic results after stent

FIGURE 4 Physiological Indexes and Interrogated Coronary Domain



The normal structure and function of coronary macrocirculation and microcirculation and the corresponding action fields of physiological techniques. Myocardial perfusion is governed by adequate orchestration of the epicardial arteries, microcirculation, and myocardial bed. Different intracoronary physiological tools can approach each of these domains. While coronary flow reserve (CFR) encompasses the overall coronary circulation, other indexes have been developed to evaluate specific domains of the heart circulation. Adapted with permission from Taqueti et al. (69). Ach = acetylcholine; HMR = hyperemic microvascular resistance; IHDVPS = instantaneous hyperemic diastolic velocity pressure slope; IMR = index of microvascular resistance; NHPR = nonhyperemic pressure ratio; Pzf = zero flow pressure; WIA = wave-intensity analysis.

implantation, post-PCI FFR reclassified 20% as inadequate physiological results that required further intervention for complete functional optimization at the time of the index procedure. The DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) trial demonstrated that significant epicardial residual ischemia after angiographically successful PCI, defined as iFR ≤0.89, occurred in 24% of patients (99). Of note, 81.6% of patients with suboptimal post-PCI iFR had focal residual disease. Interestingly, about 60% of residual focal stenoses were located outside the stented segment, although all target vessels were evaluated using iFR prior to PCI (99). Therefore, post-PCI physiological assessment may play a more important role for evaluation and localization of residual disease outside the stented segment rather than for stent optimization, for which intracoronary imaging is the established method.

Second, post-PCI physiological assessment can be used as a predictor of long-term clinical outcomes (**Table 5**). Multiple large observational studies and post hoc analyses of RCTs have established that post-PCI FFR value is an independent predictor of long-term clinical outcomes (100). Previous trials have consistently demonstrated that "higher is better," although the best cutoff value of post-PCI FFR varied from 0.86 to 0.96 for the prediction of clinical events (98,101,102). Despite increasing evidence, a recent study reported a low adoption rate (9%) of post-PCI wire-based physiological assessment, even in patients who underwent wire-based physiological assessment prior to PCI (103). The most likely deterrents are the need for pressure wire, hyperemic

agents, and prolonged procedure time. Compared with wire-derived FFR, angiography-derived FFR is a more user friendly tool for interventional cardiologists for this purpose.

Regarding angiography-derived FFR, the HAWKEYE (Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation) trial demonstrated that low post-PCI QFR (≤0.89) was associated with a higher 2-year vessel-oriented clinical endpoint rate compared with high post-PCI QFR (>0.89) (**Table 4**) (104). A subanalysis of SYNTAX II also demonstrated the same result with a slightly different cutoff value (0.91) in state-of-the-art PCI practice for 3VD (105). We have no doubt about the "higher is better" concept of post-PCI QFR, similar to post-PCI FFR, but more confirmatory data are needed, as are improvements to the QFR software for daily use, as the analyzability of post-PCI QFR is still far from perfect, with feasibility of analysis of 85% and 80% in HAWKEYE and SYNTAX II, respectively (106).

Further studies are warranted to assess whether further intervention for residual ischemia according to post-PCI physiological assessment can improve clinical outcomes. The issue will be addressed in the ongoing randomized FFR-REACT (FFR Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care) (107) and Target-FFR (An Evaluation of a Physiology-Guided PCI Optimisation Strategy; NCT03259815) trials.

CLINICAL SCENARIO 4: THE CORONARY MICROVASCULAR CIRCULATION

In the previous sections we focused only on the coronary physiology of the epicardial arteries. However, CMD is among the major causes of angina and/or ischemia with NOCAD. In clinical practice, a substantial number of patients with symptoms of angina and/or documented ischemia by noninvasive testing are diagnosed by ICA with NOCAD (108). The 2019 ESC guidelines on CCS (1) recommend considering NOCAD in patients with angina and/or documented ischemia who present either with coronary arteries free of stenoses or with stenoses showing nonischemic FFR or iFR values. NOCAD should also be considered in patients with persistent angina after complete coronary revascularization (109). The underlying cause of NOCAD should be assessed systematically using noninvasive or invasive testing for diagnosing CMD, as these patients frequently undergo repeat coronary CTA or ICA, with increased health care costs (110). Furthermore, angina and NOCAD are associated with an increased risk for adverse clinical events (111).

Pressure-derived indexes interrogate a very narrow domain of the coronary circulation. They provide an estimate of the relative contribution of stenosis to the myocardial flow impairment, which explains why FFR values become nonischemic when downstream flow-limiting microcirculatory dysfunction is present (112). Furthermore, FFR and other NHPRs are not applicable to a dynamic scenario of vasomotor disorders that involve the coronary arterioles, the epicardial vessels, or both (113). Although future research may contribute to establish the role of NHPRs in the context of CMD (47,48,58–60), it should be made clear that, like FFR, these new indexes cannot be used to interrogate the microvascular domain of the coronary circulation.

The coronary arterial system consists of 4 sequential conduits with different vessel sizes and functions (**Figure 4**): epicardial arteries (>400 μm), pre-arterioles (100to 400 μm), arterioles (40 to 100 μm), and capillaries (<10 μm). The epicardial arteries have a primary conductance and distribution function, with minimal resistance to coronary flow (5%) in the absence of stenosis, whereas pre-arterioles and arterioles are responsible for regulation and distribution of blood flow to match the dynamic needs of local tissue metabolism via the capillaries with maximal resistance to coronary flow (69). The arteriolar tone enables maintenance of constant coronary blood flow over a wide range of coronary perfusion pressures, resulting in mitigation of ischemia during the progression of obstructive epicardial atherosclerosis. Coronary angiography is basically not able to visualize the coronary microcirculation (pre-arterioles, arterioles, and capillaries) with vascular conduits <300 μm (113).

In discussing how to interrogate this complex functional and anatomic network, we should acknowledge that the term "microcirculatory dysfunction" is too vague to be used as a diagnostic target; instead the use of distinct functional or pathobiological mechanisms, generally called endotypes, is recommended (113). Thus, in patients with CCS and NOCAD, the dysfunction mechanisms can be grouped into 2 dominant endotypes: 1) structural changes in microvessels leading to reduced conductance and limited vasodilation; and 2) vasomotor disorders affecting the coronary arterioles and/or epicardial vessels. This distinction clearly illustrates why a single physiological tool cannot be used to explore all potential microcirculatory dysfunction pathways (**Figure 4**). The diagnosis of the first endotype (structural remodeling) rests largely on measuring CFR and microcirculatory resistance with endothelium-independent vasodilators, while vasomotor disorders

are diagnosed using acetylcholine (ACh; an endothelium-dependent vasodilator) challenge with concomitant electrocardiographic monitoring (1). Available methods and technical details on the use of these diagnostic techniques in the catheterization laboratory are discussed in the following paragraphs.

Invasive CFR is the ratio of hyperemic to resting blood flow by Doppler flow velocity, thermodilution-derived mean transient time, or absolute flow measurement on the basis of thermodilution. In general, endothelium-independent vasodilators such as adenosine are used to induce hyperemia. Studies demonstrating prognostic value of thermodilution-based CFR used a cutoff value of 2.0 (114), and those using Doppler-based CFR used a cutoff of 2.5 or lower (115,116). Endothelium-dependent microvascular dysfunction can be assessed by the percentage change in coronary blood flow with intracoronary flow Doppler in response to ACh (an increase >50% can be considered normal) (115). An additional advantage of ACh challenge is that it allows the diagnosis of epicardial vasospastic angina (1).

The measurement of microvascular resistance requires simultaneous recording of intracoronary pressure and flow with thermodilution-based data (index of microvascular resistance [IMR]) (117) or Doppler flow velocity (hyperemic microvascular resistance [HMR]) (118).

IMR is calculated as the distal pressure divided by the inverse of the mean transient time during maximal hyperemia. In patients with coronary stenoses with FFR >0.80, IMR >23 units increased the prognostic value of CFR (114). Furthermore, an abnormal IMR value immediately after PCI was also associated with adverse events in patients with stable CAD (119). IMR ≥25 units is considered to indicate abnormal microcirculatory function.

HMR is calculated as distal pressure divided by distal Doppler average peak flow velocity during maximal hyperemia. Currently available data suggest that HMR provides a more accurate reflection of pathological change in the microcirculation compared with IMR (120). The optimal HMR cutoff to predict abnormal microcirculatory function, as estimated using PET, is ≥2.5 mm Hg/cm/s (120).

After objective documentation of abnormal microvascular function, in patients with structural remodeling the aim of treatment is to decrease myocardial oxygen consumption, typically using beta-blockers, while addressing any cardiovascular risk factors accounting for arteriolar thickening or capillary rarefaction (such as hypertension or diabetes). Conversely, in patients with vasomotor disorders (at either the epicardial or arteriolar level) calcium-channel blockers, angiotensin-converting enzyme inhibitors and statins are recommended to control vasomotor tone and promote normal endothelial function. This tailored approach was demonstrated in the randomized CorMiCa (Coronary Microvascular Angina) trial, which showed that treatment guided by the result of CFR (<2.0), IMR (≥25), and ACh challenge resulted in a significant reduction in angina symptoms at 6 months compared with conventional nonguided treatment in patients with symptoms of angina and/or signs of ischemia and NOCAD (121). This reduction of symptoms of angina was maintained up to 1 year without any difference in clinical outcomes (122). Furthermore, this tailored approach is recommended in the current ESC guidelines (1).

CLINICAL PERSPECTIVE

Currently, there are 3 temporal opportunities to perform physiological assessment of a coronary artery stenosis. Outside the catheterization laboratory, CT-derived FFR may become not only a gatekeeper for conventional angiography but also a guide for revascularization when its cost-effectiveness is established. However, this methodology cannot detect microvascular dysfunction that may lead to myocardial ischemia.

In the catheterization laboratory before the procedure, FFR is the best known index for coronary physiological assessment because of a large and broad evidence base. However, iFR should be considered equivalent to FFR with reductions in procedure time, cost, and patient discomfort, because discordance between FFR and iFR did not translate to differences in outcomes in the 2 largest randomized trials.

New NHPRs seem promising and may contribute to further adoption of wire-based physiological assessment, although more prospective data are needed. To date, we recommend using new NHPRs for noncomplex lesions if iFR is not available.

Angiography-derived FFR shows comparable diagnostic performance for the diagnosis of hemodynamically significant stenosis defined by FFR ≤0.80. If further data on outcomes and cost-effectiveness from ongoing trials are positive, it will be a game changer in the catheterization laboratory. It is premature to discuss intracoronary imaging-derived FFR.

In the catheterization laboratory after the procedure, physiological assessment may predict future outcomes, but the clinical impact of physiology-guided PCI optimization remains to be demonstrated.

CMD is a very different field of investigation that implies the use of flow and pressure, because resistance is the issue at stake, but clinically important because in a large number of patients, microvascular obstruction contributes to myocardial ischemia and cardiovascular events. Further improvements in the noninvasive assessment of CMD may enable us to diagnose it easier.

For the time being, it is more important to adopt physiological assessment for patients with this indication rather than which indexes to use.

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REFERENCES

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019;41:407–77.

2. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 2019;380:2418–28.

3. Melikian N, De Bondt P, Tonino P, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. J Am Coll Cardiol Intv 2010;3:307–14.

4. SCOT-HEART Investigators, Newby DE, Adamson PD, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018;379:924–33.

5. Napp AE, Haase R, Laule M, et al. Computed tomography versus invasive coronary angiography: design and methods of the pragmatic randomised multicentre DISCHARGE trial. Eur Radiol 2017;27:2957–68.

6. Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. JAMA 2016;316:1051–60.

7. National Institute for Health and Care Excellence. Chest pain of recent onset: assessment and diagnosis. Clinical guideline [CG95]. 2010. Available at: https://www.nice.org.uk/guidance/cg95?unlid=28903932120171912336. Accessed May 2, 2020.

8. Williams MC, Hunter A, Shah A, et al. Symptoms and quality of life in patients with suspected angina undergoing CT coronary angiography: a randomised controlled trial. Heart 2017;103:995–1001.

9. Haase R, Schlattmann P, Gueret P, et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data. BMJ 2019;365:l1945.

10. Serruys PW, Girasis C, Papadopoulou SL, Onuma Y. Non-invasive fractional flow reserve: scientific basis, methods and perspectives. EuroIntervention 2012;8:511–9.

11. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol 2011;58:1989–97.

12. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. JAMA 2012;308:1237–45.

13. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol 2014;63:1145–55.

14. Driessen RS, Danad I, Stuijfzand WJ, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol 2019;73:161–73.

15. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR_{CT}: outcome and resource impacts study. Eur Heart J 2015;36:3359–67.

16. Douglas PS, De Bruyne B, Pontone G, et al. 1-Year outcomes of FFR_{CT}-guided care in patients with suspected coronary disease: the PLATFORM study. J Am Coll Cardiol 2016;68:435–45.

17. Patel MR, Norgaard BL, Fairbairn TA, et al. 1-Year impact on medical practice and clinical outcomes of FFR_{CT}: the ADVANCE registry. J Am Coll Cardiol Img 2020;13:97–105.

18. Ihdayhid AR, Norgaard BL, Gaur S, et al. Prognostic value and risk continuum of noninvasive fractional flow reserve derived from coronary CT angiography. Radiology 2019;292:343–51.

19. Collet C, Miyazaki Y, Ryan N, et al. Fractional flow reserve derived from computed tomographic angiography in patients with multivessel CAD. J Am Coll Cardiol 2018;71:2756–69.

20. Collet C, Onuma Y, Andreini D, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. Eur Heart J 2018;39:3689–98.

21. National Institute for Health and Care Excellence. HeartFlow FFR_{CT} for estimating fractional flow reserve from coronary CT angiography medical technologies guidance. Available at: http://nice.org.uk/guidance/mtg32. Accessed May 2, 2020.

22. Norgaard BL, Gaur S, Leipsic J, et al. Influence of coronary calcification on the diagnostic performance of CT angiography derived FFR in coronary artery disease: a substudy of the NXT trial. J Am Coll Cardiol Img 2015;8:1045–55.

23. Pontone G, Weir-McCall JR, Baggiano A, et al. Determinants of rejection rate for coronary CT angiography fractional flow reserve analysis. Radiology 2019;292:597–605.

24. Gaur S, Taylor CA, Jensen JM, et al. FFR derived from coronary CT angiography in nonculprit lesions of patients with recent STEMI. J Am Coll Cardiol Img 2017;10:424–33.

25. Coenen A, Lubbers MM, Kurata A, et al. Coronary CT angiography derived fractional flow reserve: Methodology and evaluation of a point of care algorithm. J Cardiovasc Comput Tomogr 2016;10:105–13.

26. Ko BS, Cameron JD, Munnur RK, et al. Noninvasive CT-derived FFR based on structural and fluid analysis: a comparison with invasive FFR for detection of functionally significant stenosis. J Am Coll Cardiol Img 2017;10:663–73.

27. Li Z, Zhang J, Xu L, et al. Diagnostic accuracy of a fast computational approach to derive fractional flow reserve from coronary CT angiography. J Am Coll Cardiol Img 2020;13:172–5.

28. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. JAMA 2008;300:1765–73.

29. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–8.

30. Silber S, Albertsson P, Aviles FF, et al., for the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. Eur Heart J 2005;26:804–47.

31. Zimmermann FM, Omerovic E, Fournier S, et al. Fractional flow reserve-guided percutaneous coronary intervention vs. medical therapy for patients with stable coronary lesions: meta-analysis of individual patient data. Eur Heart J 2019;40:180–6.

32. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.

33. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J 2015;36:3182–8.

34. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.

35. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation 2010; 122:2545–50.

36. van Nunen LX, Zimmermann FM, Tonino PA, et al. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015; 386:1853–60.

37. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

38. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med 2018;379:250–9.

39. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356: 1503–16.

40. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382: 1395–407.

41. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017; 376:1234–44.

42. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386: 665–71.

43. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med 2019;381: 1411–21.

44. Gotberg M, Cook CM, Sen S, Nijjer S, Escaned J, Davies JE. The evolving future of instantaneous wave-free ratio and fractional flow reserve. J Am Coll Cardiol 2017;70:1379–402.

45. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (Adenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59:1392–402.

46. Petraco R, Escaned J, Sen S, et al. Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. EuroIntervention 2013;9: 91–101.

47. Hwang D, Jeon KH, Lee JM, et al. Diagnostic performance of resting and hyperemic invasive physiological indices to define myocardial ischemia: validation with ^{13}N-ammonia positron emission tomography. J Am Coll Cardiol Intv 2017; 10:751–60.

48. de Waard GA, Danad I, Petraco R, et al. Fractional flow reserve, instantaneous wave-free ratio, and resting Pd/Pa compared with [^{15}O]H_2O positron emission tomography myocardial perfusion imaging: a PACIFIC trial sub-study. Eur Heart J 2018;39:4072–81.

49. van de Hoef TP, Meuwissen M, Escaned J, et al. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: diagnostic accuracy for stenosis-specific myocardial ischaemia. EuroIntervention 2015;11:914–25.

50. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med 2017;376:1824–34.

51. Gotberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. N Engl J Med 2017;376: 1813–23.

52. Davies J. DEFINE-FLAIR: 2-year outcomes from a randomized trial of iFR and FFR decision-making in patients with coronary artery disease. Presented at: TCT 2019; September 25–29, 2019; San Francisco, CA.

53. Nijjer SS, de Waard GA, Sen S, et al. Coronary pressure and flow relationships in humans: phasic analysis of normal and pathological vessels and the implications for stenosis assessment: a report from the Iberian-Dutch-English (IDEAL) collaborators. Eur Heart J 2016;37:2069–80.

54. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994;330: 1782–8.

55. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT registry. J Am Coll Cardiol Intv 2018;11:757–67.

56. Modi BN, Rahman H, Ryan M, et al. Comparison of fractional flow reserve, instantaneous wave free ratio and a novel technique for assessing coronary arteries with serial lesions. EuroIntervention 2019 Sep 24 [E-pub ahead of print].

57. Jeremias A, Maehara A, Genereux P, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. J Am Coll Cardiol 2014;63:1253–61.

58. Petraco R, van de Hoef TP, Nijjer S, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). Circ Cardiovasc Interv 2014;7:492–502.

59. Cook CM, Jeremias A, Petraco R, et al. Fractional flow reserve/instantaneous wave-free ratio discordance in angiographically intermediate coronary stenoses: an analysis using Doppler-derived coronary flow measurements. J Am Coll Cardiol Intv 2017;10:2514–24.

60. Lee SH, Choi KH, Lee JM, et al. Physiologic characteristics and clinical outcomes of patients with discordance between FFR and iFR. J Am Coll Cardiol Intv 2019;12:2018–31.

61. Kobayashi Y, Johnson NP, Berry C, et al. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. J Am Coll Cardiol Intv 2016;9: 2390–9.

62. Sen S, Ahmad Y, Dehbi HM, et al. Clinical events after deferral of LAD revascularization following physiological coronary assessment. J Am Coll Cardiol 2019;73:444–53.

63. Nakayama M, Chikamori T, Uchiyama T, et al. Effects of caffeine on fractional flow reserve values measured using intravenous adenosine triphosphate. Cardiovasc Interv Ther 2018;33: 116–24.

64. Lee JM, Rhee TM, Choi KH, et al. Clinical outcome of lesions with discordant results among different invasive physiologic indices—resting distal coronary to aortic pressure ratio, resting full-cycle ratio, diastolic pressure ratio, instantaneous wave-free ratio, and fractional flow reserve. Circ J 2019;83:2210–21.

65. Seto AH. Instantaneous wave-free ratio outcomes and the epistemology of ischemia. J Am Coll Cardiol Intv 2017;10:2511–3.

66. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation 2009;120:1505–12.

67. Warisawa T. Safety of revascularization deferral of left main stenosis based on instantaneous wave-free ratio evaluation. Presented at: TCT 2019; September 25–29, 2019; San Francisco, CA.

68. Warisawa T, Cook CM, Howard JP, et al. Physiological pattern of disease assessed by pressure-wire pullback has an influence on fractional flow reserve/instantaneous wave-free ratio discordance. Circ Cardiovasc Interv 2019;12: e007494.

69. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:2625–41.

70. Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. J Am Coll Cardiol 2019;74: 1772–84.

71. Andell P, Berntorp K, Christiansen EH, et al. Reclassification of treatment strategy with instantaneous wave-free ratio and fractional flow reserve: a substudy from the iFR-SWEDEHEART trial. J Am Coll Cardiol Intv 2018;11:2084–94.

72. Serruys PW, Kogame N, Katagiri Y, et al. Clinical outcomes of state-of-the-art percutaneous

coronary revascularisation in patients with three-vessel disease: two-year follow-up of the SYNTAX II study. EuroIntervention 2019;15:e244–52.

73. Serruys PW, Chichareon P, Modolo R, et al. The SYNTAX score on its way out or…towards artificial intelligence: part II. EuroIntervention 2020. In press.

74. Escaned J, Ryan N, Mejia-Renteria H, et al. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. J Am Coll Cardiol Intv 2018;11:1437–49.

75. van der Hoeven NW, Janssens GN, de Waard GA, et al. Temporal changes in coronary hyperemic and resting hemodynamic indices in nonculprit vessels of patients with ST-segment elevation myocardial infarction. JAMA Cardiol 2019;4:736–44.

76. Mejia-Renteria H, Lee JM, van der Hoeven NW, et al. Coronary microcirculation downstream non-infarct-related arteries in the subacute phase of myocardial infarction: implications for physiology-guided revascularization. J Am Heart Assoc 2019;8:e011534.

77. Choi KH, Lee JM, Kim HK, et al. Fractional flow reserve and instantaneous wave-free ratio for nonculprit stenosis in patients with acute myocardial infarction. J Am Coll Cardiol Intv 2018;11:1848–58.

78. Pesarini G, Scarsini R, Zivelonghi C, et al. Functional assessment of coronary artery disease in patients undergoing transcatheter aortic valve implantation: influence of pressure overload on the evaluation of lesions severity. Circ Cardiovasc Interv 2016;9:e004088.

79. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. Circulation 2003;107:3170–5.

80. Yamanaka F, Shishido K, Ochiai T, et al. Instantaneous wave-free ratio for the assessment of intermediate coronary artery stenosis in patients with severe aortic valve stenosis: comparison with myocardial perfusion scintigraphy. J Am Coll Cardiol Intv 2018;11:2032–40.

81. Ahmad Y, Vendrik J, Eftekhari A, et al. Determining the predominant lesion in patients with severe aortic stenosis and coronary stenoses: a multicenter study using intracoronary pressure and flow. Circ Cardiovasc Interv 2019;12:e008263.

82. Wijns W, Serruys PW, Reiber JH, et al. Quantitative angiography of the left anterior descending coronary artery: correlations with pressure gradient and results of exercise thallium scintigraphy. Circulation 1985;71:273–9.

83. Kobayashi Y, Johnson NP, Zimmermann FM, et al. Agreement of the resting distal to aortic coronary pressure with the instantaneous wave-free ratio. J Am Coll Cardiol 2017;70:2105–13.

84. Cook CM, Ahmad Y, Shun-Shin MJ, et al. Quantification of the effect of pressure wire drift on the diagnostic performance of fractional flow reserve, instantaneous wave-free ratio, and whole-cycle Pd/Pa. Circ Cardiovasc Interv 2016;9:e002988.

85. Van't Veer M, Pijls NHJ, Hennigan B, et al. Comparison of different diastolic resting indexes to iFR: are they all equal? J Am Coll Cardiol 2017;70:3088–96.

86. Lee JM, Choi KH, Park J, et al. Physiological and clinical assessment of resting physiological indexes. Circulation 2019;139:889–900.

87. Johnson NP, Li W, Chen X, et al. Diastolic pressure ratio: new approach and validation vs. the instantaneous wave-free ratio. Eur Heart J 2019;40:2585–94.

88. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, 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. J Am Coll Cardiol 2017;69:2212–41.

89. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circ Res 1978;43:242–53.

90. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. J Am Coll Cardiol Intv 2016;9:2024–35.

91. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol 2017;70:3077–87.

92. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. J Am Heart Assoc 2018;7:e009603.

93. Westra J, Tu S, Winther S, et al. Evaluation of coronary artery stenosis by quantitative flow ratio during invasive coronary angiography: the WIFI II study (Wire-Free Functional Imaging II). Circ Cardiovasc Imaging 2018;11:e007107.

94. Fearon WF, Achenbach S, Engstrom T, et al. Accuracy of fractional flow reserve derived from coronary angiography. Circulation 2019;139:477–84.

95. Masdjedi K, van Zandvoort LJC, Balbi MM, et al. Validation of 3-dimensional quantitative coronary angiography based software to calculate fractional flow reserve: Fast Assessment of Stenosis Severity (FAST)-study. EuroIntervention 2019 May 14 [E-pub ahead of print].

96. Collet C, Onuma Y, Sonck J, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J 2018;39:3314–21.

97. Jeremias A, Kirtane AJ, Stone GW. A test in context: fractional flow reserve: accuracy, prognostic implications, and limitations. J Am Coll Cardiol 2017;69:2748–58.

98. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. J Am Coll Cardiol Intv 2016;9:1022–31.

99. Jeremias A, Davies JE, Maehara A, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. J Am Coll Cardiol Intv 2019;12:1991–2001.

100. Rimac G, Fearon WF, De Bruyne B, et al. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: a systematic review and meta-analysis. Am Heart J 2017;183:1–9.

101. Piroth Z, Toth GG, Tonino PAL, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. Circ Cardiovasc Interv 2017;10:e005233.

102. Li SJ, Ge Z, Kan J, et al. Cutoff value and long-term prediction of clinical events by FFR measured immediately after implantation of a drug-eluting stent in patients with coronary artery disease: 1- to 3-year results from the DKCRUSH VII registry study. J Am Coll Cardiol Intv 2017;10:986–95.

103. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving routine standards in invasive hemodynamic assessment of coronary stenosis: the nationwide Italian SICI-GISE Cross-Sectional ERIS Study. J Am Coll Cardiol Intv 2018;11:1482–91.

104. Biscaglia S, Tebaldi M, Brugaletta S, et al. Prognostic value of QFR measured immediately after successful stent implantation: the international multicenter prospective HAWKEYE study. J Am Coll Cardiol Intv 2019;12:2079–88.

105. Kogame N, Takahashi K, Tomaniak M, et al. Clinical implication of quantitative flow ratio after percutaneous coronary intervention for 3-vessel disease. J Am Coll Cardiol Intv 2019;12:2064–75.

106. Serruys PW, Kogame N, Onuma Y. Was the ball inside or outside the court? Ask the Hawk-Eye System. J Am Coll Cardiol Intv 2019;12:2089–92.

107. van Zandvoort LJC, Masdjedi K, Tovar Forero MN, et al. Fractional flow reserve guided percutaneous coronary intervention optimization directed by high-definition intravascular ultrasound versus standard of care: rationale and study design of the prospective randomized FFR-REACT trial. Am Heart J 2019;213:66–72.

108. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

109. Li Y, Yang D, Lu L, et al. Thermodilutional confirmation of coronary microvascular dysfunction in patients with recurrent angina after successful percutaneous coronary intervention. Can J Cardiol 2015;31:989–97.

110. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA 2005;293:477–84.

111. Jespersen L, Hvelplund A, Abildstrom SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J 2012;33:734–44.

112. Echavarria-Pinto M, Escaned J, Macias E, et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: a combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. Circulation 2013;128:2557–66.

113. Mejia-Renteria H, van der Hoeven N, van de Hoef TP, et al. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. The international journal of cardiovascular imaging 2017;33:1041–59.

114. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. J Am Coll Cardiol 2016;67:1158–69.

115. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. J Am Coll Cardiol Intv 2015;8:1445–53.

116. AlBadri A, Bairey Merz CN, Johnson BD, et al. Impact of abnormal coronary reactivity on long-term clinical outcomes in women. J Am Coll Cardiol 2019;73:684–93.

117. Fearon WF, Balsam LB, Farouque HM, et al. Novel index for invasively assessing the coronary microcirculation. Circulation 2003;107:3129–32.

118. Meuwissen M, Chamuleau SA, Siebes M, et al. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. Circulation 2001;103:184–7.

119. Nishi T, Murai T, Ciccarelli G, et al. Prognostic value of coronary microvascular function measured immediately after percutaneous coronary intervention in stable coronary artery disease: an international multicenter study. Circ Cardiovasc Interv 2019;12:e007889.

120. Williams RP, de Waard GA, De Silva K, et al. Doppler versus thermodilution-derived coronary microvascular resistance to predict coronary microvascular dysfunction in patients with acute myocardial infarction or stable angina pectoris. Am J Cardiol 2018;121:1–8.

121. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. J Am Coll Cardiol 2018;72:2841–55.

122. Ford TJ, Stanley B, Sidik N, et al. 1-Year outcomes of angina management guided by invasive coronary function testing (CorMicA). J Am Coll Cardiol Intv 2020;13:33–45.

KEY WORDS angiography-derived FFR, computed tomography-derived fractional flow reserve, coronary microvascular disease, fractional flow reserve, instantaneous wave-free ratio, nonhyperemic pressure ratio