THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Invasive FFR and Noninvasive CFR in the Evaluation of Ischemia

What Is the Future?

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ABSTRACT

This review provides an integrative and forward-looking perspective on the gamut of coronary physiology for the diagnosis and management of atherosclerosis. Because clinical events serve as the ultimate gold standard, the future of all diagnostic tests, including invasive fractional flow reserve and noninvasive coronary flow reserve, depends on their ability to improve patient outcomes. Given the prominent role of acute coronary syndromes and invasive procedures in cardiology, we practically consider 2 broad categories of patients with coronary disease: acute and stable. For patients with acute coronary disease, coronary physiology may potentially refine treatment of the culprit lesion. For both patients with stable and acute nonculprit disease, reducing hard endpoints with revascularization potentially occurs at the severe end of the focal physiological spectrum, an area under-represented in existing trials. Nonepicardial disease and diffuse atherosclerosis remain underexplored aspects of coronary physiology for testing of novel treatments. (J Am Coll Cardiol 2016;67:2772–88) © 2016 by the American College of Cardiology Foundation.

This review provides an integrative and forward-looking perspective on the gamut of coronary physiology for the diagnosis and management of atherosclerosis. It ranges from acute coronary syndrome (ACS) as a “perfect storm” (1,2) of pathophysiological progression (3), visualized as a severe anatomic stenosis (4) benefitting from revascularization, to stable coronary artery disease (CAD) as a complex interplay of focal and diffuse plaque burden (5). Although atherosclerotic severity and complexity have long been associated with symptoms and risk, a presumed revascularization benefit has not been confirmed using an anatomic assessment. Rather, we suggest that coronary physiology, with its mechanistic link between intracoronary hemodynamic stress and plaque failure (6), provides a natural set of tools to quantify both focal and diffuse disease of a severity that may be associated with improved hard outcomes, independent of symptom relief. Accordingly, this review on the future of clinical coronary physiology starts with interventions in ACS, the extreme and final common pathway associated with severe anatomic stenosis, marked flow-pressure abnormalities, and vasomotor dysfunction. From there,
we extrapolate from pre-ACS coronary physiology, leading to testable hypotheses for personalized interventions. The Central Illustration provides a visual summary of the paper.

THE GOLD STANDARD

Clinical outcomes serve as the ultimate gold standard for diagnostic tests. Unlike a therapy that directly affects patients, a useful diagnostic test must influence management decisions that in turn alter outcomes. As evidence of this trend, several recent reports highlight the surprisingly small effect of most noninvasive cardiac stress testing on clinical care (7-9). The ongoing ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial asks if abnormal stress test results can change hard endpoints of death and myocardial infarction (MI) using revascularization (10). Thus, the future of all diagnostic tests depends on their ability to improve patient outcomes.

Within the broad community of diagnostic tests, measurements like fractional flow reserve (FFR) and coronary flow reserve (CFR) belong to the category of clinical coronary physiology. Invasively, we can directly measure intracoronary pressure and flow (and indirectly speak of resistance), whereas non-invasively, we can image myocardial perfusion (in either relative or absolute units). Although a deep foundation of basic physics, molecular and genetic mechanisms, and fundamental animal and human physiology underlie these tools, our goal as physicians remains pragmatic: how can we help the patient before us?

Consequently, we reframe this review as a discussion of an important tool to improve the end goal of patient well-being. To remain practical, we consider 2 broad categories of patients with CAD: acute and stable. For decision-making and ethical, informed discussion with patients, we distinguish among 3 easily understood outcomes: death, MI, and angina. Although the most common therapeutic decision made using coronary physiology remains revascularization, we also consider customized medical therapy distinct from treating general risk factors, as detailed later.

PATIENTS WITH ACUTE CORONARY DISEASE

Existing studies of patients with acute coronary disease provide 3 profound, but often overlooked insights for assessing physiologically-guided interventions. First, simultaneous “perfect storms” causing an MI in 2 or more distinct coronary arteries in the same patient are rare. Second, the majority of ACS arises from a very severe lesion that evolved rapidly via sequential, asymptomatic plaque ruptures that healed with progressive stenosis (3,4,11). Third, the long-term risk after revascularized ACS typically returns to the background level of patients with known, but stable CAD. These 3 insights together suggest that nonculprit stenosis in patients with acute coronary disease likely reflects the same background of disease known to exist in patients with stable coronary disease, in contrast to the culprit lesion, whose revascularization without physiological assessment has already been shown to reduce death and MI (12). As such, the concepts derived for stable CAD likely apply to the nonculprit lesions noted at the time of acute presentation, thereby linking the 2 scenarios. Therefore, this connection and commonality necessitates our initially reviewing acute manifestations.

Acute presentations account for approximately 70% to 80% of the contemporary total number of patients undergoing coronary revascularization (13,14), an inversion of the balance from 25 years ago (14). Due to improved clinical outcomes demonstrated in randomized trials, most patients with acute coronary disease proceed directly to invasive angiography and revascularization of culprit lesions without physiological assessment. However, as detailed next, 2 key questions have emerged recently and need future answers. First, can physiology refine treatment in the culprit vessel in some patients? Second, if intervention on nonculprit stenosis fails to reduce death and MI, how much do patients value a reduction in future revascularization procedures? Definitive answers will require trials in large populations with rational selection criteria and hard endpoints.

ROUTINE INVASIVE ANGIOGRAPHY WITHOUT PHYSIOLOGICAL ASSESSMENT. The definition of acute MI includes “imaging evidence of new loss of viable myocardium” (15), thereby acknowledging the need for noninvasive perfusion imaging to clarify the diagnosis in some cases. However, relying on noninvasive testing or symptoms to guide invasive angiography in patients with acute coronary disease with non-ST-segment elevation myocardial infarction (NSTEMI), a “selective invasive” strategy, has proved inferior to immediate angiography, a “routine invasive” strategy (12). Specifically, routine compared with selective angiography reduced cardiovascular death (from 8.1% to 6.8%; hazard ratio [HR]: 0.83; 95% confidence interval [CI]: 0.68 to 1.01; p = 0.068) and MI (from 12.9% to 10.0%; HR: 0.77; 95% CI: 0.65 to 0.90; p = 0.001) over 5 years (12). The relative reduction in events remained constant across the
spectrum of absolute risk. Thus, the largest benefits from a routine invasive strategy accrued to the highest-risk patients—a theme that will re-emerge later for stable populations as well. For ST-segment elevation myocardial infarction (STEMI) patients undergo rapid cardiac catheterization and mechanical reperfusion when geographically available, or intravenous lytic treatment and transfer for angiography within 24 h if invasive management exists only distantly (16,17).

WHAT IS THE ACUTE CULPRIT LESION: A ROLE FOR CORONARY PHYSIOLOGY? In the majority of ACS, a single culprit lesion can be identified using a combination of angiographic appearance, regional left ventricular dysfunction, and localizing electrocardiographic changes. Some patients have no obvious culprit, whereas rare patients have 2 simultaneous culprits.

For patients with no obvious culprit, a wide differential diagnosis exists, including both non-coronary (e.g., pulmonary embolism or myocarditis) and coronary (e.g., spasm or dissection) etiologies. Depending on the clinical context, invasive physiology provides objective quantification of stenosis severity as a potential cause of the acute presentation because the majority of older individuals with risk factors have some degree of atherosclerosis (18). For example, a high FFR value may direct the clinician to search for an alternative diagnosis, such as pulmonary embolism (19). Alternatively, advanced physiological assessment may uncover a host of abnormalities (20), although establishing causal links with the presentation and proven courses of treatment remains difficult.

CULPRIT LESION PHYSIOLOGY TO GUIDE TREATMENT. For patients with 1 or more culprit lesions, invasive
CORONARY PHYSIOLOGY OF NONCULPRIT LESIONS.

Depending on the population and precise definition of angiographic severity, a nonculprit, or “bystander” or “incidental,” lesion is found in approximately 50% of patients presenting acutely (17). Currently, no consensus exists regarding proper treatment. European guidelines state that “the best strategy for STEMI patients with multivessel disease, who underwent primary PCI of the infarct-related artery in the acute phase with remaining multivessel disease, is still not well established” (16). American guidelines note the “great variability in the evaluation and management of nonculprit coronary artery disease in stable patients without [heart failure] or shock, both at the time of primary PCI and later during the hospital course” (17).

Three recent randomized trials of managing nonculprit stenosis in ACS have been completed, with several others ongoing. Heterogeneity and subjectivity of anatomic definitions for multivessel disease led to trials that incorporated invasive coronary physiology. As examples of anatomic variation, the PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) trial used a 50% diameter stenosis limit (34), whereas the CvLPRIT (Complete Versus Lesion-Only Primary PCI) trial allowed over 70% in a single view or over 50% in 2 views (35). By contrast, the physiology-guided PRI-MULTI trial required 50% diameter nonculprit stenosis plus FFR ≤0.8, or over 90% diameter stenosis without FFR (36), and the COMPLETE (Complete vs Culprit-only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI) trial will include at least a 50% diameter stenosis plus FFR ≤0.8, or at least a 70% lesion without FFR (37).

Preliminary results demonstrated that 56.5% of nonculprit lesions of at least 50% diameter stenosis had an FFR >0.8 (38), indicating the same marked disagreement between anatomy and physiology as the 38.2% discordance in the acute subset of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial (39) or the 39.1% discordance in the NSTEMI population of the FAMOUS trial (21). Therefore, 40% to 60% of angiographically significant nonculprit lesions may have an FFR >0.8 at the time of acute presentation.

Although anatomic-functional discordance occurs frequently in both stable and unstable patients, the clinical effect of both high and low FFR values in nonculprit lesions in the setting of acute MI remains to be determined for several reasons. In ACS, multifocal heterogeneous inflammation, endothelial...
Future of FFR and CFR et al. Johnson which was not successful in 93% of lesions in the UA/NSTEMI cohort, of modest infarct size. FFR measurement was successful in a medically stabilized cohort 5 days and UA/NSTEMI with high peak creatine kinase, thus producing a medically stabilized cohort of subjects enrolled in the multicenter and international FAME trial (328 of 1,005 patients) presented with unstable angina (UA) or NSTEMI and were analyzed in a post hoc substudy (39). Note that FAME excluded patients with STEMI in the preceding 5 days and UA/NSTEMI with high peak creatine kinase, thus producing a medically stabilized cohort of modest infarct size. FFR measurement was successful in 93% of lesions in the UA/NSTEMI cohort, which was not significantly different than in the stable population (94%). Although the cohort with acute coronary disease had a higher event rate than subjects with stable angina (24.1% vs. 18.2% after 2 years; p = 0.03), there was no difference between them in the benefit of FFR-guided treatment on outcomes (relative risk reduction of 19% vs. 18%; p = 0.92). Outcomes in both groups with acute and stable disease favored FFR guidance over angiography. However, due to the smaller size of the UA/NSTEMI cohort, hard endpoints trended lower with an FFR strategy, but did not reach statistical significance: death 2.7% versus 4.5%, and MI 8.0% versus 13.5% (both p > 0.05). Freedom from angina at 2 years did not differ between an FFR-guided versus an angiographic-guided strategy in this subgroup with acute disease (60.7% vs. 64.6%; p = 0.54).

The multicenter FAMOUS-NSTEMI trial in the United Kingdom focused exclusively on NSTEMI in 350 patients with at least one 30% diameter stenosis (21). Importantly, a median of 3 days (interquartile range: 2 to 5 days) elapsed between the index clinical episode and invasive angiography, reflecting the underlying health care system. Subjects were randomized equally between FFR- and angiographic-guided revascularization, although all lesions had successful FFR measurements in 99.7% of cases, with only 2 coronary dissections attributed to the pressure wire. After 1 year of clinical follow-up, all-cause death did not differ significantly between the angiographic- and FFR-guided groups (risk difference 1.1% favoring angiography; 95% CI: –2.4% to 5.0%; p = 0.54), nor did spontaneous MI (risk difference 1.1% favoring angiography; 95% CI: –3.1% to 5.5%; p = 0.69).

Recently, the Danish multicenter PRIMULTI study enrolled 627 patients with STEMI and a significant (over 50% diameter stenosis) nonculprit lesion in a major vessel (36). All STEMI culprit lesions were treated, and nonculprit lesions were randomized to standard care as per the local routine or to FFR-guided revascularization (unless over 90% diameter stenosis visually, in which case no FFR was required) before hospital discharge, but at least 48 h after the index procedure. After a minimum follow-up of 1 year, all-cause death did not differ significantly between the 2 groups (HR: 1.4; 95% CI: 0.63 to 3.00; p = 0.43), but cardiac death trended lower with FFR-guided revascularization of the nonculprit lesion (HR: 0.56; 95% CI: 0.19 to 1.70; p = 0.29). Nonfatal MI was statistically unchanged (HR: 0.94; 95% CI: 0.47 to 1.90; p = 0.87). However, future revascularization was lower in the FFR-guided group after discounting the initial procedure (HR: 0.31; 95% CI: 0.18 to 0.53; p < 0.001). No significant differences existed among admissions for significant angina (HR: 1.1; 95% CI: 0.75 to 1.70; p = 0.6) or residual angina class.

Two ongoing randomized outcome trials of non-culprit lesions in STEMI incorporate FFR physiological assessment. The multicenter, international CompareAcute (Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD) trial will enroll 885 subjects with at least a 50% diameter stenosis in a nonculprit vessel (42); baseline data from the first 408 subjects were presented in 2014 (38). Like PRIMULTI, all culprit lesions will be treated by PCI with nonculprit lesions randomized to standard care or FFR-guided revascularization, with a primary endpoint of all-cause death, MI, any revascularization, and cerebrovascular accident. The multicenter, international COMPLETE trial will enroll 3,900 subjects with either at least a 70% diameter stenosis without FFR or 50% to 70% diameter stenosis with FFR = 0.8 in a nonculprit vessel (37). Although the randomized groups are as in PRIMULTI and CompareAcute, the primary endpoint includes only cardiovascular-related death and nonfatal MI. Results from these 2 new trials are anticipated in 2018.

**Figure 1** summarizes the existing outcomes trials of FFR in patients with acute coronary disease.

**SUMMARY OF NONCULPRIT PHYSIOLOGICAL ASSESSMENT TO GUIDE TREATMENT.** For the vast
majority of patients who stabilize either before or rapidly during the index PCI, assessment of FFR in the acute or semiacute settings has proved to be safe, and its absolute numeric value is acceptably reproducible. Importantly, a significant discordance exists between anatomic and physiological assessment of nonculprit severity, with 40% to 60% of lesions demonstrating an FFR >0.8, just as for stable CAD (43) (to be reviewed later). Because approximately 50% of patients with acute coronary disease undergoing invasive angiography have a noteworthy nonculprit stenosis, an objective basis for its intervention or deferral is essential.

Given the reductions in cardiovascular death and MI seen with routine angiography in patients with acute coronary disease, trials are needed to determine if these same endpoints can be improved by treating the nonculprit lesion. Hypothesis-generating, yet modestly sized recent trials (<800 patients total) using angiographic criteria alone have suggested marked benefits of 50% to 70% reduction in hard events (34,35). By contrast, recent

![FIGURE 1 FFR in Patients With Acute Coronary Disease](image-url)

Outcomes in randomized trials that studied an FFR-guided strategy. (A) The FAME trial demonstrated the same treatment effect in patients with acute (dashed lines) and stable (solid lines) coronary disease, with improved outcomes when using an FFR strategy (blue lines) versus an angiographic strategy (orange lines). Reprinted with permission from Sels et al. (39). (B) The FAMOUS-NSTEMI trial found a trend toward better outcomes when using an FFR strategy (solid line) instead of an angiographic strategy (dashed line) in an NSTEMI population that included both culprit and nonculprit lesions. Reprinted with permission from Layland et al. (21). (C) The PRIMULTI trial showed a lower rate of events when treating nonculprit lesions noted at the time of STEMI using an FFR strategy (orange line) versus standard of care (blue line). Reprinted with permission from Engstrøm et al. (36). Angio = angiographic; ARR = absolute risk reduction; CI = confidence interval; FFR = fractional flow reserve; HR = hazard ratio; MACE = major adverse cardiac event(s); NSTEMI = non-ST-segment elevation myocardial infarction; RRR = relative risk reduction; SA = stable angina; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.
intermediate-sized, FFR-guided trials of nonculprit intervention (<1,500 patients total) indicate more modest or no benefit, as detailed previously. Thus, we currently lack a consistent or plausible signal of clinical benefit for routine intervention of nonculprit lesions in patients with acute coronary disease. Without a reduction in death or MI, nonculprit PCI at the acute presentation would at least need to improve symptoms or future quality of life, including functional limitation or urgent revascularization.

In conclusion, large, definitive studies using hard outcomes are essential to prove any value of physiologically guided treatment of nonculprit lesions in patients with acute coronary disease. Although COMPLETE meets these criteria, it mixes anatomic and physiological criteria, thereby providing less clarity than either strategy alone.

**PATIENTS WITH STABLE CORONARY DISEASE**

Stable CAD patients account for approximately 20% to 30% of coronary revascularizations (13,14). However, the total population of patients with stable coronary disease (approximately 15.5 million Americans have known coronary heart disease) dwarfs the number of patients with acute coronary disease (44). Additionally, those who present with new chest symptoms but with no elevation in cardiac biomarkers or electrocardiographic changes comprise a frequently encountered category of patients with known or suspected CAD, which may include patients with or without known cardiovascular risk factors. Thus, patients with stable CAD comprise the majority of clinical practice, but account for a minority of revascularizations. Notably, revascularization of patients with stable CAD has failed to improve hard outcomes, as summarized by the American guidelines in 2011: “PCI … reduces the incidence of angina … has not been demonstrated to improve survival in stable patients … may increase the short-term risk of MI … does not lower the long-term risk of MI” (45).

Nevertheless, a recent study suggests that this specific aspect regarding the potential benefit of revascularization or alternative treatment strategies is rarely included in informed consent discussions between cardiologists and their patients (46).

In the future, how will coronary physiology assessments affect the diagnosis and management of stable CAD patients? For clinical care and trials alike, an important conceptual step separates “harder” outcomes of death and MI from “softer” outcomes of angina relief and recurrent procedures. A physiological risk-benefit continuum exists that may profoundly affect the magnitude, as well as the method of revascularization (5,47). Coronary physiology already provides objective and quantitative tools for patient care that may further refine recruitment into outcomes trials of meaningful clinical endpoints for validation of beneficial treatments. Prospective randomized trials on the basis of these concepts are feasible, despite associated practical and economic challenges (5).

**PHYSIOLOGICAL CONTINUUM OF RISK.** Outcomes data over the past several years have identified a consistent relationship between coronary physiological measurements and subsequent clinical events. The broadest data have been acquired using either invasive FFR or noninvasive CFR, although prognostic data is now emerging for several parameters that combine measurements. Noninvasive CFR equals the ratio of absolute coronary flow or myocardial perfusion between hyperemia and rest, and can be assessed using a variety of technologies, although the broadest data exists for positron emission tomography (PET) (48). Developed as a relative CFR (49), invasive FFR practically equals the ratio of coronary to aortic pressure during hyperemia.

In addition to being distinct, yet complimentary physiological measures of CAD severity, FFR and noninvasive CFR differentially emphasize revascularization as an outcome. The published prognostic data on FFR has been more highly influenced by the use of revascularization, as opposed to noninvasive CFR, with generally hard endpoints that have more ominous prognostic implications. As a final distinction between them, FFR-guided PCI reduces subsequent major adverse cardiac events in randomized trials compared with angiographic-guided PCI and compared with medical treatment alone. No such trials exist for CFR. Here, we summarize the existing studies on the FFR (Figure 2) and CFR (Figure 3) severity-risk continuum as the basis for discussing their clinical implications in the next section, which profoundly reorders assessment of CAD severity from anatomy to physiology.

A meta-analysis of FFR outcomes studies included 9,173 study-level lesions and 6,961 patient-level lesions from predominately observational published data (47). Both types of analysis supported a continuous, inverse relationship between the numeric FFR value and adverse outcomes, with a parallel increase in the absolute risk for medically treated lesions associated with a larger absolute benefit from revascularization. The medical treatment and revascularization curves generally crossed in the 0.75 to 0.80 range, but the source data was primarily limited...
due to confounding by indication. FFR measured immediately after PCI also showed an inverse relationship with clinical outcomes, likely reflecting residual diffuse disease.

A retrospective, single-center analysis of 882 deferred lesions explored predictive variables for subsequent intervention (50). In a multivariable model, the numeric FFR value remained a significant predictor of future revascularization, of which 65% were urgent. For every 0.05 decrease in the FFR value, the hazard increased by 21% (HR: 1.21; 95% CI: 1.03 to 1.42; p = 0.02) after adjusting for other factors.

Preliminary data from the randomized, international, and multicenter FAME 2 trial focused on the natural history of 1,027 lesions treated medically in the FFR ≤0.8 group and the FFR >0.8 registry (51). Again, a significant and inverse relationship existed between the FFR value and a clinical composite of death, MI, and target lesion revascularization. For every 0.05 decrease in the FFR value, the risk (especially target lesion revascularization) increased by 31% (HR: 1.308; 95% CI: 1.219 to 1.403; p < 0.001) after adjusting for other factors.

A multicenter registry in South Korea enrolled deferred coronary lesions of over 30% diameter stenosis by visual estimation with an FFR >0.8 (52). A total of 5,006 patients have been enrolled, for whom preliminary results were presented from 3,534 lesions that had at least 6 months of clinical follow-up after deferral from revascularization (53). The 2-year rates of cardiac death (1.0%) and nonfatal MI (0.9%) highlight the low-risk natural history of lesions with a high FFR value. As in other studies, a significant, inverse relationship existed between the numeric FFR value and repeated interventions at 2 years.

Another retrospective, single-center analysis of 1,459 patients with FFR lesions between 0.70 and 0.85 compared clinical outcomes after medical therapy versus revascularization (54). Among medically treated lesions, a significant, inverse relationship was seen between the numeric FFR value and a composite outcome of death, MI, and revascularization. The medical therapy and revascularization curves crossed at an FFR of 0.80, a threshold again biased due to confounding by indication. All-cause death alone was higher for medically treated lesions between FFR 0.70 to 0.80 than for FFR 0.81 to 0.85 (HR: 2.62; 95% CI: 1.28 to 6.8; p < 0.001).

Noninvasive CFR (occasionally termed myocardial flow or perfusion reserve, although we prefer CFR to emphasize the fundamental and common physiology)
as a binary prognostic variable has been assessed in several single-center series using cardiac PET or cardiac magnetic resonance. Binary CFR <2 identified a higher risk of cardiac death alone or when combined with MI, revascularization, and cardiac hospitalization in 229 patients over approximately 5 years after initial medical treatment, even when adjusting for other variables (55). Similarly, in 677 patients after initial medical treatment, CFR <2 was an independent predictor of both hard events of cardiac death plus MI alone, and when combined with revascularization and cardiac hospitalization (56). Both CFR <2.11 and absolute stress flow <1.90 ml/min/g (derived from the median values in the population) significantly separated risk in 224 patients over about 1 year after initial medical treatment, although only CFR remained significant in a multivariable model (57). A substudy of 222 subjects in MESA demonstrated an inverse relationship between the predicted 10-year risk of coronary heart disease and absolute stress flow and CFR (p < 0.0001 for trend) (58).

Global CFR physiologically quantifies the global burden of diffuse CAD over a spectrum of severity that directly relates to a continuum of risk. This risk might be modifiable by revascularization (5). Global CFR <1.5 by PET is associated with a high risk of coronary events, as compared with global CFR >2.0 carrying relatively lower risk, and with an intermediate risk in between (59,60). As shown in Figure 4, coronary artery bypass graft (CABG), but not PCI, in patients with global CFR <1.6 may modify this high-risk natural history (61). However, neither PCI nor CABG had any effect on the natural history of patients with global CFR ≥1.6, and the overall cohort was of
modest size, at 329 patients. These retrospective observations require randomized outcomes trials of revascularization or novel medical treatment, but for now they suggest that the risk/benefit continuum may be modified by physiology-guided revascularization.

Finally, some studies have explored the prognostic continuum for combined invasive FFR and invasive CFR measurements. A retrospective, single-center analysis examined the outcomes of 157 lesions treated with initial medical therapy (62). Lesions with both FFR >0.8 and CFR >2 experienced the lowest rates of approximately 30% combined death, MI, and revascularization over the subsequent decade of follow-up. Lesions with FFR ≤0.8, but CFR >2 had a slightly higher event rate at 40%, whereas the highest event rate of 80% occurred in lesions with FFR >0.8, but CFR ≤2 (although revascularizations dominated). On the basis of these and related findings (63), a multicenter international pilot study is examining the hypothesis that PCI in lesions with CFR >2, despite FFR ≤0.8, can be safely deferred and treated with medical therapy alone (64).

**IMPLICATIONS OF THE SEVERITY-RISK CONTINUUM ON HARD OUTCOMES.** Disease severity and its associated risk represent a continuum that challenges the patient-specific selection of diagnostic testing and management. Precision medicine focuses therapies on those most likely to derive the greatest benefit. Accordingly, it is helpful to view the design and interpretation of clinical trials through the continuum lens. Because fully informed patient consent includes a “discussion of the pros and cons of the alternatives” as well as “the uncertainties associated with the decision” (46), the risk continuum also has practical implications for clinical care. Moreover, in the absence of trials proving reduced MI and death, the common belief by patients and physicians that PCI will reduce either of these events (65) might be considered a fundamental violation of true informed consent. This potential becomes realistic because in a real-world analysis of discussions with cardiologists, better-informed patients were less likely to select invasive angiography and potential PCI (46). For example, between an FFR of 0.75 and 0.80, the modestly elevated risk from the stenosis physiology warrants consideration of other factors, such as the amount of distal myocardium, severity and pattern of symptoms, technical feasibility of revascularization, and ability to tolerate antianginal and dual

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**FIGURE 4** Potential Benefit of Revascularization for Low CFR

Adjusted annualized rates of cardiovascular death and heart failure admission among patients referred for coronary angiography by CFR and early revascularization (Revasc) strategy (CABG, PCI, or neither). No difference in event rates was seen in patients with high CFR (light blue, orange, or gray), regardless of the revascularization strategy pursued. In patients with low CFR, those who underwent CABG (aqua) had lower event rates than those who underwent PCI (purple; p = 0.006) or no revascularization (maroon; p = 0.001), and had event rates similar to those with high CFR who underwent CABG (gray). Annualized event rates were adjusted for pre-test clinical score, LV ejection fraction, LV ischemia, and coronary artery disease prognostic index. Reprinted with permission from Taqueti et al. (61). LV = left ventricular; other abbreviations as in Figures 2 and 3.
antiplatelet medications. However, the greatly elevated risk from an FFR < 0.60 should tilt the balance strongly toward revascularization if all other factors remain equal. We already make these continuous and integrative decisions for blood pressure, dyslipidemia, and ejection fraction; thus, the application to lesion physiology is a natural extension.

No trial comparing optimal medical therapy to revascularization in patients with stable CAD has conclusively demonstrated a statistically significant reduction in hard outcomes of death or MI. Until revascularization trials prove a reduction in hard events by selecting more severe focal and diffuse CAD than previously, the risk/benefit continuum remains the only valid basis for personalized decision-making with informed consent. This view will likely play such an important future role in both clinical practice and trial design that a further discussion of current trials in stable CAD is essential for revealing this commonly-overlooked interpretation of what their data actually shows.

The FAME 2 trial showed a nonsignificant reduction in death and MI from 8.2% after 2 years with initial medical therapy to 6.5% with upfront PCI (HR: 0.79; 95% CI: 0.49 to 1.29; p = 0.35) for lesions with FFR ≤ 0.8 (66). Using these event rates plus standard assumptions for a power calculation (2-sided, < 0.05 significance, 80% power) yields a trial size of 3,784 patients (5)—over 4-fold higher than the 888 patients randomized in FAME 2, and larger than any contemporary revascularization trial in patients with stable coronary disease: 408 in MASS II (Medicine, Angioplasty, or Surgery Study) (67), 1,605 in BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) (68), and 2,287 in COURAGE (69). Given the current recruitment trajectory of ISCHEMIA (now at n = 2,851 [10] of a target 8,000 after 3 years of enrollment), randomizing 3,784 patients with stable coronary disease with FFR ≤ 0.8 does not seem feasible within current research frameworks.

However, the continuum of risk implies a larger treatment benefit for more severe lesions. Assume that lowering the inclusion criterion from FFR ≤ 0.8 to ≤ 0.7 would increase both the relative benefit (from 0.79 to 0.7 with upfront PCI) and the absolute event rate (from 8.2% to 9% with medical therapy). Now the sample size falls from 3,784 to 1,670—a decrease of about 55%—resulting in a trial comparable in size to BARI 2D and smaller than COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation). Not only has sample size decreased, but so too the absolute number of death and MI events: 277 in the larger trial to 116 in the smaller trial (5). Thus, examining for a potential benefit of PCI on hard outcomes in more severe patients makes a clinical trial both feasible and more ethical. Figure 5 provides a general framework for this trial.

Additionally, the typical FFR values around 0.83 seen in a recent diagnostic accuracy study from investigators seeking to avoid hyperemia (70) (such that approximately 2 of 3 patients had an FFR > 0.8, and probably 8 of 10 patients had an FFR > 0.75) fall on the flat portion of the risk/benefit continuum, thereby reducing event rates and hence hampering the ability to exclude a clinically meaningful inferiority when using resting metrics. In this range of mild physiology, a more vigorous upstream trial of medical therapy, coupled with a higher symptom or noninvasive testing threshold, could likely avoid invasive angiography completely, without compromising outcomes.

Finally, the risk continuum has implications for noninvasive physiological testing. Advanced imaging tools all have similar and high diagnostic
Microvascular disease is only now emerging.

Although a complete description of stenosis physiology requires both pressure and flow measurements (48), the risk continuum at very low FFR or CFR identifies lesions with a worse natural history potentially benefited by revascularization. At these lower FFR and CFR values, lesion severity is rarely underestimated by advanced imaging, with pressure flow concordance for optimally guiding revascularization to reduce hard endpoints.

**Matching Revascularization Strategy to Physiology Profile.** At its most general, 3 options exist for treating stable CAD: medical therapy, PCI, and CABG. Medical therapy forms the foundation of treatment, although patients differ in their ability to tolerate and adhere to optimal management. PCI relieves a focal stenosis, providing improved angina relief compared with medical therapy (74), but at a cost of small (but nonzero) procedural risk (18) and the need for dual antiplatelet therapy of potentially longer duration (75). CABG may excel at treating diffuse and complex CAD (76), but with a higher procedural risk (18) and without the need for dual antiplatelet therapy.

Historically, the benefit of PCI rested on assumptions that are now challenged by the following 2 realizations. First, visual estimation of stenosis severity performs poorly compared with coronary physiology (43). Second, unrecognized and unquantified diffuse disease carries a similar risk to focal disease (61,77). This was also illustrated in the PROSPECT study, wherein nonculprit lesions accounted for a comparable frequency of events versus culprit lesions after an ACS (11.6% vs. 12.9% over 3 years, respectively) (11), and in a pooled analysis of post-PCI measurements of FFR that found an inverse relationship with outcomes due to residual diffuse disease (48).

Although a series of randomized trials has already moved the evaluation of stenosis severity from angiography to physiology, specifically by using FFR (66,78,79), the awareness regarding diffuse and microvascular disease is only now emerging.

Matching the strengths of each treatment to the individual patient implies PCI for focal disease of sufficient physiological severity as detailed previously, but without extreme anatomic complexity (76) or severe diffuse disease, which may be better treated by CABG or medical therapy, depending on anatomic and patient specifics (5). Distinguishing focal from diffuse disease thus takes on heightened importance, and 2 general physiological techniques exist. Invasively, a pressure pullback along the length of the epicardial artery can separate focal drops in pressure from diffuse, gradual pressure loss (80). However, a distal FFR measurement will overestimate the relative flow increase from treating a focal stenosis in the presence of diffuse disease, thereby uncoupling FFR from relative CFR. Noninvasively, a global CFR or absolute stress flow reduction in the absence of a relative regional perfusion defect identifies diffuse disease and/or microvascular dysfunction (63). The particular strength of CFR using absolute perfusion measurements resides in its common units for both focal stenosis and diffuse disease, thereby quantifying their relative importance or weight for optimizing the revascularization method (5).

Identifying the physiological pattern affects both patient care and the design of clinical trials to guide informed consent. Treating a focal and severe angiographic stenosis that is physiologically mild exposes patients to procedural risk and heightened antithrombotic therapy without improving symptoms or reducing the risk of hard events (78,79). Treating a mild focal stenosis in a vessel with low FFR due mainly to diffuse disease leaves the patient at increased residual risk (47). It is possible that both of these physiology-to-treatment mismatches took place in prior outcome trials that failed to find benefit of revascularization compared with medical therapy (69).

**Coronary Physiology to Diagnose Symptoms and Guide Treatment.** Apart from the questions of altering hard endpoints of death and MI in stable CAD, we frequently encounter patients with symptoms who want to feel better. Of patients without known CAD who present with new chest pain symptoms, only a small minority has a coronary etiology. For example, in the ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography) trial of 1,000 patients presenting to the emergency department with symptoms suggestive of an ACS, but with an initial negative troponin and no significant changes on electrocardiography, 8% of patients were diagnosed with an ACS (81). Furthermore, 89% of patients with symptoms prompting emergency medical evaluation in this study had noncardiac or noncoronary chest pain. The similarly low rates of revascularization after 90 days seen in
Thus, on the basis of the selected populations described in the preceding text, patients with stable coronary disease without known CAD have a pre-test probability of approximately 5% for a coronary etiology of their chest symptoms. This figure mirrors the prevalence of angina pectoris at just over 3% of the entire adult population in the United States, resulting in 22,000 hospital discharges each year (44). Although these figures imply a small population with symptomatic, stable epicardial coronary disease, such patients comprise a significant portion of cardiology practice and resource utilization due to diagnostic testing, clinic visits, hospital admissions, medication prescriptions plus associated adverse reactions, and revascularization procedures plus associated complications. Coronary physiology may play 2 important roles in symptomatic, patients with stable coronary disease. First, it may help to separate the small minority of patients with a coronary etiology for presenting chest pain from the background majority with noncoronary or noncardiac diagnoses. Unlike index CT screening (81,82), upfront physiological testing can likely screen without increasing unnecessary downstream procedures. Second, it may help to select patients likely to experience superior angina relief with revascularization compared with medical therapy, as reported in the FAME 2 (66) and COURAGE (69) trials.

A wide body of evidence supports invasive quantification of coronary physiology to identify symptomatic fixed stenosis and guide improvement using revascularization. By comparing FFR against a multitest reference standard of exercise electrocardiography, exercise single-photon emission computed tomography perfusion, and dobutamine echocardiography, both before and after revascularization, the threshold of 0.75 was established almost 20 years ago in symptomatic patients with “uncertainty about whether the chest pain was related to reversible ischemia caused by the moderate stenosis” (49). For FFR >0.75 lesions in the DEFER trial, upfront PCI compared with medical therapy did not improve angina burden or need for antianginal medications during the subsequent 5 years (78). From 1 month to 5 years, upfront PCI for these stenoses did not increase the proportion of patients with Canadian Cardiovascular Society (CCS) class I angina (57% vs.

67% actually favoring medical therapy; p > 0.05). Conversely, the FAME 2 trial demonstrated superior angina relief when treating FFR ≤0.8 lesions with PCI compared with medical therapy (66). From 1 to 24 months, upfront PCI for these stenoses reduced CCS class II to IV angina by about 50% to 60% compared with initial medical therapy (risk ratios: 0.36, 0.41, 0.39, and 0.49 at 1, 6, 12, and 24 months, respectively; p < 0.002 at all time points), despite an approximate 40% crossover to revascularization in patients treated medically.

However, the improvement in angina after revascularization noted in FAME 2 and other studies may overestimate benefit due to unblinding of patients and their physicians (83). Thus, ORBITA (Comparison of Coronary Angioplasty and Optimum Medical Therapy Versus Optimal Medical Therapy in the Stable Angina), an ongoing multicenter study in the United Kingdom, will randomize a total of 200 patients with stable angina to real versus sham PCI under blinded conditions (84). Baseline coronary physiology measurements will occur before PCI in all patients, with a primary endpoint of treadmill exercise time after 6 weeks. The coronary physiology data will provide valuable predictors for identifying patients whose angina improves with real PCI, providing an evidence-based evaluation of the added value for hyperemia because stable angina occurs with stress, not at rest.

Noninvasive physiological measurements during angina provide quantitative limits that could form the basis for future randomized outcomes trials. A study of 1,674 cardiac PET scans imaged absolute stress flow and CFR with vasodilation using, as the independent standard, a new or worse perfusion defect during vasodilation in conjunction with significant ST-segment depression and/or severe angina requiring pharmacological treatment (85). Absolute stress flows of 0.91 ml/min/g and CFR of 1.74 demonstrated excellent diagnostic performance (area under ROC curves of 0.98 and 0.91, respectively) for identifying this well-defined ischemia. A multicenter and international study of 330 patients who underwent both cardiac PET and invasive angiography with frequent FFR used an over 90% diameter stenosis or FFR ≤0.8 as its reference standard (71). Although we should bear in mind that a complete description of stenosis physiology requires both pressure and flow measurements (48), absolute stress flow of 2.3 ml/min/g and CFR of 2.5 showed good diagnostic performance (per-vessel accuracy 85% and 81%, respectively), and these flow levels have been associated with low risk (59–61).

Noninvasive simulations and resting physiological predictions of hyperemic conditions assume a uniform, predictable, biological response to stress in
proportion to resting measurements. Documented biological variability fundamentally contravenes such assumptions (86), which can be generally classified as due to heterogeneous responses to hyperemia (the capacity to increase flow varies greatly and unpredictably among patients) or imperfect resolution (in the case of physiological simulation of FFR from invasive or noninvasive imaging of anatomy). As a net effect, these nonstress tools have demonstrated an imperfect pooled 79% per-vessel accuracy from the 3 major FFR_CT diagnostic accuracy studies (87–89), by the approximate 80% per-lesion accuracy of invasive resting physiology (70,90,91) to predict invasive FFR ≤0.8, and by the Bland-Altman SD for both techniques of 0.10 to 0.15 compared with invasive FFR (86,90). For example, a predicted FFR of 0.85 (via invasive resting gradient or noninvasive simulation) could overlap with actual FFR values from 0.70 to 1.0, whose prognosis and treatment differ widely. Therefore, such resting tools rely on assumptions that may not be valid when compared with actual physiological measurements necessary for accurate personalized therapy.

**DIAGNOSIS AND TREATMENT OF ANGINA WITHOUT OBSTRUCTIVE EPICARDIAL CAD.** Two scenarios occasionally arise that are distinct from classic stable angina due to a physiologically severe stenosis, as previously discussed. First, atypical angina can occur at rest or inconsistently with activity. Chest symptoms that occur at rest in patients with stable coronary disease are unlikely to arise solely from a fixed coronary stenosis. Typically, such complaints are either noncoronary or result from a variable combination of fixed stenosis plus functional disease (e.g., abnormal blood pressure or heart rate, adrenergic medications, endothelial dysfunction, or coronary spasm). As an advantage, vasodilator imaging and invasive measurements minimize physiological variability to reveal the severity of fixed disease alone, whereas exercise stress or dobutamine infusion stimulate physiology severity over and beyond the fixed structural component (92). Because the vast majority of functional coronary disease (e.g., vasospasm, myocardial bridging, or endothelial dysfunction) can be treated with widely available, generally well-tolerated, and relatively inexpensive medications (e.g., beta-blockers, calcium-blockers, and nitrates), it has received less attention than revascularization of fixed coronary disease. However, it is increasingly recognized that such conventional therapies do not lead to similar symptom control as that seen in patients with focal epicardial stenosis.

Beyond symptoms, the presence of angina with angiographically nonobstructive or normal coronary arteries may not necessarily associate with low clinical risk. Indeed, a large European registry demonstrated that patients with angina and normal coronary arteries or nonobstructive CAD were associated with a 52% and 85% increased risk of combined cardiovascular mortality, hospitalization for MI, heart failure, or stroke, and with 29% and 52% increased risk of all-cause mortality, respectively, with no differences between men and women (93). Similar physiological observations were seen in studies using invasive (94) or noninvasive (95) CFR assessment.

Second, classic angina may present without a significant stenosis. Interestingly, the group of patients with angina but FFR >0.75 to 0.80 has a clear subset with refractory symptoms, despite medical therapy. In both the DEFER and FAME 2 trials, lesions with high FFR had inferior angina relief compared with low FFR lesions that underwent PCI. Specifically, the FFR <0.75 cohort treated by initial PCI in the DEFER trial reached a 72% freedom from angina, whereas both FFR ≥0.75 cohorts had lower levels, at 67% and 57% free of angina (p = 0.028) (78). Similarly, the FFR >0.8 registry of the FAME 2 trial had a similar angina burden at baseline that improved by 1 month, but thereafter remained worse than the FFR ≤0.8 cohort treated by PCI (risk ratios: 0.47, 0.38, and 0.40 at 6, 12, and 24 months, respectively, favoring low FFR with PCI; all p ≤ 0.002) despite 12% crossover to PCI (66).

These subgroup analyses highlight other mechanisms for angina that are separate from a severe epicardial stenosis. Such functional coronary disease may be elucidated through a variety of physiological techniques, such as noninvasive quantification of global CFR (61), Doppler-derived (62) or bolus thermodilution-based (20) measures of myocardial resistance, pressure or flow interrogation of myocardial bridges (96), or provocation testing for endothelial dysfunction (97).

However, currently, only hypothesis-generating studies suggest potential links to existing therapies. Additionally, many of these therapies cost little and could thus be tried anyway in patients with residual symptoms, after excluding significant fixed epicardial disease. Novel systemic therapies for cardiovascular disease, such as methotrexate and PCSK9 inhibitors, are currently being tested in general populations, and coronary physiology may provide a risk stratification tool to refine their cost-effective use.
CONCLUSIONS

We conclude by summarizing a vision for the future of coronary physiology. Given the prominent role of ACS and invasive procedures in cardiology, our schema focuses on those themes. Nonetheless, many (if not most) patients now undergoing interventional cardiovascular procedures may not meet the severity criteria for intervention to reduce death and MI beyond what modern medical treatment can achieve. It is our view that new interventional trials driven by quantitatively severe focal and diffuse disease may help to define the roles of integrated diagnostic testing and intervention for reducing hard outcomes.

Of course, no clinical diagnostic test stands apart from an associated therapy. The future of invasive FFR, noninvasive CFR, and other related physiological measurements rests firmly on establishing meaningful links to effective treatments and improved clinical outcomes. For patients with acute coronary disease, coronary physiology may potentially refine treatment of the culprit lesion. Here, endpoints of death and MI will dominate clinical trials, just as they have in the past for ACS. For both patients with stable and acute coronary disease with nonculprit disease, reducing death and MI with revascularization potentially occurs at the severe end of the focal physiological spectrum, an area underrepresented in existing trials. We can use the continuum of risk clarified by coronary physiology to tailor our discussions with patients to achieve truly informed consent regarding risks and benefits from therapy. For the large number of patients with chest symptoms, physiology measurements identify the small proportion of them who have coronary disease with focal severity likely to benefit from revascularization in addition to medical therapy. Nonepicardial disease and diffuse CAD remain underexplored aspects of coronary physiology for testing of novel treatments.

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