The interesting study by Stuijfzand et al\textsuperscript{1} in this issue of *Circulation: Cardiovascular Imaging* compares positron emission tomography (PET)-measured coronary flow reserve (CFR), maximum absolute stress perfusion (MBF) in cc/min/g, and relative CFR (RFR) for predicting pressure-derived fractional flow reserve (FFR) in patients undergoing coronary angiography for suspected CAD.\textsuperscript{2,3} RFR was determined as the ratio of regional MBF of stenotic arteries to MBF of nonstenotic arteries. The authors report no significant difference between flow-based RFR and pressure-derived FFR ($\Delta P$=0.04, paired $P$ value 0.12) but imperfect agreement (standard deviation of difference $=0.16$, area under the curve 0.82, accuracy 82%). All flow measurements showed notable discordances with FFR, specifically illustrated by the RFR–FFR correlation.

## Question 1: What Does the Data Really Tell Us?

**The Truth: A Continuous Range of Complex, Interacting Physiology?**

Figure 3 of Stuijfzand et al\textsuperscript{1} plots RFR against FFR. To see its hidden reality, draw a vertical line up from an FFR of 0.8 and a horizontal line left to right from an RFR of 0.8 to make 4 quadrants from these equal cutoffs of 0.8. The upper left quadrant contains 10 points showing discordance where FFR $\leq 0.8$ but RFR $\geq 0.8$. For a normal CFR of 3.32 as reported for nonstenotic reference arteries in this study, absolute CFR for this RFR of 0.8 would be 0.8× 3.32 or 2.7 that indicates adequate stress flow capacity well above ischemic levels reported for the entire literature.\textsuperscript{4–7} Similarly, MBF for mildly stenotic arteries was 2.98 cc/min/g in this article where a relative reduction or RFR of 0.8× 2.98 is 2.4 cc/min/g that is also well above any ischemic flow reported.\textsuperscript{4–6}

Therefore, the upper left quadrant of Figure 3 identifies half of the patients with FFR $\leq 0.8$ having myocardial perfusion capacity that is substantially greater than any low-flow ischemic threshold reported in the literature.\textsuperscript{4–7} Consequently, these patients are unlikely to have flow-limited ischemia, despite an FFR $\leq 0.8$. One then might reasonably ask whether revascularization benefits these patients or exposes them to a procedural risk that may be greater than the risk of nonflow limiting CAD. The observed flow-based threshold of RFR in Figure 3 could also be interpreted as 0.83 where the vertical line up from FFR of 0.8 intersects the solid regression line. In that case, CFR and MBF at an FFR of 0.8 would be even higher than any low-flow ischemic thresholds in the literature.

Similar discordance is documented for absolute CFR versus FFR or other physiological or anatomic combinations of severity.\textsuperscript{7,8} The lower right quadrant of Figure 3 in this article\textsuperscript{1} shows a different kind of discordance—a high FFR with low coronary flow capacity characterizing diffuse CAD\textsuperscript{4–7} associated with high risk of coronary events; its natural history may be improved by coronary artery bypass surgery,\textsuperscript{9} but that hypothesis remains untested in a randomized trial.
FFR: A Single Gold Standard of Severity?
The present study used FFR as the standard reference of severity based on the profoundly important FAME randomized trials that moved interventional thinking from anatomic to physiological stenosis severity as the optimal guide to percutaneous coronary intervention (PCI). However, FFR has also been challenged as the gold standard reference of severity for several reasons.

Continuous pressure gradient flow curves define comprehensive physiology not captured by a single pressure or flow measurement. The discordances among single indexes reflect complex, interacting combinations of segmental stenosis, diffuse disease, associated microvascular dysfunction, or preserved microvascular vasodilation, despite epicardial disease. Assessing this reality for binary interventional decisions requires some quantification of relative severity like FFR, CFR, RFR, or relative uptake on perfusion images and some measure of absolute flow, such as MBF in cc/min/g or absolute CFR for parsing global and segmental disease. Because diffuse disease carries substantial quantitative risk that may contravene potential benefit from PCI of focal stenosis, flow or pressure measurements of both localized stenosis and diffuse disease are essential for optimally guiding revascularization.

Finally, FFR-guided PCI in FAME 2 showed that PCI can be safely deferred for FFR ≥0.8 but showed a nonsignificant trend toward reduced myocardial infarction (MI) or mortality compared with medical treatment when procedure-related events were included (hazard ratio 0.61 [95% confidence interval, 0.28–1.35] at cessation of recruitment, 2 P = 0.22; and 0.79 [95% confidence interval 0.49–1.29] at 2-year follow-up, 3 P = 0.35). A strict interpretation to FAME 2 is that all patients with FFR ≤0.8 could be deferred with a risk (≈15% [≈1 in 6]) of having urgent revascularization or (≈25% [≈1 in 4]) of having nonurgent revascularization later without significant excess MI or death over medical treatment alone. Larger trials would be necessary to test FFR-guided PCI over medical therapy using only hard end points of death or nonfatal MI.

Statistically Right or Wrong?

Meta-analysis shows FFR to have a continuous relation to events that differs between medical therapy and revascularization. Therefore, the risk-versus-benefit tradeoff from PCI immediately adjacent to a threshold remains closely balanced. By contrast, the greatest benefit or harm occurs at extreme values. Instead of larger trials to test FFR-guided (or CFR-guided, MBF-guided, RFR-guided) PCI for hard end points of death or nonfatal MI, an alternative approach would be to focus on more extreme thresholds to augment the effect size from treatment. Rather than CFR, MBF, RFR, or FFR’s being right or wrong as a binary threshold for intervention, these continuous measures of severity reflect the hidden reality of graded risk and therefore graded benefit.

Hidden Reality 1

Binary thinking in cardiology needs evolution to integrate multiple, continuous, physiological measurements of CAD severity into criteria for binary interventional decisions to account for the continuum of risk.

Question 2: What Is the Threshold of Physiological Severity for Revascularization to Reduce MI or Mortality?

From this article and related literature, diverse data suggest surprising, potentially profound, paradigm-changing answers to this question as follows.

Severity Threshold in the Current Article?

In Table 4 and Figure 3 of this article, the severest stenoses are comparable to those in acute coronary syndromes by intravascular imaging. These severe stenosis are clearly identified by CFR, MBF, and RFR compared with the intermediate severity for which FFR was measured. They also compare with reduced coronary flow capacity associated with high risk of stress-induced angina, ECG changes, and coronary events. Thus, at greater severity, all of these pressure- and flow-based measures of severity converge to essential correspondence for binary interventional decisions with augmented treatment effect for revascularization reducing MI and mortality compared with medical treatment. In our nonrandomized experience, these severe flow thresholds of CFR, MBF, or relative defects identify patients for whom revascularization prevents MI and death.

High Risk Diffuse CAD may Contravene Benefit of PCI for Stenosis?

Diffuse CAD quantified by reduced global CFR carries high risk of adverse events. Because significant stenosis is usually associated with diffuse disease, the residual diffuse disease may contravene the potential benefit of PCI as also evidenced by significant risk of residual FFR after PCI. For PCI to reduce MI or mortality, a stenosis has to be severe enough to pose a greater risk than the diffuse disease and the revascularization procedure, as seen by the increased hazard ratio of 9.01 (95% confidence interval 1.13–72.0) for death or MI compared with medical therapy within 7 days of PCI in FAME. 2

Low FFR with Mild Anatomic or Physiological Severity

Measuring FFR in all coronary arteries, not just those with significant angiographic stenosis as for the FAME studies, questions whether FFR should be used for bidirectional reclassification instead of only deferring revascularization. Such studies show that FFR may be low, despite only mild stenosis on angiogram or with good CFR. Given the low risk associated with mild anatomic stenosis and good coronary flow capacity or stress perfusion, even a low FFR for such lesions may not identify sufficient benefit from revascularization.

Normal FFR With High Risk Diffuse Disease

FFR may be high with reduced global CFR reflecting high-risk diffuse disease. Similarly, post-PCI FFR correlates inversely with risk, likely because of residual diffuse disease. The FFR threshold fails to address this high-risk condition, whereas MBF or CFR identify such patients.

Hidden Reality 2

FFR represents an enormous advance over angiographic percent diameter stenosis for safely deferring revascularization. However,
to prove a significant reduction in MI and mortality from PCI, either larger trials or more extreme FFR thresholds will be necessary. At these lower thresholds, the discordances among RFR, MBF, CFR, and FFR resolve into a concordant measure of severity for which revascularization is more likely to reduce MI and mortality but needs testing in future randomized trials.

Hidden Reality 3
A final aspect of this article is so obvious as to be unseen. It reflects a remarkable evolution of cardiology thinking from anatomy to physiology in patient management that began in the first author’s experimental laboratory 42 years ago before any technology to address these issues clinically.9 Although this article by Stuijfzand et al reflects binary thinking, uni-measurements and overlooks Hidden Realities, it continues the evolution toward truths about the human heart that are complex, multidimensional, and require integration of several continuous variables to arrive at a binary procedural decision for optimal patient benefit.

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References


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