As stated in American College of Cardiology/American Heart Association Guidelines, randomized trials have not demonstrated that elective percutaneous coronary intervention (PCI) reduces myocardial infarction (MI) or mortality over medical treatment. Even the Fractional Flow Reserve (FFR) Versus Medical Therapy in Stable Coronary Disease (FAME) trial showed no statistically significant benefit of PCI over the deferred group by traditional intention-to-treat, nonbenchmark analysis starting at randomization that includes procedure-related events. Benchmark analysis in FAME 2 beginning 1 week after PCI removed procedure-related events that counterbalanced subsequent reduced MI and mortality compared with the deferred group. Meta-analysis of the literature on risk of events related to fractional flow reserve (FFR), including FFR Versus Angiography in Multivessel Evaluation (FAME), and other physiological measures of severity reveal an underappreciated, powerful interdependence among physiological severity of stenosis, diffuse coronary artery disease (CAD), event rates, sample size, and statistical certainty of differences. This analytic review synthesizes an evidenced-based, quantitative hypothesis and potential solution to this issue based on hard data from the literature by coauthors of diverse cardiovascular disciplines in trial design, biostatistics, invasive procedures, coronary physiology, fluid dynamics, coronary pathology, and quantitative imaging. Our synthesis elucidates a dual hypothesis for failure of elective PCI in stable CAD to reduce MI or mortality and novel trial design for selecting patients for whom PCI will likely reduce these events. First, a large burden of global diffuse CAD carries a high risk of coronary events unmitigated by PCI of a focal stenosis. Second, focal stenosis severity in previous randomized revascularization trials has been too modest without objectively quantified sufficient severity to observe benefit of PCI. In previous trials, mixture of diffuse coronary disease and intermediate stenosis may not incur high enough risk for potential benefit by PCI for sample size of reported trials. Greater quantitative severity with higher event rates may overcome this limitation. Because it powerfully alters sample size, event rates, and statistical certainty in randomized trials, quantitative physiological severity of not only focal but also diffuse CAD must inform patient selection in future revascularization trials if reduction in MI and mortality is to be a scientific basis for revascularization and evidenced-based, objectively informed patients.

Overview: A Central Issue in Cardiology: Who Benefits From Revascularization to Reduce MI or Mortality?

Forty-one years ago the senior author reported the concept of coronary flow reserve (CFR) as a physiological measure of stenosis severity. Nineteen years later Pijls et al with the senior author proved experimentally the concept of FFR as a practical relative CFR. Twenty-one years after that saw publication of the primary, 2-year FAME 2 follow-up. While gratifying, this evolution provides a unique longitudinal view for addressing critically but constructively the issue of FFR-guided revascularization for reducing MI and mortality.

CFR (also called absolute CFR) is the ratio of peak coronary flow in mL/min or myocardial perfusion in mL/min per gram during vasodilator stress to resting flow or perfusion as a quantitative measure of increasing capacity. It is blunted by stenosis, diffuse, or small-vessel disease. Relative CFR is the ratio of peak flow or perfusion in an abnormal region of a relative perfusion image to the most normal appearing region that, however, may have reduced absolute CFR. Therefore, it reflects relative severity of focal disease but fails to identify superimposed or associated diffuse disease. FFR is a measure of relative flow reserve derived from the stenosis pressure...
gradient measured by intracoronary pressure wire at peak vasodilator stress. The pressure gradient along the entire length of a coronary artery may identify diffuse disease but cannot quantify it. Because FFR reflects relative flow reserve, it may be low (abnormal with high pressure gradient) because of high flow through a mild to moderate stenosis. Alternatively, FFR may be high (normal with no pressure gradient) because of low flow caused by diffuse or small-vessel disease despite a severe stenosis.

Acute PCI reduces the risk of death or recurrent MI for focal CAD of sufficient severity to cause acute coronary syndromes (ACSs). However, reducing death or MI after elective revascularization in stable CAD remains uncertain. American College of Cardiology/American Heart Association guidelines conclude that elective revascularization does not reduce the risk of death or MI9 although it helps relieve angina. Two recent reports suggest reduced mortality and MI after elective revascularization when compared with medical management, but in different ways do not definitively resolve the issue.

Both reports contain a strong signal on the potential benefit of revascularization. Analysis of these 2 positive reports here reveals critically important, perhaps unexpected lessons on the underappreciated interdependence of physiological CAD severity, diffuse anatomic CAD burden, risk of events, sample size, statistical certainty for differences, and trial design. Together, these essential concepts coalesce into a novel framework for selecting patients to prove fewer hard end points with revascularization compared with medical management. Although currently only one third of PCI involves stable CAD, evidence-based practice requires definitive resolution of this issue.

Coronary Physiology and Statistics of Recent Randomized Trials

In FAME 2, landmark analysis beginning 1 week after PCI removed procedure-related MI to show reduced MI and mortality compared with the medical therapy group. However, if outcomes were counted from time of randomization to include procedure-related MI, then FAME 2 showed no statistically significant difference by the traditional intention-to-treat analysis. 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 has to be accounted for in any objective assessment of benefits and risk of PCI. In addition, all patients in the immediate PCI group underwent revascularization, but it did not count as an event as it did for medically treated patients during follow-up. Finally, FFR-guided PCI in FAME 2 showed a nonsignificant trend toward reduced MI or mortality compared with medical treatment even when including all events (hazard ratio, 0.61; 95% confidence interval, 0.28–1.35 at cessation of recruitment); P=0.22 and 0.79; 95% confidence interval, 0.49–1.29 at 2-year follow-up; P≈0.35).

A strict interpretation to FAME 2 is that all patients with FFRs<0.8 could be deferred with a risk between 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.

For a definitive, traditional, intention-to-treat analysis using hard end points of mortality or MI, what sample size would be required using event rates in FAME 2 to power the study? After 2 years, FAME 2 had 6.5% (immediate PCI) versus 8.2% (deferred PCI) death or nonfatal MI. Therefore, assume a 2-year trial with 8% death/MI in the medical arm and 0.8×8%=6.4% in the PCI arm, for a 20% relative risk reduction. Standard sample size calculations yield a required 4085 patients in total. For the PCI group (n=2000), expect 6.4%×2000 or 128 events (versus 29 in FAME 2) and for medical therapy (n=2000) expect 8%×2000=160 events (versus 36 in FAME 2). Thus, the =440 patients in each FAME 2 arm were only ≈1/5 of the required sample size.

However, a 4000 patient trial would be larger than any other previous study: the Medicine, Angioplasty or Surgery Study (MASS II) enrolled 408 patients; Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), 2287; Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D), 1605; and FAME 2, 888. Among them, only FAME 2 hinted at a reduction in hard events because all other risk ratios were close to unity. Thus, in general, all trials failed to show significantly reduce MI or mortality because of small sample sizes, whereas only physiology-based lesion selection trended toward a reduction.

Physiological–Statistical Interactions for Revascularization to Reduce MI and Mortality

Per-patient meta-analysis of a large outcomes literature showed that FFR related continuously to adverse events and differed between medical therapy and revascularization. Adapted from this meta-analysis, Figure 1 shows event-free survival curves for revascularization versus medical treatment alone (controls). The crossover point of these curves marked by the black dot indicates where potential risk associated with the procedure exceeds the potential benefit of eliminating the stenosis. Although that meta-analysis was limited because of confounding by indication and few unrevascularized lesions below 0.75, its methods provide a template for deriving an outcomes-based threshold. The risk versus benefit tradeoff from PCI immediately adjacent to any FFR threshold remains closely balanced. As a threshold is chosen farther toward lower FFR or CFR, implying greater physiological severity, the benefit of revascularization can be more readily detected if it exists. Instead of larger samples sizes to test FFR-guided revascularization (or CFR guided, myocardial blood flow guided, or relative CFR guided) for hard end points of death or nonfatal MI, an alternative approach would use more stringent, more severe thresholds to augment the effect size from treatment, such as an FFR of 0.65.

Finally, recent studies of FFR measured systematically in all 3 coronary arteries report ≤35% to 40% of cases as discordant with low FFR, despite no or 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, a low FFR in the absence of other data may not identify disease benefitting from revascularization.

If patient selection were enriched for higher event rates by selecting more physiologically severe disease, such as FFR<0.65 or CFR ≤1.5 to 1.7, then sample size would be markedly reduced to half the sample size almost proportionally as follows. For example, an augmented 16% event rate in the medical arm >2 years instead of 8% would reduce the total sample size to 1884, similar to BARI 2D or COURAGE.

A recent network meta-analysis of 100 revascularization trials in nonacute CAD (using bypass grafting or PCI) involving 93,553 patients reported 5346 deaths >30 years or 5.7%. Comparing coronary artery bypass with medical therapy yielded a survival benefit ratio 0.8 (95% credibility interval, 0.70–0.91). An assumed 6% event rate with medical therapy implies 83 revascularization procedures to prevent 1 death, the so-called number needed to treat. Moreover, no single trial in nonacute CAD (using bypass grafting or PCI) involving 93,553 patients reported 5346 deaths >30 years or 5.7%.

Randomized revascularization trials have primarily relied on segmental stenosis by angiography or FFR, with no comparable quantification of the underlying diffuse disease. Their failure to demonstrate a significant and consistent reduction in mortality and nonfatal MI may, in part, reflect the high risk of poorly defined diffuse disease, despite elimination of segmental stenosis.

### Tandem Development of Focal and Diffuse CAD

After peer review, we reported a cohort of 1500 consecutive patients who underwent diagnostic cardiac PET imaging at...
our center for known or suspected CAD as detailed for methodology, patient selection, and predefined disease severity by quantitative perfusion imaging. Figure 2 displays an important result extracted from the peer-reviewed, published, main table. For 5 clinical groups of progressive severity, it shows average left ventricular (LV) CFR quantifying global burden of diffuse CAD, the worst quadrant CFR, and the relative perfusion defects quantifying focal stenosis. In these groups of patients, the average global CFR reflecting severity of diffuse disease worsens in parallel with the worst regional CFR and worst focal relative perfusion defects reflecting localized stenosis severity.

The red zone of Figure 2 shows the threshold of regional absolute stress flow and regional CFR associated with angina or significant ECG ST depression with a regional stress defect during the stress test. The low flow threshold causing this documented ischemia is 0.9 mL/min per gram, CFR of 1.7, and a relative stress defect reduced to 60% of maximum myocardial radionuclide uptake for ≥10% of the LV. This red zone also corresponds to the high-risk threshold for global CFR of 1.5 associated with high risk of adverse coronary events reported in the literature. By serial PET imaging, CAD most often progresses in an arterial distribution different than the worst baseline defect, thereby reflecting the importance of the global burden of coronary atherosclerosis in progression to events that can be measured in the same quantitative units as for localized stenosis.

Two consequences follow from Figure 2. First, diffuse and focal CAD develop in tandem, such that by the time a severe stenosis has matured, typically it exists on a background of moderate to severe global disease. Second, the mixture of severe focal and diffuse disease may define what type of disease PCI or coronary artery bypass are best suited in trials, or identify poor targets for localized revascularization compared with optimal medical management.

Anatomic Severity of Diffuse and Focal Disease Associated With Coronary Events

Coronary pathology studies demonstrate that the vast majority of acute coronary events (perhaps 90%) represents the final step in a series of preceding, subclinical, smaller plaque ruptures that heal with progressive narrowing to a severe stenosis before the final event or ACS. This progression to severe stenosis may develop over days, weeks, months, or years. Focal events, therefore, represent the tip of a global iceberg of coronary atherosclerosis. An optical coherence tomography-intravascular ultrasound study in ACSs demonstrated that a combination of large global plaque burden plus severe focal lumen narrowing (70%–80% diameter stenosis) associate with events, implying a substantial background of diffuse disease with superimposed severe focal stenosis.

Severe stenosis underlie most ACSs, even 89%, not the large nonstenotic lumen with a virgin plaque rupture. Finally, the gradient of risk indicated by FFR measured immediately after PCI suggests that residual diffuse disease untreated by focal therapy continues to cause clinical events. This residual risk of events caused by diffuse disease may outweigh the lower risk of an intermediate stenosis, thereby contravening benefit of the PCI.

The continuum of heterogeneous diffuse and segmental disease among patients comprises a spectrum of potential benefit of revascularization from probably lifesaving to negative benefit where the procedure carries greater risk than medical treatment. Although some binary threshold of severity is necessary for randomized trials, the risk–benefit ratio close to either side of any arbitrary threshold is not a binary certainty but has small probability differences on either side of the threshold, as exemplified by Figure 1.

Thresholds of Physiological and Anatomic Severity Associated With High Risk

Quantitative physiological severity of stenosis and diffuse disease burden throughout the entire coronary artery tree is essential for selecting high-risk patients for whom revascularization may reduce MI and mortality in definitive randomized trials of reasonable size. The question then becomes: what are the separate and combined thresholds of physiological severity of stenosis and diffuse disease for which revascularization reduces MI and mortality in nonacute CAD? Currently, coronary pressure as a physiological measure of severity has had the greatest impact on guiding PCI of stenosis in randomized trials. However, its limitations are also real: invasive, lacking a threshold proven to reduce MI and mortality, failure to quantify diffuse disease, and high prevalence of discordance with low FFR, despite adequate flow capacity or absence of significant stenosis.

All previous revascularization trials have selected focal lesions based on some feature of severity, either anatomic (like percentage diameter stenosis) or physiological (like FFR). Figure 3 summarizes published threshold severity of percentage diameter stenosis, diffuse narrowing, CFR and FFR for
low or high risk of coronary events. It is a visual condensation of hard data integrated from complex fluid dynamic, anatomic and flow literature, experimental stenosis models, and some clinical trials, published in >200 peer-reviewed articles in these diverse fields.\(^1\),\(^12\),\(^\text{30–36}\)

The stenosis and diffuse narrowing shown in black on white paralleling coronary cine angiograms are precisely scaled fluid dynamic simulations matching experimental data,\(^1\) clinical studies, meta-analysis of PCI for threshold of risk,\(^2\) and review of the English literature on quantitative myocardial perfusion related to ischemia and risk of coronary events.\(^3\) Figure 3 is not a hypothetical illustration but rather a visual summary of published data in an extensive literature not otherwise clearly or easily presented.

Even with these magnified precise images, the subtle anatomic differences are difficult to visualize and impossible to quantify adequately on clinical angiograms\(^1\),\(^\text{34,35}\) for predicting physiological severity determining low versus high risk narrowing as a guide for PCI. Nearly all randomized revascularization trials have selected patients with visually >50% or >70% diameter stenosis that is well documented to overestimate severity substantially\(^3\) and poorly related to physiological severity. Many trials included only visually intermediate stenosis for randomization that are likely on the low-risk portion of Figure 1 such that PCI provided little benefit over medical treatment given the lack of improvement in death or MI compared with medical therapy.

Although anatomic severity and its visual estimation have several limitations,\(^\text{31,36,37}\) Figure 3 illustrates that anatomic selection might produce an enriched high-risk population by enrolling truly more severe, objectively measured lesions by validated quantitative coronary angiography of 80% diameter stenosis associated with CFR of 1.5 to 1.7 and FFR of 0.65. However, current literature and technical limitations of all angiographic and CT imaging indicate that physiological measurements such as FFR and CFR provide more robust entry criterion for selecting severe high-risk lesions for which PCI may likely reduce MI and mortality as illustrated by FAME 2.\(^3\)

Perhaps most importantly, anatomic stenosis severe enough to cause high risk would not likely be randomized in current trials because of clinical judgment that withholding revascularization exposes patients unethically to a high risk of adverse events—a judgment or belief without validation by existing randomized trials. Indeed, the terms ischemia, refractory angina, and severe stenosis are loaded and imply the need for intervention. However, they are not well defined and have proven inadequate guides for elective PCI to reduce death or MI in existing trials. Angina may or may not be a specific marker of high risk depending on the underlying coronary pathophysiology causing it. Moreover, relief of angina by revascularization is not associated with reduced MI or mortality.\(^3\),\(^\text{39,40}\)

**Clinical Example**

Figure 4 illustrates a patient with a large, severe perfusion defect caused by a high-grade right coronary artery lesion jeopardizing 38% of the LV\(^3\) yet with minimal angina. Before PCI, the inferior absolute CFR by quantitative PET was 0.4 indicating severe myocardial steal in the absence of visible collaterals indicating severe high-risk stenosis. In other areas outside the stress defect, global CFR was only mildly reduced at 2.6\(^\text{32,33}\) in the low-risk range of Figure 2.\(^\text{17,18,32,33}\) After PCI, the angiogram and relative PET images look normal but global CFR remained unchanged indicating remaining low-risk diffuse disease needing medical treatment. In our view for this case, the high risk of the anatomically and physiologically severe stenosis outweighed the lower risk of his global diffuse disease, thereby justifying focal PCI.

The inset of Figure 4 shows precise, scaled, computer modeled, 67% diameter stenosis\(^1\) and cine angiogram of a phantom with exactly the same machined stenosis, both compared with the more severe 83% diameter stenosis on the clinical angiogram. The visual borders on the cine angiogram of the phantom (red lines) overestimate severity at 75% diameter stenosis in the high-risk range compared with true less severe 67% diameter stenosis of the computer model and cine phantom in the low-risk range. The computer stenosis analysis\(^\text{16}\) for 83% diameter stenosis on the clinical angiogram predicted myocardial steal of 0.6 comparable with 0.4 measured by quantitative stress PET perfusion imaging. Visual estimates, invasive quantitative coronary angiography, or CT quantitative coronary angiography cannot quantitatively separate these intermediate stenosis having profoundly different physiological severity and associated high or low risk as guides to PCI for reducing MI or mortality.

Existing trials have likely not selected lesions with quantitative severity of the case in Figure 4 for randomization to PCI to assess potential reduction of death or MI. Rather such patients have probably been excluded from trials in favor of an intermediate stenosis whose risk of diffuse disease or risk of the procedures may outweigh the risk of the intermediate lesion with little benefit on MI or mortality by PCI compared with medical treatment. Because the terms intermediate and severe are not quantitative or well defined in terms of risk, Figures 3 and 4 define what we use and recommend as

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**Figure 3.** Summary of threshold severity for percentage diameter stenosis, diffuse narrowing, coronary flow reserve (CFR), and fractional flow reserve (FFR) for low and high risk of coronary events based on integration of published clinical trials, experimental data, and fluid dynamic models.\(^1\),\(^\text{3,12–20}\) The stenosis and diffuse narrowing shown are precisely scaled fluid dynamic simulations matching experimental and clinical data.\(^1\) Green low-risk and red high-risk severities match similar color-coded low- and high-risk regions of Figures 4 and 5.
Patient Selection to Improve Event-Free Survival by Revascularization

This synthesis proposes a dual hypothesis to explain the previous failures of elective PCI in stable CAD for reducing MI or mortality as the basis for new trial design addressing this issue. First, a large burden of global diffuse CAD carries a high risk of coronary events unmitigated by PCI of a focal stenosis. Second, focal stenosis severity in previous randomized revascularization trials may have been too modest to observe a treatment benefit. The interplay between diffuse and focal CAD must inform individualized clinical decisions and patient selection in future revascularization trials, as illustrated conceptually in Figure 5.

Continuous predictive variables generally follow a curvilinear risk/severity relationship as shown in Figure 1 with a threshold range separating lower and higher risk groups as seen for percentage diameter stenosis, age, blood pressure, low-density lipoprotein, CFR, and quantitative stress perfusion defects. The diagram of trial design in Figure 5 illustrates the consequences of this continuous curvilinear risk/severity relationship. Four distinct phenotypes can be distinguished at each corner, with overlapped expression in the central diamond. Schema S (stenosis) in the upper left corner includes severe focal stenosis jeopardizing a large myocardial volume on a background of mild low-risk diffuse disease. In this case, PCI of severe focal stenosis may potentially reduce death and MI given the high risk of severe stenosis but low risk of mild diffuse disease.

By contrast, schema D (diffuse disease) in the lower right corner includes severe diffuse CAD with no or only mild superimposed focal stenosis. Here, focal PCI has limited benefit because it cannot treat the global culprit, whereas coronary artery bypass grafting might favorably alter the natural history. Schema SD (stenosis plus diffuse disease) in the upper right corner likely carries the worst prognosis given its mixture of severe diffuse CAD plus severe focal lesion. In this scenario, either PCI or coronary artery bypass grafting might reduce MI and mortality depending on the relative severity of focal and diffuse disease needing a randomized trial of this specific type of patients with quantification of diffuse and focal disease.

The central diamond of intermediate stenosis with undefined diffuse disease likely characterizes most randomized trials, where risk of events caused by focal stenosis is low, is not changed by PCI, has ongoing risk from diffuse disease, and incurs potentially added risk of procedures that may be greater than its potential benefit for intermediate stenosis. Because the terms intermediate and severe stenosis are imprecise, non-quantitative, and therapeutically loaded terms, Figures 3 and 4 define intermediate low risk in green colors and severe high risk in red colors.

Implications for Trial Design: Severity Stratified Randomization and Analysis

In trial design, greater severity thresholds increase event rates and thereby augment the risk that could potentially be reduced by revascularization. Figure 6 illustrates conceptually the trial...
alternatives based on quantitative ischemic flow thresholds for focal and diffuse disease. Although this example uses PET, the concept applies to any other technology validated for quantifying focal and diffuse disease, including MRI, CT, echocardiography, or intracoronary technologies. For Figure 6, green color-coded low-risk and red high-risk severities match similar color-coded low- and high-risk regions of Figure 3.

This severity stratified randomization trial design would test PCI or coronary bypass surgery versus medical management for reduced MI or mortality and identify specifically which patients benefit from which procedure. If randomizing such patients to immediate revascularization or deferred revascularization as later needed is not feasible, the severity stratified randomization design above can also be the basis for a gatekeeper trial whereby patients with moderate severity thresholds shown above have an angiogram or not based on physiological severity and clinical circumstances. The remaining patients with mild segmental or even intermediate stenosis and diffuse disease could undergo intense medical and lifestyle management as appropriate for clinical circumstances.

Adverse outcomes of MI and mortality in the 2 groups would indicate whether the quantitative gatekeeper criteria benefitted patient optimal patient management with only necessary revascularization by objective criteria. As an example of applying gatekeeper criteria in the first author’s second opinion practice, 70% of patients with previous recommended invasive procedures had adequate myocardial stress perfusion and no regional ischemia by quantitative PET that, when integrated with clinical evaluation, indicated medical management of evidence-based objectively informed patients (nonrandomized). At ≤7-year follow-up, there were no MI and no deaths in these patients with procedures deferred based on PET.

Because severity by whatever measure often displays a skewed distribution in the population, patients with marked lesion severity come to attention less frequently. However, although recruitment, therefore, would take longer, a smaller study population than the larger size illustrated above may demonstrate a significant difference in MI and mortality because of enriched event rates suitable for potential revascularization. The current International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial may be moot because of potential confounding issues of unquantified diffuse and segmental disease that single photon emission computed tomography imaging or CT angiogram do not provide at entry screening.

As a simplified example, for severe disease in protocol S of Figures 5 and 6, let the estimated reduction of MI/mortality in the group with severe PET abnormalities or severe stenosis drive sample size. For severe PET abnormalities or severe stenosis based on the literature, assume that MI/mortality would be at least 3% per year or 6% >2 years in the medically treated group versus 1.5% per year or 3% >2 years in the PCI group with such severe disease. Sample size for β of 0.2, and δ of 3.0% (50% relative risk reduction), would be 729 total randomized subjects for the study. By contrast, for less severe, intermediate severity disease associated with a smaller δ of events between the groups of 1.5% (25% relative risk reduction), sample size for β of 0.2, and δ of 1.5% (25% relative risk reduction) would require 3453 total randomized subjects for the study. Thus, quantitative severity of stenosis and diffuse disease has potentially profound effects on risk, the effect of revascularization on risk, and hence study sample size and statistical certainty.

Severity Thresholds for Trial Design or Clinical Decisions

The central question in testing revascularization for reducing MI or mortality in nonacute CAD is quantifying focal and diffuse CAD severity physiologically, not diagnosis of CAD or the broad spectrum of potential diagnosis of microvascular disease, syndrome X, spasm, or so on. As suggested by Figures 5 and 6, trials of revascularization for reducing MI and death may need to select patients with sufficiently severe segmental stenosis causing as great or greater risk than the underlying diffuse global CAD by ≥1 of the following criteria: (1) FFR of 0.65 by pressure wire of a major epicardial coronary artery supplying at least 10% to 15% of the LV; (2) CFR≤1.7 by quantitative perfusion imaging; (3) stress flow of ≤0.9 mL/ min per gram; (4) relative stress perfusion defect of ≤0.6 for 15% to 20% of the LV; (5) objective, quantitative diameter stenosis ≥80% by invasive angiography that supplies 15% to 20% of LV; and (6) stenosis of above severities with only mild diffuse CAD with global CFR≥2.0 to minimize risk of diffuse disease contravening any benefit from PCI of focal stenosis.

However, the well-documented limitations of anatomy for predicting physiological severity36,37 and failing to account for diffuse CAD limit the value of anatomic severity and make direct physiological measures of severity the optimal approach. As an additional caveat, determining the low-flow...
ischemic threshold potentially indicating PCI requires a potent vasodilator stress agent, such as dipyridamole or adenosine, that increases coronary flow or myocardial perfusion by 4x baseline in young healthy volunteers. Less potent vasodilators fail to quantify physiological severity adequately for clinical decisions. These trial design concepts apply to any technology validated for accurately quantifying absolute perfusion and CFR, such as PET, MRI, CT, echocardiography, or intravascular technologies. Currently, however, these other technologies do not have an extensive literature supporting this application as PET.

A severity stratified randomized trial as in Figure 7 might show reduced MI and mortality, thereby proving the scientific basis for revascularization and the severity criteria for clinical application outside a trial. Alternatively, revascularization even in severe stable CAD as defined above might not reduce MI or mortality. Either result would have profound clinical importance separately from and in addition to statistical significance for definitively guiding management of stable CAD. The outcome of such a trial would become the basis for objective, evidence-based, review of risks, benefits and potential outcomes with patients when compared with the current commonly invoked but unproven, biased justification for revascularization given as preventing heart attacks and death.

Conclusions
Existing randomized trials of PCI likely failed to reduce death and MI because patient selection did not account for the quantitative physiological severity of both stenosis and diffuse CAD that powerfully alter sample size, event rates, and statistical certainty of group differences in randomized trials. Quantitative physiological severity of not only focal but also diffuse CAD must inform patient selection in future revascularization trials if reduction in MI and mortality is to be a scientific basis for revascularization and evidenced-based, objectively informed patients.

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