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ORIGINAL INVESTIGATIONS

Prognostic Value of Fractional Flow Reserve

Linking Physiologic Severity to Clinical Outcomes

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CME Objective for This Article: After completing this article, the reader should: 1) appreciate the continuous relationship between fractional flow reserve (FFR) and subsequent major adverse clinical events (MACE) in a broad range of clinical scenarios; 2) integrate the degree of FFR abnormality with other clinical data and patient preference to reach a personalized decision regarding coronary revascularization; 3) favor an FFR-assisted strategy to guide revascularization over an anatomy-based strategy given that it lowers MACE while providing superior angina relief; 4) recognize the prognostic value of FFR as an indication of residual diffuse disease when measured immediately following percutaneous coronary intervention (PCI); 5) consider tracking the aggregate FFR distribution in his or her cardiac catheterization laboratory to optimize referral patterns and lesion selection; and 6) enrich future clinical trials of revascularization for preventing hard endpoints of MI and mortality by selecting lesions with lower FFR values.

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All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Prognostic Value of Fractional Flow Reserve

Linking Physiologic Severity to Clinical Outcomes

ABSTRACT

BACKGROUND Fractional flow reserve (FFR) has become an established tool for guiding treatment, but its graded relationship to clinical outcomes as modulated by medical therapy versus revascularization remains unclear.

OBJECTIVES The study hypothesized that FFR displays a continuous relationship between its numeric value and prognosis, such that lower FFR values confer a higher risk and therefore receive larger absolute benefits from revascularization.

METHODS Meta-analysis of study- and patient-level data investigated prognosis after FFR measurement. An interaction term between FFR and revascularization status allowed for an outcomes-based threshold.

RESULTS A total of 9,173 (study-level) and 6,961 (patient-level) lesions were included with a median follow-up of 16 and 14 months, respectively. Clinical events increased as FFR decreased, and revascularization showed larger net benefit for lower baseline FFR values. Outcomes-derived FFR thresholds generally occurred around the range 0.75 to 0.80, although limited due to confounding by indication. FFR measured immediately after stenting also showed an inverse relationship with prognosis (hazard ratio: 0.86, 95% confidence interval: 0.80 to 0.93; $p < 0.001$). An FFR-assisted strategy led to revascularization roughly half as often as an anatomy-based strategy, but with 20% fewer adverse events and 10% better angina relief.

CONCLUSIONS FFR demonstrates a continuous and independent relationship with subsequent outcomes, modulated by medical therapy versus revascularization. Lesions with lower FFR values receive larger absolute benefits from revascularization. Measurement of FFR immediately after stenting also shows an inverse gradient of risk, likely from residual diffuse disease. An FFR-guided revascularization strategy significantly reduces events and increases freedom from angina with fewer procedures than an anatomy-based strategy. (J Am Coll Cardiol 2014;64:1641–54) © 2014 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license.

Most medical conditions form a continuum from nearly normal to extremely pathologic, for example hypertension or hypercholesterolemia. Often treatment of such graded diseases offers only a dichotomous choice, like revascularization in atherosclerotic coronary disease. The spectrum of coronary artery disease (CAD) requires a threshold of severity for making a binary decision for 1 therapy (optimal medical therapy alone) or another (addition of percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]).

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Since its introduction more than 20 years ago (1), fractional flow reserve (FFR) has become an important tool for selecting revascularization or medical treatment alone for a coronary stenosis. On the basis of comparisons to noninvasive stress tests, most lesions display some features of "ischemia" when the FFR falls below 0.75 to 0.80 (2). Consequently, randomized outcomes trials of FFR utilized fixed cutoff values in this range (3–5). However, an independent technique instead uses clinical outcomes to define a threshold. Accordingly, an analysis of prognosis with and without revascularization, along the spectrum of FFR values, offers an appropriate and complementary alternative to the noninvasive tests originally examined at the clinical introduction of FFR.

The **Central Illustration** displays the conceptual hypothesis for the current study. At near normal (high) FFR values, event rates should be lowest and the risk of PCI or CABG offers no or even negative net benefit (3,4). At lower FFR values tracking with reduced flow capacity, event rates should increase, and revascularization provides growing benefit (5). Between the extremes of FFR, the 2 survival curves cross, thereby defining an outcomes-based FFR threshold for treatment decisions without reference to noninvasive tests or other surrogate criteria.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

FFR = fractional flow reserve

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

Using the existing FFR outcomes literature, we sought to answer 3 questions linking physiologic severity to prognosis. First, does FFR provide a continuous and independent marker for clinical outcomes? Second, can FFR risk stratify prognosis for a coronary stenosis as modulated by revascularization? And, third, will the FFR value measured immediately after PCI predict subsequent events?

METHODS

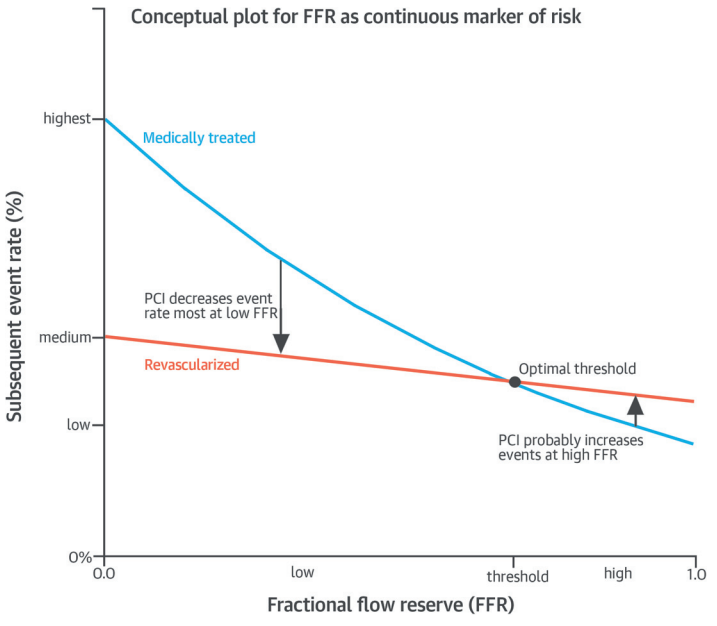
We used 2 parallel and complementary types of analysis. For the study-level meta-regression, each published manuscript provided single data points of summary values for the group mean FFR and subsequent major adverse cardiac event (MACE) rates. For the patient-level meta-analysis on the basis of publications whose authors agreed to participate in this collaborative project, raw data for every patient served as single data points using lesion FFR value(s), clinical characteristics, and subsequent events. Comparing study- and patient-level analyses allows for a more complete sampling of the published data and identification of common results.

PUBLISHED DATA SEARCH AND DATA COLLECTION. The existing FFR literature was searched to identify manuscripts with suitable outcomes data. The first author manually reviewed all PubMed abstracts through February 12, 2014, which contained the terms *fractional flow reserve* or *FFR*, as well as all related manuscripts and citations without abstracts. Any match that studied humans and mentioned clinical outcomes was flagged for detailed review of the whole manuscript. For multiple publications resulting from a common set of patients (e.g., serial follow-up during a randomized trial), the most complete manuscript with the longest length of follow-up was selected.

For the study-level analysis, each manuscript was examined for inclusion on the basis of the following criteria: follow-up duration of at least 180 days to ensure meaningful clinical observation, mean or median FFR value provided for a homogeneous treatment group (initial medical therapy versus revascularization, but not mixed), and exclusion of nonatherosclerotic disease (e.g., transplant vasculopathy or myocardial bridging) or culprit lesions in acute myocardial infarction (MI). Papers that contained 1 or more applicable cohorts (e.g., a study may report a subset treated with medical therapy and another subset treated by PCI) had typical demographics, clinical history, lesion characteristics, treatment modality, and clinical outcomes abstracted for each group from the full manuscript. No ethics board review was sought for the study-level analysis, as it involved only aggregation of previously published data.

For the collaborative patient-level analysis, we attempted to contact the corresponding authors for all FFR outcome manuscripts identified during the literature search. Interested authors supplied deidentified patient-level data in a standardized template as allowed by the variables collected for each study. No further ethics board review was sought for the patient-level analysis because each included study had already obtained it for the primary publication and the provided data contained no confidential identifiers.

Multiple lesions were allowed per patient, but only 1 lesion per major epicardial distribution (left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) plus any graft conduits. Included patients had to meet the following



CENTRAL ILLUSTRATION Conceptual Relationship Between FFR and Outcomes

Similar to many continuous "biomarkers" such as blood pressure and lipids, fractional flow reserve (FFR) potentially relates to subsequent outcomes in a graded fashion. Near normal (high) FFR values indicate a favorable prognosis, where the risk from revascularization procedures equals or even exceeds any potential benefit. Worse (low) FFR values increase the risk of events such that the absolute benefit from percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) accrues in parallel. In between these extremes the curves cross, providing an outcomes-based FFR optimal threshold.

criteria: either a clinical event of known date or a minimum of 180 days of MACE-free follow-up after FFR measurement to ensure meaningful clinical observation; pre-treatment FFR value; recorded treatment decision (medical or revascularization); and exclusion of nonatherosclerotic disease or culprit lesions in acute MI. To explore the prognostic value of post-revascularization FFR measurements, a small, additional group of patients was included that had only post-treatment FFR results. As variably collected by each study, patient demographics, clinical history, lesion characteristics, treatment modality, and clinical outcomes were recorded.

Clinical events of interest to study- and patient-level analyses were death, MI, and target lesion or vessel revascularization. Clearly documented revascularizations in off-target vessels were excluded as being unrelated to the initial lesion studied by FFR. Too few studies and patient-level data specified cardiac versus noncardiac death to enable its separation. Similarly, myocardial infarction was inconsistently noted if due to target vessel or elsewhere and therefore could not be meaningfully distinguished.

Two composite MACE rates were studied: first, the triad of death, MI, and target lesion or vessel revascularization; second, only death and MI. In the patient-level meta-analysis, only the first event was included if several occurred.

GENERAL STATISTICAL METHODS. Statistical analyses were performed in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), using the metafor package (version 1.9-2) for meta-analysis. We used standard summary statistical tests. Quantile-quantile plots identified the following continuous variables as significantly non-normal: FFR, weight, body mass index, minimal lumen diameter, and reference vessel diameter. Applicable tests were 2-tailed, and $p < 0.05$ was considered statistically significant. Further statistical methods can be found in the Online Appendix.

STUDY-LEVEL META-REGRESSION. For the study-level meta-regression, length of follow-up was heterogeneous. To adjust for the differences, 2 methods were compared. The simple method normalized each MACE rate to 12 months. For example, 10 events in 100 subjects over 8 months would yield a normalized MACE rate of $[(10/100)/8]\cdot 12 = 15\%$ at 1 year. The more complex method adjusted the normalized event rates on the basis of a Poisson regression predicting MACE as a continuous function of length of follow-up. Fixed and random (DerSimonian and Laird) effects meta-regressions of the incidence rate included the mean FFR value, revascularization as a binary variable, and an interaction term. The optimal outcomes-based threshold occurred at the intersection of the unrevascularized and revascularized fitted curves. Note that some intersections did not occur within the plausible FFR range from 0 to 1, particularly with small or parallel event rates between treatment groups.

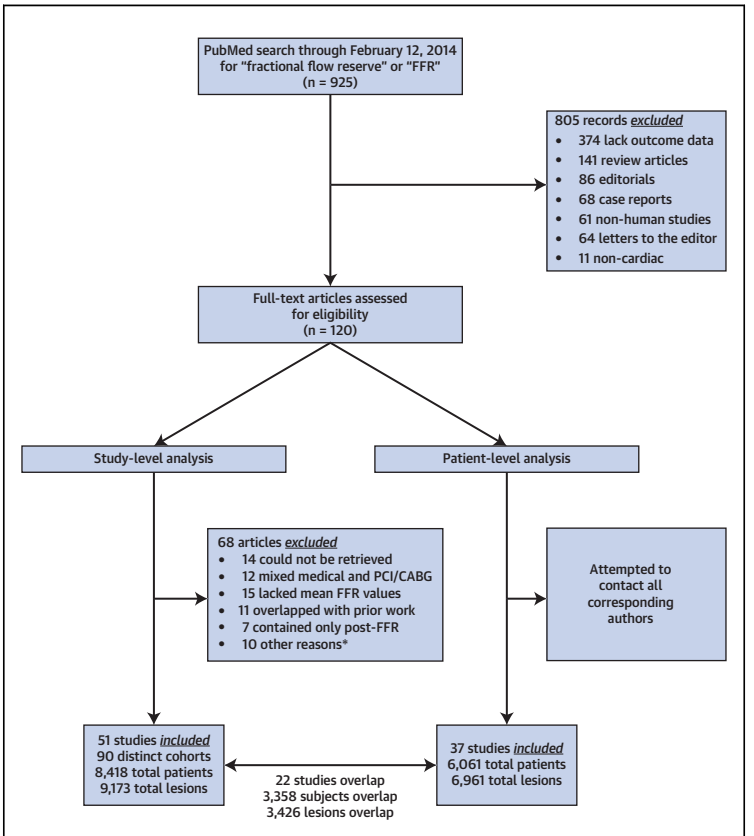


FIGURE 1 Details of PubMed Search

Details of PubMed search that led to study-level and patient-level data. *Other reasons for exclusion were no (2 articles) or too short (1) follow-up, unclear or mixture of treatment methods when describing outcomes (3), myocardial bridging (1), simulation-derived fractional flow reserve (FFR) (1), trial design (1), and meta-analysis (1). CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

PATIENT-LEVEL META-ANALYSIS. To explore the hypothesis that FFR might simply reflect demographic characteristics, classic cardiovascular risk factors, or basic angiographic features, we studied the capability of other variables to predict the measured FFR value in the patient-level data. Each variable was studied in isolation using logistic regression (quasibinomial link function in a generalized linear model). Continuous predictors also were examined using correlation methods, whereas binary predictors summarized by median and interquartile range were compared using the Mann-Whitney *U* test. Because only quantitative percent diameter stenosis showed a

TABLE 1 Baseline Characteristics

	Study-Level Analysis				Patient-Level Analysis			
	All Cohorts	Unrevascularized	Revascularized	p Value	All Patients	Unrevascularized	Revascularized	p Value
n (subjects)	8,418 (100)	5,041 (60)	3,377 (40)	N/A	6,061 (100)	3,102 (51)	2,959 (49)	N/A
n (lesions)	9,173 (100)	5,518 (60)	3,655 (40)	N/A	6,961 (100)	3,729 (54)	3,232 (46)	N/A
Follow-up, months	16 (12–30)	16 (12–30)	17 (10–30)	0.32	14 (12–32)	17 (12–38)	12 (7–27)	<0.001
Demographics (per subject)								
Age, yrs	63 ± 11	63 ± 11	63 ± 10	0.28	64 ± 11	65 ± 11	63 ± 11	<0.001
Male	71	68	75	<0.001	73	70	77	<0.001
Height, cm					169 ± 9	167 ± 10	171 ± 9	<0.001
Weight, kg					77 (67–88)	75 (65–85)	79 (69–90)	<0.001
Body mass index, kg/m^2	28.1 (25.0–31.0)	28.4 (25.1–31.5)	27.8 (24.9–30.5)	0.001	26.4 (24.1–29.4)	26.0 (23.9–29.4)	26.8 (24.3–29.4)	0.012
Country (over 19 total)				<0.001				<0.001
Belgium	10	13	7		23	28	19	
Canada	5	6	3		6	8	4	
China	1	<1	2		1	<1	2	
Denmark					2	<1	5	
France	4	5	4		17	20	15	
Germany	2	2	2		5	2	8	
Greece	1	1	<1		1	1	<1	
Israel	2	2	2					
Italy					2	2	2	
Japan	4	3	4		5	3	8	
Korea	9	11	6		6	6	5	
the Netherlands	2	2	3		11	9	13	
Poland	<1	<1	<1					
Portugal	3	5	<1		<1	<1	<1	
Spain	6	8	2		8	10	5	
Sweden					<1	<1	1	
Turkey	2	4	<1		4	8	1	
United Kingdom	1	<1	2		2	<1	3	
United States	17	18	14		6	3	10	
Multicountry study	31	18	47					
Risk factors								
Diabetes	28	30	26	0.001	26	26	27	0.28
Hypertension	60	59	60	0.62	58	59	56	0.038
Tobacco	34	32	35	0.006	42	43	42	0.57
Dyslipidemia	61	60	64	<0.001	61	60	62	0.15
Family CAD	33	28	38	<0.001	27	23	31	<0.001
History								
Multivessel CAD	38	36	41	0.001	59	51	68	<0.001
Prior MI	27	26	30	0.003	33	30	37	<0.001
Prior PCI	30	30	32	0.24	31	28	35	<0.001
Prior CABG	3	3	4	0.26	5	6	4	0.038
Medications								
Antiplatelet	87	85	89	<0.001	89	89	90	0.38
Beta blocker	65	64	67	0.20	66	64	69	0.005
Calcium blocker	32	33	31	0.64	25	26	24	0.46
Nitrates	51	50	51	0.83	27	25	30	0.014
ACE inhibitor	55	52	59	0.001	54	57	51	0.001
Statin	67	67	67	1.00	72	73	71	0.38

Continued on the next page

clinically relevant association with FFR, the adjusted model added this single variable. Additional adjustment for the type of revascularization (e.g., bare-metal stent, drug-eluting stent, unspecified PCI, or CABG) produced similar FFR thresholds. In the subset with post-PCI measurements, we found no significant interaction between FFR and the revascularization technique. Additional adjustment for the type of revascularization did not significantly alter the prognostic value of FFR in this subset. Multiple

TABLE 1 Continued

	Study-Level Analysis				Patient-Level Analysis			
	All Cohorts	Unrevascularized	Revascularized	p Value	All Patients	Unrevascularized	Revascularized	p Value
Presentation characteristics								
Ejection fraction, %	60 ± 12	60 ± 11	60 ± 13	0.08	61 ± 13	62 ± 13	61 ± 13	0.07
Presentation				<0.001				<0.001
Stable	71	64	89		68	64	74	
Unstable angina	15	18	8		20	23	16	
NSTEMI	13	16	3		9	9	9	
STEMI	1	2	<1		3	4	1	
CCS angina	2.4 ± 1.1	2.1 ± 1.0	2.6 ± 1.1	<0.001				<0.001
No angina					9	18	3	
Class I					16	15	16	
Class II					45	45	45	
Class III					23	16	28	
Class IV					7	5	8	
NYHA heart failure								<0.001
No heart failure					29	30	29	
Functional class I					42	55	29	
Functional class II					23	13	33	
Functional class III					6	2	9	
Functional class IV					<1	<1	<1	
Procedure characteristics (per lesion)								
Vessel				<0.001				<0.001
LMCA	10	10	9		7	8	7	
LAD	57	59	54		57	58	55	
LCx	14	14	15		15	16	15	
RCA	18	16	22		19	17	22	
Graft (IMA, SVG, radial)	<1	<1	<1		1	1	1	
In-stent restenosis	20	22	18	0.17	4	3	5	0.008
%DS by QCA	51 ± 15	46 ± 12	56 ± 16	<0.001	52 ± 18	44 ± 13	63 ± 19	<0.001
MLD, mm	1.44 (1.03–1.91)	1.66 (1.28–2.07)	1.19 (0.85–1.69)	<0.001	1.35 (1.00–1.70)	1.50 (1.26–1.81)	1.06 (0.75–1.44)	<0.001
RVD, mm	3.00 (2.51–3.54)	3.06 (2.55–3.65)	2.94 (2.49–3.42)	<0.001	2.90 (2.49–3.31)	2.85 (2.45–3.30)	2.99 (2.50–3.40)	0.014
Pd, mm Hg	71 ± 17	83 ± 14	63 ± 15	<0.001	77 ± 17	82 ± 16	67 ± 15	<0.001
Pa, mm Hg	94 ± 16	94 ± 15	94 ± 17	0.77	94 ± 17	94 ± 17	93 ± 17	0.28
FFR	0.80 (0.69–0.88)	0.87 (0.82–0.91)	0.69 (0.61–0.77)	<0.001	0.81 (0.71–0.88)	0.87 (0.83–0.92)	0.70 (0.59–0.76)	<0.001
FFR post-PCI			0.92 (0.87–0.96)	N/A			0.92 (0.86–0.96)	N/A
Hyperemia				<0.001				<0.001
IC adenosine	42	51	28		59	71	48	
IV adenosine	14	10	20		38	27	47	
IC or IV adenosine	41	35	49					
ATP or papaverine	4	4	3		3	1	5	
Revascularization method				N/A				N/A
BMS			21				30	
CABG			4				11	
DES			9				27	
PCI			44				30	
CABG or PCI			14					
Other (POBA, DEB)			9				2	

Values are n (%), median (interquartile range), mean ± SD, %.

ACE = angiotensin-converting enzyme; ATP = adenosine triphosphate; BMS = bare-metal stent(s); CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; DEB = drug-eluting balloon; DES = drug-eluting stent(s); %DS = percent diameter stenosis; FFR = fractional flow reserve; IC = intracoronary; IMA = internal mammary artery; IV = intravenous; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; MLD = minimal lumen diameter; N/A = not applicable; NSTEMI = non-ST-segment elevation myocardial infarction; NYHA = New York Heart Association; Pa = aortic pressure; Pd = distal coronary pressure; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.

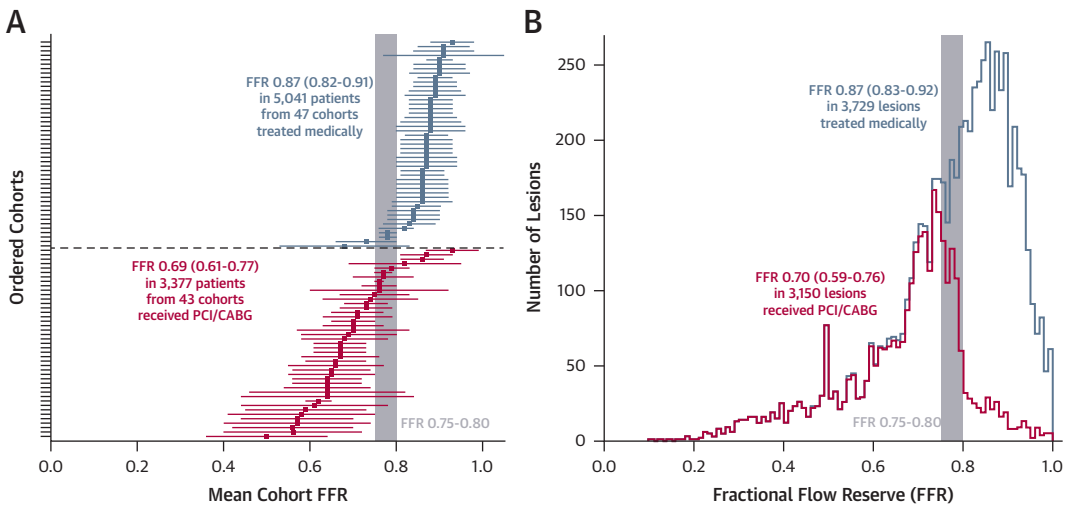


FIGURE 2 FFR Distributions

(A) Study-level analysis. Each point details the mean **(squares)** and SD **(horizontal lines)** for fractional flow reserve (FFR) in a published cohort treated with either revascularization **(red)** or medical therapy **(slate)**. Note that sample sizes varied markedly among cohorts (over 100-fold), and Online Table 1 provides further details. The **shaded region** denotes FFR 0.75 to 0.80. **(B)** Patient-level analysis. Lesion-level histogram of FFR values from the patient-level analysis treated with either revascularization **(red)** or medical therapy **(slate)**. Note that some patients contributed more than 1 lesion and some total occlusions were assigned a value of 0.50. The shaded region denotes FFR of 0.75 to 0.80. Abbreviations as in Figure 1.

imputation was not used due to the sizable number of missing fields for covariates with a statistically or clinically insignificant association with FFR.

For the patient-level meta-analysis, length of follow-up was also heterogeneous. Therefore, we primarily performed a time-to-event analysis using a Cox proportional hazards model. However, to examine the dependence of our findings on the specific model, we also entered binary events within 12 months into a logistic regression model. For both Cox and logistic models, the optimal outcomes-based threshold was determined from the coefficients as the intersection of the unrevascularized and revascularized fitted curves. Initially, the model only included the lesion-specific FFR value, revascularization as a binary variable, and an interaction term. Next, the model was expanded to adjust for percent diameter stenosis in the subset of lesions with that information.

The size of the patient-level data allowed for exploration of several important subsets. We repeated the previous analysis for the following subgroups: left main lesions, acute coronary syndromes (unstable angina and acute MI), known diabetes mellitus, graft conduits (internal mammary arteries, free radial vessels, and saphenous veins), and in-stent restenosis.

PROGNOSTIC VALUE OF FFR MEASURED IMMEDIATELY AFTER PCI. A subset of patient-level data provided immediate post-PCI measurements of FFR, either in conjunction with pre-PCI measurements (the vast majority) or by themselves (a small minority). Due to variable length of follow-up, we primarily performed a time-to-event analysis using a Cox proportional hazards model. Hazard ratios are expressed per 0.05 change of FFR, which equals half the interquartile range. The basic model included only the post-PCI measurement of FFR, whereas the adjusted model added the pre-PCI measurement of FFR. For visual presentation, we additionally divided the subset into tertiles and compared Kaplan-Meier survival curves using the log-rank test.

META-ANALYSIS OF STRATEGY-BASED STUDIES. During the comprehensive literature review, manuscripts were identified that compared clinical outcomes after a strategy-based approach between FFR-assisted and anatomy-guided revascularization. Event counts and angina status for each strategy were extracted from the manuscript and used to summarize the relative risk using fixed and random effects meta-analysis. The proportion of lesions treated with revascularization was summarized for each strategy.

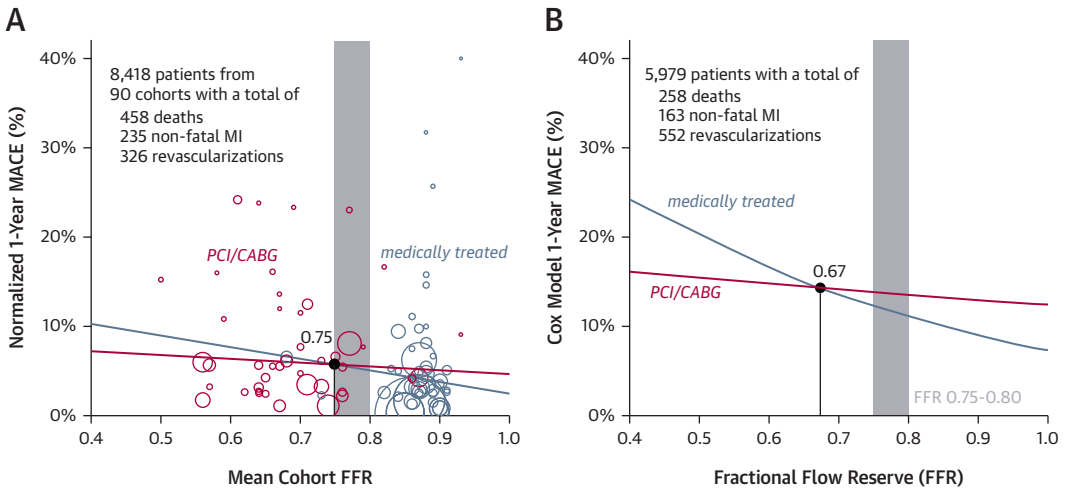


FIGURE 3 Outcomes as a Function of FFR Value

(A) Normalized 1-year major adverse cardiac event (MACE) rate for study-level analysis. Meta-regression for the study-level data fits the normalized 1-year MACE rate (**circles** whose size reflects the number of patients) for cohorts treated with either revascularization **(red)** or medical therapy **(slate)** as a function of mean lesion FFR. **Colored lines** depict the meta-regression fit. These curves cross at the optimal FFR threshold, shown here for a univariate model with random effects. See Table 2 for results from other models. **(B)** Cox model 1-year MACE rate for patient-level analysis. Patient-level analysis fits the outcomes data to a Cox proportional hazards model of survival, shown here with the best-fit 1-year MACE rate as a function of individual lesion FFR. **Colored lines** depict the model fit for revascularization **(red)** or medical therapy **(slate)** treatment. These curves cross at the optimal FFR threshold, here shown for the unadjusted model. See Table 2 for results from other models. FFR = fractional flow reserve; MI = myocardial infarction.

RESULTS

PUBLISHED DATA SEARCH AND BASELINE CHARACTERISTICS. Figure 1 summarizes the published data search and study inclusion leading to a total of 9,173 (study-level) and 6,961 (patient-level) lesions. Table 1 summarizes demographics, clinical details, lesion characteristics, and treatment methods for study- and patient-level data. Online Table 1 details which manuscripts were included for the study-level analysis, and Online Table 2 details those papers for which patient-level data were provided as part of the collaborative analysis. Not all studies collected or provided information for every parameter. Although the vast majority of 6,061 subjects only had a single lesion examined by FFR, in 589 subjects (10%), 2 lesions underwent FFR, and in 151 subjects (2%), 3 or more lesions underwent FFR.

FFR DISTRIBUTION. Figure 2A depicts the mean and spread of FFR values for each cohort in the study-level meta-regression, ordered first by received treatment (medical versus revascularization) and second by mean lesion severity. Figure 2B shows the lesion-level histogram from the patient-level data. Very few lesions with FFR <0.75 received medical treatment, comprising only 67 of the 3,729 patient-level lesions (2%). Conversely, a small minority of lesions with FFR >0.80 were treated with revascularization, making up 309 of the 3,150 lesions (10%). A transition in treatment patterns occurred in the FFR 0.75 to 0.80 range, containing 1,062 of the 6,879 lesions (15%).

PREDICTION OF FFR. As detailed in Online Table 3, several variables were associated with FFR values in the patient-level data. However, most of the statistically significant associations were either negligible, with correlation coefficients of ≤0.10 (implying that the parameter explains at most 0.1^2 or 1% of the group variation in FFR), or clinically insignificant, with FFR differences ≤0.04 between groups (equal to the 95% limits of agreement for repeated FFR measurements of the same lesion made minutes apart) (6). Only 2 variables showed both statistically and clinically significant associations with FFR: quantitative percent diameter stenosis (Pearson correlation coefficient -0.56; $p < 0.001$) and minimal lumen diameter (Pearson correlation coefficient 0.49; $p < 0.001$). Given the highly collinear nature of these 2 variables, only the stronger percent diameter stenosis was used for an adjusted model. Its coefficient of determination equals 0.56^2 or 31%, implying that less than one-third of the population variation

TABLE 2 FFR Thresholds on The Basis of Outcomes Using Various Models

Model	FFR Threshold (Composite MACE)	FFR Threshold (Death, MI Only)
Study Level Meta-Regression		
Fixed effects (n = 8,418 patients), unadjusted	N/A*	N/A
Adjusted	0.90	0.90
Random effects, unadjusted	0.75†	0.75
Adjusted	0.90	0.90
Patient Level Meta-Analysis		
Cox model (n = 5,979 total patients), unadjusted	0.67‡	N/A
Adjusted	0.76	0.49
Logistic model, unadjusted	0.62	N/A
Adjusted	0.75	N/A
Logistic model with random effects, unadjusted	0.69	N/A
Adjusted	0.72	N/A
Important Subgroups of Patient-Level Meta-Analysis (Cox Model)		
Left main s2tenosis (n = 511 patients), unadjusted	0.86	0.83
Adjusted	0.84	0.82
Acute coronary syndrome (n = 1,196 patients), unadjusted	0.81	N/A
Adjusted	0.83	0.75
Diabetes mellitus (n = 1,511 patients), unadjusted	0.79	N/A
Adjusted	0.77	0.50
Graft conduits (n = 92 patients), unadjusted	0.87	0.94
Adjusted	N/A	N/A
In-stent restenosis (n = 120 patients), unadjusted	0.88	0.48
Adjusted	0.77	0.63

*N/A indicates that model did not converge to a threshold value within the fractional flow reserve (FFR) range from 0 to 1. †Figure 3A depicts raw data and fit leading to this threshold. ‡Figure 3B depicts best fit leading to this threshold.

MACE = major adverse cardiac event(s); MI = myocardial infarction.

in FFR can be explained by focal angiographic severity.

CLINICAL OUTCOMES. Figure 3A shows the normalized 1-year MACE rate from the study-level meta-regression. The optimal FFR threshold for a composite of death, MI, and revascularization occurred at 0.75, rising to 0.90 after Poisson adjustment for variable length of follow-up, suggesting a sensitivity to how events are temporally distributed after the procedure. Figure 3B depicts the 1-year MACE rate on the basis of the unadjusted Cox regression from the patient-level meta-analysis. The optimal FFR threshold for a composite of death, MI, and revascularization occurred at 0.67, rising to 0.76 after adjustment for percent diameter stenosis, likely due to its significant correlation with FFR as detailed previously.

Table 2 summarizes the results from study- and patient-level analyses focusing on different endpoints (composite MACE versus only death and MI alone), specific subgroups (e.g., left main or acute coronary syndrome), covariate adjustment (unadjusted vs. adjusted for percent diameter stenosis), and statistical model (Cox proportional hazards vs. logistic regression). Further results can be found in the Online Appendix for more complex approaches such as constrained regression and random effects within subjects (to account for multiple coronary lesions belonging to the same patient).

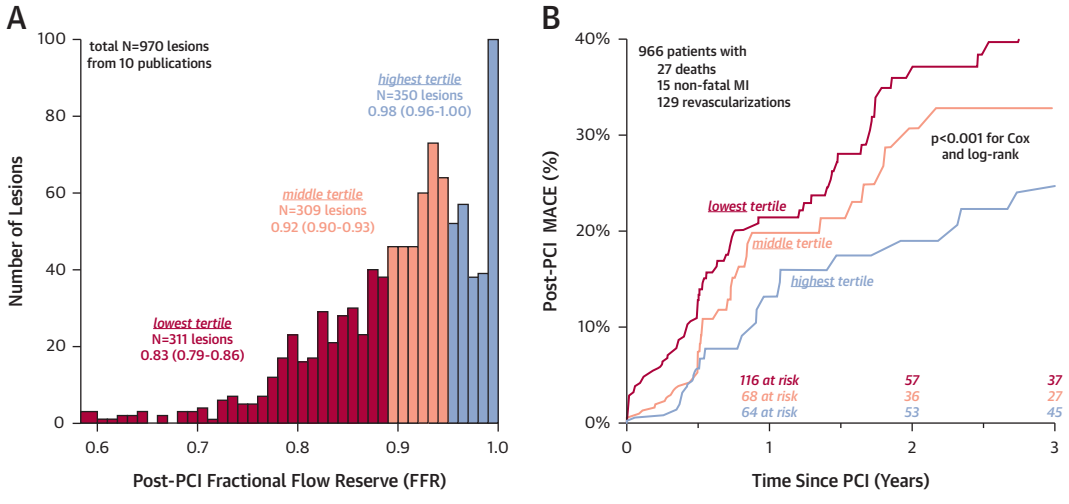


FIGURE 4 FFR Measurements Made Immediately After PCI

(A) Histogram. Lesion-level histogram of post-PCI FFR values from the patient-level analysis colored by tertiles **(red, salmon, periwinkle)**. **(B)** Survival curves. Kaplan-Meier event curves for tertiles of post-PCI FFR values (colors match histogram). Both continuous Cox regression and tertile-based log-rank tests demonstrated a significant ($p < 0.001$), inverse relationship between post-PCI FFR and subsequent clinical events. Abbreviations as in Figures 1 and 2.

TABLE 3 Summary of Published Data Comparing FFR-Guided or FFR-Assisted Strategy to an Anatomy-Based Strategy

First Author (Study) (Ref. #)	Number of Patients		Relative Outcome*		Frequency of PCI or CABG	
	FFR	Anatomy	Composite MACE†	Freedom From Angina‡	FFR	Anatomy
Randomized Trials Comparing FFR to Angiography						
Pijls (DEFER) (3)	91	90	0.69 (95% CI: 0.43–1.11)	1.15 (95% CI: 0.91–1.46)	0%	100%
Pijls (FAME) (14)	509	496	0.80 (95% CI: 0.62–1.02)	1.05 (95% CI: 0.98–1.13)	58%	92%
Observational Studies Comparing FFR to Angiography						
Wongpraparut et al. (15)	57	80	0.37 (95% CI: 0.15–0.93)	NR	41%	100%
Puymirat et al. (16)	222	495	0.46 (95% CI: 0.31–0.68)	NR	35%	100%
Li et al. (17)	1,090	6,268	0.85 (95% CI: 0.71–1.01)§	NR	34%	100%
Di Serafino et al. (18)	65	158	0.47 (95% CI: 0.30–0.75)	1.31 (95% CI: 1.01–1.71)	35%	57%
Toth et al. (19)	198	429	0.97 (95% CI: 0.59–1.59)	1.95 (95% CI: 1.36–2.79)	518 vs. 1373 graft conduits	
Park et al. (20)	2,178	2,178	0.55 (95% CI: 0.43–0.70)	NR	30 vs. 46 mm total stent length	
Observational Studies Comparing FFR to IVUS						
Nam et al. (21)	83	94	1.13 (95% CI: 0.23–5.46)	NR	34%	91%
de la Torre Hernandez et al. (22)	400	400	1.06 (95% CI: 0.56–1.98)	NR	28%	49%
Meta-Analysis of Studies in this Table Comparing FFR to Anatomy						
All 10 studies listed (fixed effects)	4,893	10,688	0.83 (95% CI: 0.78–0.87)	1.10 (95% CI: 1.03–1.17)	42%	95%
(Random effects)			0.71 (95% CI: 0.59–0.86)	1.22 (95% CI: 1.02–1.45)		

*Risk, hazard, or odds ratio depending on publication; however, meta-analysis used published data to compute and summarize relative risk for all studies (see statistical methods section for details). †All rows represent composite major adverse cardiac events (MACE) (death, myocardial infarction [MI], revascularization) except where noted; values <1 favor fractional flow reserve (FFR) (lower rate of MACE), while values >1 favor anatomy. ‡Values >1 favor FFR (superior freedom from angina), while values <1 favor anatomy. §Endpoint of death plus MI only (no revascularization).

CI = confidence interval; IVUS = intravascular ultrasound; NR = not reported; other abbreviations as in Table 1.

PROGNOSIS ON THE BASIS OF FFR MEASURED IMMEDIATELY AFTER PCI. Figure 4A displays the histogram of immediate post-PCI measurements of FFR, whereas Figure 4B depicts the corresponding Kaplan-Meier survival curves by tertiles. FFR measured after PCI showed an inverse relationship with subsequent events in both continuous (Cox hazard ratio: 0.86, 95% confidence interval [CI]: 0.80 to 0.93; $p < 0.001$) and tertile (log-rank $p < 0.001$) analyses. Adjusting for both pre- and post-PCI measurements demonstrated that the final FFR value retained prognostic value (adjusted Cox hazard ratio: 0.90, 95% CI: 0.82 to 0.99; $p = 0.032$) unlike baseline FFR (adjusted Cox hazard ratio: 0.97, 95% CI: 0.92 to 1.02; $p = 0.28$).

META-ANALYSIS OF STRATEGY-BASED STUDIES. Table 3 summarizes the 10 studies totaling more than 15,000 patients that compared an FFR-assisted revascularization strategy to one that only used anatomy. Whereas an FFR-assisted strategy led to treatment roughly half as often as an anatomy-based strategy, it not only lowered MACE by at least 20% but also provided superior angina relief of at least 10%.

DISCUSSION

We demonstrated that FFR provides a continuous and independent marker of subsequent MACE as modulated by treatment (medical therapy vs. revascularization) in a broad range of clinical scenarios comprising thousands of patients from more than 12 countries and spanning more than 15 years of publications. Both the study-level analysis in Figure 3A and patient-level analysis in Figure 3B support the conceptual hypothesis proposed in the Central Illustration. Therefore, FFR can be seen not only as a physiologic "biomarker," because of its continuous and independent relationship to outcomes, but also as a target for treatment because revascularization alters the outcome curve.

As a clear corollary from the conceptual curve in the Central Illustration, revascularization offers a greater absolute benefit for more severe FFR values. Close to either side of the FFR threshold, the net benefit or risk from PCI or CABG therapy remains small. By analogy to the idea of "tailored treatment" for disease spectrums such as hypercholesterolemia (7), FFR provides the clinician with an objective tool to personalize risk/benefit tradeoffs continuously

instead of in binary fashion. Our data support the concept that ischemia exists not as a dichotomous state, but rather as a graded continuum.

The FFR distributions in **Figure 2** highlight the major limitation of our analysis, namely that the FFR value strongly influenced the treatment decision—what has been termed "confounding by indication" in the epidemiology literature. As a result, we possess a limited understanding of the natural history of low FFR lesions. For example, unrevascularized lesions with an FFR <0.75 made up less than 2% of all medically treated lesions in **Figure 2B**. Although we used various statistical techniques to compensate, all FFR threshold values in **Table 2** should be considered only as hypothesis generating. The ongoing FAME-2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2) trial (5) randomized 441 patients to initial medical therapy with 625 lesions having FFR ≤0.80 (mean FFR 0.68 ± 0.15). Compared to the 443 medically treated lesions with FFR ≤0.80 in our meta-analysis (mean FFR 0.77), the 2-year primary endpoint results from the FAME-2 trial will provide a larger, more severe, and randomized exploration of outcomes for medically treated lesions with low FFR.

Rather than changing the FFR thresholds of 0.75 or 0.80 validated in randomized outcomes trials (3–5), our analysis should be interpreted generally as supporting a larger treatment benefit from revascularization at lower FFR values. As made explicit by **Figure 3** and **Table 2**, a range of plausible FFR thresholds exists in our data depending on the clinical endpoint, statistical model, patient versus population analysis, and subgroup. However, our results can be used to enrich revascularization benefit when using FFR either for clinical care or in future research trials.

In the lesion-level FFR histogram in **Figure 2B**, a majority of FFR measurements (3,595 of 6,879; 52%) exceeded 0.80. This prevalence of high FFR reflects a combination of the patient population referred for invasive angiography and also lesion selection by operators for FFR measurement. As with other "normal rates" for medical tests or surgical procedures (e.g., myocardial perfusion imaging, invasive angiography, or appendectomy), no specific limits can or should be imposed. In any particular case, clinical judgment and integration of all available data must guide patient care. Rather, **Figure 2B** suggests that prevalence of high FFR could provide a system-level metric when studying patterns of CAD care, independent of classic angiographic metrics that correlate poorly with physiology.

Immediate post-PCI measurements of FFR carry prognostic value with an inverse relationship to subsequent clinical events. Indeed, pre-PCI FFR values no longer showed a statistically significant association with events after accounting for post-PCI FFR measurements in that subgroup. Although revascularization can "reset" the numerical FFR value, clearly the event rates in **Figure 4** after PCI remain higher than matched, unrevascularized levels in **Figure 3**. Therefore, the prognostic value of the same FFR number differs between no-PCI and immediate post-PCI scenarios. Additionally, these results suggest a mechanism for the inverse prognostic gradient for post-PCI FFR, namely residual diffuse disease (assuming optimal stent implantation). Other potential mechanisms appear unlikely, as PCI largely removed focal disease. Microvascular dysfunction, which carries an adverse prognosis (8), would lower hyperemic flow levels and therefore raise the FFR value, creating a direct relationship between post-PCI FFR and outcomes, opposite to the observed pattern.

The technique of meta-analysis historically developed to summarize treatment effects. By contrast, FFR provides a diagnostic test. Although meta-analyses have been extended to diagnostic procedures, they require a reference metric to judge performance. Our technique used outcomes as the patient-relevant gold standard to link the diagnostic test of FFR to treatment choices of medical therapy or revascularization for CAD. Alternatively, several prior studies compared an FFR-assisted to an anatomy-based decision strategy that, however, does not directly address the "threshold continuum" of our analysis. As summarized in **Table 3**, their results indicate superior clinical outcomes and freedom from angina with an FFR-guided strategy while reducing the need for PCI or CABG. Together, these results provide different yet additive clinical insights linking FFR-based physiology to outcomes.

COMPARISON TO EXISTING PUBLISHED DATA. Because our analysis draws from the existing FFR literature, its findings parallel but extend and integrate prior publications with new insights on the continuous spectrum of FFR and its outcomes. The conceptual curve in the **Central Illustration** for FFR appears similar to work using nuclear perfusion imaging (9) in that "ischemia" by either technique relates continuously to outcomes as modulated by treatment (medical therapy vs. revascularization).

Preliminary results from the FAME-2 study (10) mirror the continuous relationship between FFR for untreated lesions and subsequent outcomes as seen in our **Figure 3**. Additionally, the significant treatment interaction reported in the FAME-2 trial, showing larger benefit for PCI when FFR <0.65 and smaller benefit when FFR ≥0.65 (5), supports the similar threshold values found in our **Table 2**. Both of these

early findings from the FAME-2 trial will be clarified at completion of its primary 2-year endpoint analysis. Therefore, patient-level FAME-2 trial data was excluded from this analysis (5).

STUDY LIMITATIONS. Similar to any meta-analysis, our study shares the limitations of its primary sources. Almost all of the study- and patient-level data comes from nonrandomized, observational designs. Baseline characteristics reported in **Table 1** were neither standardized nor collected uniformly among publications. Clinical endpoints (death, MI, and revascularization) largely did not undergo blinded adjudication or have common definitions. PCI techniques spanned the entire spectrum from balloon-only angioplasty to the latest drug-eluting stents. Administered treatment closely followed the FFR value and was rarely randomized ("confounding by indication").

As demonstrated by intravascular ultrasound, a significant number of subsequent events do not arise from the stenosis of interest. Roughly half of all events in a prospective study following a baseline acute coronary syndrome arose from nonculprit sites (11.6% from nonculprits alone compared to 20.4% cumulative event rate) after a median of 3.4 years (11). Therefore, an important number of events in our meta-analysis may be unrelated to the lesion interrogated with FFR. Performance or deferral of focal revascularization on the lesion examined using FFR would not be expected to alter the natural history of these remote plaques. Similarly, noncardiac deaths and some cardiac deaths may not be caused by the lesion measured with FFR. Such nuanced classification of subsequent clinical events as related or unrelated to the FFR lesion was largely absent from the primary studies.

Our analysis did not address in detail the amount of myocardium at risk distal to a lesion undergoing FFR measurement. We hypothesize that the same numeric FFR value has greater prognostic importance when the distal mass is large. Therefore, although the higher FFR threshold seen for left main stenosis in **Table 2** makes intuitive sense, we could not explore the issue further due to lack of an angiographic risk score.

Finally, the conceptual curve in the **Central Illustration** might be too simplistic. At low FFR values, a larger proportion of net myocardial flow often comes from the collateral circulation (12). A broad literature assessment has demonstrated a better prognosis in patients with more mature collaterals (13). Therefore, it may be possible that a low FFR inflection point exists in the **Central Illustration** for untreated lesions, below which event rates flatten or even decrease. The natural history of medically treated lesions with very low FFR values will become available from the FAME-2 trial.

CONCLUSIONS

FFR demonstrates a continuous and independent relationship between its numeric value and subsequent outcomes, modulated by medical therapy versus revascularization. Lesions with lower FFR values receive larger absolute benefits from PCI or CABG. Outcome-derived FFR thresholds on the basis of a composite MACE of death, MI, and revascularization generally fall around the range of 0.75 to 0.80, although limited due to confounding by indication. Measurement of FFR immediately after PCI also shows an inverse gradient of risk, likely from residual diffuse disease. An FFR-guided revascularization strategy significantly reduces MACE and increases freedom from angina with less PCI or CABG than an anatomy-based strategy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: A strategy based on FFR leads to revascularization roughly half as often as one based only on coronary anatomy and lowers major adverse cardiac events by at least 20% while providing superior angina relief.

COMPETENCY IN INTERPERSONAL & COMMUNICATION SKILLS: In discussions with patients about the balance between risk and benefit from coronary revascularization, physicians can explain FFR as an objective, continuous variable that informs personalized treatment decisions.

TRANSLATIONAL OUTLOOK: The results of future clinical trials will help refine the role of FFR to guide revascularization decisions in various patient populations, including measurements made immediately after PCI.

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KEY WORDS fractional flow reserve, meta-analysis, prognosis, threshold

APPENDIX For expanded Methods and Results sections as well as supplemental tables, please see the online version of this article.

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