Global Coronary Flow Reserve Is Associated With Adverse Cardiovascular Events Independently of Luminal Angiographic Severity and Modifies the Effect of Early Revascularization

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Background—Coronary flow reserve (CFR), an integrated measure of focal, diffuse, and small-vessel coronary artery disease (CAD), identifies patients at risk for cardiac death. We sought to determine the association between CFR, angiographic CAD, and cardiovascular outcomes.

Methods and Results—Consecutive patients (n=329) referred for invasive coronary angiography after stress testing with myocardial perfusion positron emission tomography were followed (median 3.1 years) for cardiovascular death and heart failure admission. The extent and severity of angiographic disease were estimated with the use of the CAD prognostic index, and CFR was measured noninvasively by positron emission tomography. A modest inverse correlation was seen between CFR and CAD prognostic index (r=−0.26; P<0.0001). After adjustment for clinical risk score, ejection fraction, global ischemia, and early revascularization, CFR and CAD prognostic index were independently associated with events (hazard ratio for unit decrease in CFR, 2.02; 95% confidence interval, 1.20–3.40; P=0.008; hazard ratio for 10-U increase in CAD prognostic index, 1.17; 95% confidence interval, 1.01–1.34; P=0.032). Subjects with low CFR experienced rates of events similar to those of subjects with high angiographic scores, and those with low CFR or high CAD prognostic index showed the highest risk of events (P=0.001). There was a significant interaction (P=0.039) between CFR and early revascularization by coronary artery bypass grafting, such that patients with low CFR who underwent coronary artery bypass grafting, but not percutaneous coronary intervention, experienced event rates comparable to those with preserved CFR, independently of revascularization.

Conclusions—CFR was associated with outcomes independently of angiographic CAD and modified the effect of early revascularization. Diffuse atherosclerosis and associated microvascular dysfunction may contribute to the pathophysiology of cardiovascular death and heart failure, and impact the outcomes of revascularization. **(*Circulation*. 2015;131:00-00.)**

Key Words: angiography ■ coronary artery disease ■ ischemia ■ positron emission tomography ■ revascularization

Diffuse coronary atherosclerosis is highly prevalent among patients with known or suspected coronary artery disease (CAD),[1] increases the severity of inducible myocardial ischemia (beyond the effects of epicardial coronary obstruction),[2] and identifies patients at high risk for serious adverse events, including cardiac death.[1,3–5] These associations are evident across heterogeneous-risk cohorts, including patients with diabetes mellitus.[6]

Coronary flow reserve (CFR; calculated as the ratio of hyperemic to rest absolute myocardial blood flow [MBF]) is a measure of coronary vasomotor dysfunction that integrates the hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis, and microvascular dysfunction on myocardial tissue perfusion.[2]

Clinical Perspective on p XXX

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Coronary angiography is a cornerstone of modern cardiovascular care, but its ability to identify physiologically and prognostically important coronary stenoses in stable ischemic heart disease remains controversial.[2,7] Recent randomized trials[8,9] did not show an event-free survival benefit for the addition of coronary revascularization to guideline-directed medical therapy, whereas an approach in which fractional flow reserve–guided revascularization[10] was used to identify lesion-specific ischemia was beneficial. To date, no studies have investigated the relative contributions of noninvasive measures of CFR and luminal angiographic CAD on cardiovascular outcomes, particularly as related to revascularization. We utilized the validated CAD prognostic index (CADPI)[11] to quantify the extent and severity of epicardial CAD. We hypothesized that global CFR, as quantified by noninvasive positron emission tomography (PET), and overall luminal angiographic disease, as estimated by CADPI, would show limited correlation and that CFR would be associated with the risk of future cardiovascular events independently of anatomic score and revascularization.

Methods

Study Population

Study participants were consecutive patients clinically referred for invasive coronary angiography within 90 days after stress myocardial perfusion PET at Brigham and Women's Hospital between 2006 and 2012. Indications for testing most commonly included evaluation for chest pain, dyspnea, or their combination. Patient history and medication use were ascertained at time of PET imaging. From a cohort of 841 patients, those with prior coronary artery bypass grafting (CABG), left ventricular ejection fraction (LVEF) <40%, or clinical diagnosis of heart failure were excluded, leaving a final cohort of 329 individuals. The median time from PET to invasive angiography was 2.6 (interquartile range, 0.3–13.5) days, reflecting that both diagnostic evaluations occurred in the same tertiary care center and were coordinated, when possible, for optimal care delivery. Any patients with an intervening cardiovascular event or revascularization between PET and angiography were excluded. A pretest clinical score integrating age, sex, type of chest pain, prior history of myocardial infarction, presence of diabetes mellitus, hyperlipidemia, current smoking, and ECG abnormalities into a pretest probability of obstructive angiographic CAD was calculated as described previously.[12] Early revascularization with CABG or percutaneous coronary intervention (PCI), considered to be triggered by imaging results, was defined as occurring within 90 days of PET.[5] The study was approved by the Partners Healthcare institutional review board and was conducted in accordance with institutional guidelines.

PET Imaging

Patients were imaged with a whole-body PET–computed tomography scanner (Discovery RX or STE LightSpeed 64, GE Healthcare, Milwaukee, WI) with the use of ^{82}rubidium (1480–2200 MBq) or ^{13}N-ammonia (700–900 MBq) as a flow tracer at rest and pharmacological stress, as described previously.[13] Computed tomography was used for attenuation correction only. For semiquantitative assessment of myocardial scarring and ischemia, 17-segment visual interpretation of gated myocardial perfusion images was performed by experienced operators using a standard 5-point scoring system.[14] Summed rest and difference (stress–rest) scores were converted to percent myocardium by dividing by the maximum score of 68.[15] For each of these variables, higher scores reflect larger areas of myocardial scar or ischemia, respectively. Rest LVEFs were calculated from gated myocardial perfusion images with commercially available software (Corridor4DM, Ann Arbor, MI).

Absolute global MBF (in milliliters per minute per gram) was quantified at rest and at peak hyperemia with the use of automated factor analysis and a validated 2-compartment kinetic model, as described previously.[13] Per-patient global CFR was calculated as the ratio of stress to rest absolute MBF for the whole left ventricle (LV). MBF and CFR values were not clinically available to referring physicians. Radiation exposure per study was ≤4.6 mSV. Quantitative measures of CFR were obtained in patients undergoing PET myocardial perfusion at no additional clinical cost, imaging time, or radiation exposure.

Coronary Angiography

All patients underwent selective coronary angiography with the use of standard clinical techniques, with ≥2 projections obtained per vessel distribution and angles of projection optimized for cardiac position. In each patient, the CADPI was adapted and quantified as described previously.[11] Luminal diameter stenoses of the major epicardial coronary arteries were clinically graded by subjective visual consensus of experienced operators on an ordinal scale and applied to the CADPI classification in blinded fashion. The CADPI classification is a hierarchical index (0–100) that assigns overall prognostic weights to increasing percent stenoses (50–100%) in 1-, 2-, or 3-vessel classification, with higher weights for proximal left anterior descending or left main artery involvement (Table I in the online-only Data Supplement).

Outcomes

Patients were followed for a median of 3.1 years (interquartile range, 1.7–4.3) for the occurrence of major adverse cardiovascular events (MACE), including death, cardiovascular death, and hospitalization for heart failure or myocardial infarction. The prespecified primary end point was a composite of cardiovascular death and heart failure hospitalization. Selection of the primary end point was informed by emerging data suggesting a role for subtle cardiac structural abnormalities in predicting cardiovascular death and especially incident heart failure,[16–18] whereas obstructive CAD classically is associated with myocardial infarction and revascularization. Prespecified secondary analyses were performed for a composite end point of all-cause death and heart failure hospitalization and also for cardiovascular death and hospitalization for heart failure or myocardial infarction. Ascertainment of clinical end points was determined by blinded adjudication of the longitudinal medical record, the Partners Healthcare Research Patient Data Registry, the Social Security Death Index, and the National Death Index by 2 independent cardiologist members of the Clinical End Points Committee. For an event to be classified as nonfatal admission for heart failure or myocardial infarction, discharge with a primary hospitalization cause of heart failure or myocardial infarction, respectively, was required. The date of the last consultation was used to determine follow-up. All patients not meeting a clinical end point had >30 days of follow-up.

Statistical Analysis

Baseline characteristics are reported as rates with percentages for categorical variables and medians with interquartile ranges for continuous variables. We used the Fisher exact test and the Wilcoxon rank sum test to assess differences in dichotomous and continuous baseline characteristics. CFR, rather than MBF, was defined as the primary variable of interest because of the clinical convenience of a ratio, as well as the known association between CFR and outcomes.[1,3–5] For simplicity in the descriptive display, we selected the median CFR of 1.6 as a cut point. This value, lower than the all-comer cut point of 2,[2] is consistent with the more comorbid population referred for coronary angiography. Where indicated (and for modeling), we report values of CFR as a continuous variable. The Spearman correlation was used to describe the association between CFR and CADPI. Similar results were obtained after logarithmic transformation, and results are presented untransformed for ready clinical applicability.

Cumulative event-free survival curves for the primary end point were compared across dichotomous categories of CFR median (<1.6 versus ≥1.6) and CADPI clinical cut point of ≥37 versus <37 with the use of the log-rank test. The CADPI cut point was selected to reflect a >70% stenosis in >1 major epicardial coronary artery, a clinically actionable threshold for revascularization; this is also the cut point at which a survival benefit has been demonstrated previously for

revascularization.[11] Where indicated (and for modeling), we report values of CADPI as a continuous variable.

Cox proportional hazards models were used to examine the association between CFR, CADPI, and outcome events after controlling for effects of clinically important covariates. Data were censored at the time of the last visit. Model development was tested on the primary end point, and the final model was applied to the secondary end points already described. Univariate associations were tested, and Cox models sequentially added age, sex, medical history, medications, pretest clinical score, imaging, and angiography variables, with the collinearity index used to check for linear combinations among covariates and the Akaike information criterion assessed to avoid overfitting, with final covariates chosen on the basis of clinical knowledge. The proportional hazards assumption was evaluated with the use of martingale residuals. The final model with CFR and CADPI was adjusted for pretest clinical score, global LV ischemia (summed difference score), and time-dependent variables of early revascularization and was stratified by binary category of LVEF (<50% versus ≥50%) because LVEF showed mild departure from proportionality. Adjusted event-free survival was plotted with the use of survival probabilities from the Cox model and stratified by categories of impaired CFR and elevated CADPI. Interaction terms for CFR and CADPI, as well as CFR and revascularization strategy, were tested for significance in the adjusted model.

In an exploratory analysis, we stratified patients by revascularization across medians of CFR to better visualize differences in outcomes across categories of no revascularization and revascularization with PCI or CABG. Poisson regression was performed to compute annualized event rates of the primary end point, after adjustment for pretest clinical score, LVEF, global LV ischemia, and CADPI, to evaluate the effect of baseline CFR on revascularization benefit. Model fit was assessed with the goodness-of-fit χ^2 test, with a nonsignificant result indicating adequate fit. Event-free survival curves for the primary end point of cardiac death and heart failure admission were compared across dichotomous categories of CFR median and revascularization with the log-rank test and were also plotted after adjustment for pretest clinical score, LVEF, global LV ischemia, and CADPI. To increase power for display of revascularization subgroups, curves for revascularized patients were then plotted for all-cause death and heart failure admission. A P value of <0.05 was considered to indicate statistical significance, and all tests were 2-sided. The SAS analysis system, version 9.3, was used for all analyses (SAS Institute).

Results

Baseline Characteristics

Distribution of baseline characteristics is shown in Table 1. The median (interquartile range) age of patients in the overall cohort was 67 (59–75) years, 42.6% were women, 76.0% were white, and median pretest clinical score was 58.2% (28.4–84.8). Nearly a third of patients had prior myocardial infarction, 31.9% had prior PCI, and 58.7% underwent revascularization by either PCI or CABG within 90 days of PET imaging. Compared with patients with CFR ≥1.6 (n=166), those with CFR <1.6 (n=163) were older, had more comorbidities and higher use of cardiovascular medications, and showed increased amounts of ischemia and scar on noninvasive imaging, with higher CADPI scores on coronary angiography and higher rates of early revascularization.

Distribution of CFR by Angiographic Disease

As expected, there was a significant but limited inverse correlation between global CFR and the CAD angiographic score as assessed by CADPI (r=−0.26; P<0.0001), likely reflecting that CFR is a measure of not only the effects of epicardial CAD but also diffuse atherosclerosis and microvascular dysfunction on myocardial tissue perfusion. A scatterplot of CFR versus CADPI values, shown in Figure 1, illustrates a wide range of CFR values even among those subjects with CADPI of 0 (reflecting angiographically normal or nonobstructive [<50%] stenosis in the epicardial coronary arteries).

CFR, Angiographic Disease, and Clinical Events

Cardiovascular Death or Heart Failure Admission

During follow-up, 64 subjects met the primary composite end point of cardiovascular death or heart failure admission, including 31 deaths (Table II in the online-only Data Supplement). Freedom from cardiovascular death or heart failure was significantly different for subgroups stratified by CFR and angiographic score (log-rank P=0.03). Subjects with low CFR, independently of angiographic disease score, experienced higher rates of MACE, whereas those with high CFR and low angiographic score experienced the greatest freedom from events (Figure 2A).

In a univariable model, the cumulative probability of freedom from MACE was significantly associated with CFR (hazard ratio per unit decrease in CFR, 2.17; 95% confidence interval, 1.34–3.52; P=0.002) but did not meet statistical significance for angiographic score (hazard ratio per 10-U increase in CADPI, 1.10; 95% confidence interval, 0.99–1.21; P=0.07). Association of CFR with MACE was driven by MBF at peak hyperemia and not by MBF at rest. The addition of clinically important covariates into the model, including pretest clinical score, LVEF strata, global LV ischemia, and time-dependent early revascularization with CABG or PCI, led to significant associations with MACE (hazard ratio for CFR, 2.02; 95% confidence interval, 1.20–3.40; P=0.008; hazard ratio for CADPI, 1.17; 95% confidence interval, 1.01–1.34; P=0.03; Table 2). Inclusion of global LV ischemia or scar into the adjusted model did not significantly alter results, suggesting that CFR is a more sensitive measure of myocardial tissue perfusion and ischemia than semiquantitative perfusion scores. In adjusted analysis, subjects with low CFR experienced rates of events similar to those of subjects with high angiographic scores, and those with low CFR or high CADPI showed the highest cumulative incidence of events (P=0.001; Figure 2B). CFR thus was associated with cardiovascular death and heart failure admission independently of angiographic score, and CFR or angiographic score identified patients at highest risk of events.

Death or Admission for Heart Failure or Myocardial Infarction

In secondary analyses, we tested the association between CFR and 2 additional and related composite end points of (1) all-cause death or heart failure hospitalization and (2) cardiovascular death or hospitalization for heart failure or myocardial infarction. Ninety and 74 subjects met these secondary end points, respectively. Our results confirmed that CFR remained significantly associated with these additional MACE, independently of luminal angiographic score (Table 2).

Effect of Interactions of CFR, Angiographic Disease, and Early Revascularization on Outcomes

Although there was no apparent interaction between global CFR and overall angiographic score, there was a significant interaction between global CFR and revascularization by CABG (P for interaction=0.04) in terms of the primary end point of cardiovascular death and heart failure admission. This

Table 1. Baseline Characteristics of Patients by Low Versus High Coronary Flow Reserve

Characteristic	Overall (n=329)	Coronary Flow Reserve* <1.6 (n=163)	Coronary Flow Reserve* ≥1.6 (n=166)	*P* Value†
Demographic characteristics				
Age,‡ y (IQR)	67 (59–75)	69 (61–78)	64 (57–71)	<0.001
Female sex, %	140 (42.6)	76 (46.6)	64 (38.6)	0.15
White race, %	250 (76.0)	117 (71.8)	133 (80.1)	0.09
Body mass index,‡ kg/m^2	29.9 (26.3–34.5)	29.9 (26.2–34.7)	29.9 (26.6–34.4)	0.72
Pretest clinical score,‡§ %	58.2 (28.4–84.8)	60.3 (31.0–85.6)	57.7 (20.9–83.1)	0.09
Medical history				
Myocardial infarction, %	108 (32.8)	63 (38.7)	45 (27.1)	0.03
Percutaneous coronary intervention, %	105 (31.9)	49 (30.1)	56 (33.7)	0.48
Peripheral arterial disease, %	48 (14.6)	28 (17.2)	20 (12.1)	0.21
Diabetes mellitus, %	132 (40.1)	75 (46.0)	57 (34.3)	0.03
Hypertension, %	290 (88.2)	156 (95.7)	134 (80.7)	<0.001
Dyslipidemia, %	241 (73.3)	129 (79.1)	112 (67.5)	0.02
Current smoker, %	29 (8.8)	16 (9.8)	13 (7.8)	0.56
Chronic obstructive lung disease, %	45 (13.7)	18 (11.0)	27 (16.3)	0.20
Renal hemodialysis, %	11 (3.3)	10 (6.1)	1 (0.6)	<0.01
Medications				
Antiplatelet therapy, %	253 (76.9)	127 (77.9)	126 (75.9)	0.70
Statin, %	231 (70.2)	124 (76.1)	107 (64.5)	0.02
β-Blocker, %	229 (69.6)	126 (77.3)	103 (62.1)	<0.01
Angiotensin inhibitor, %	149 (45.3)	71 (43.6)	78 (47.0)	0.07
Nitroglycerin, %	58 (17.6)	33 (20.3)	25 (15.1)	0.25
Diuretic, %	108 (32.8)	64 (39.3)	44 (26.5)	0.02
Insulin, %	62 (18.8)	33 (20.3)	29 (17.5)	0.57
Noninvasive imaging parameters				
Left ventricular ejection fraction,‡ %	57 (50–65)	57 (49–64)	57 (52–65)	0.31
Left ventricular scar,‡ %	0 (0–2.9)	0 (0–5.9)	0 (0–1.5)	<0.01
Left ventricular ischemia,‡ %	10.3 (5.9–16.2)	11.8 (7.4–20.6)	7.4 (4.4–13.2)	<0.001
Rest myocardial blood flow,‡ mL/g per minute	1.0 (0.8–1.2)	1.0 (0.8–1.3)	0.9 (0.7–1.1)	<0.001
Stress global myocardial blood flow,‡ mL/g per minute	1.6 (1.1–2.0)	1.3 (1.0–1.7)	1.8 (1.4–2.3)	<0.001
Coronary flow reserve‡	1.6 (1.2–2.0)	1.2 (1.1–1.5)	2.0 (1.8–2.4)	<0.001
^{82}Rubidium radiopharmaceutical, %	293 (89.1)	147 (90.2)	146 (88.0)	0.60
Invasive angiography and early revascularization¶				
CADPI#	32 (23–48)	37 (23–56)	32 (0–42)	<0.001
Any early revascularization,¶ %	193 (58.7)	106 (65.0)	87 (52.4)	0.03
Percutaneous coronary intervention, %	157 (47.7)	85 (52.2)	72 (43.4)	0.12
Coronary artery bypass grafting, %	39 (11.9)	22 (13.5)	17 (10.2)	0.40

*Coronary flow reserve is stratified by median values.

†The *P* value is for the comparison between groups and is based on the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

‡Continuous variables are presented as median (interquartile range [IQR]).

§Pretest clinical score is the pretest probability of >70% stenosis in ≥1 major coronary artery on angiography.[12]

¶Early revascularization is defined as within 90 days of noninvasive imaging. Three patients underwent both percutaneous coronary intervention and coronary artery bypass grafting.

#Coronary artery disease prognostic index (CADPI) is a hierarchical index (0–100) assigning prognostic weights to increasing percent stenoses (50–100%) in 1-, 2-, or 3-vessel classification, with higher weights for proximal left anterior descending or left main artery involvement. CADPI 0 (<50% stenosis), 37 (>70% stenosis in >1 major epicardial coronary artery).[11]

interaction was additionally significant (*P*=0.006) in terms of the more inclusive secondary end point of cardiovascular death and admission for heart failure or myocardial infarction.

To better visualize the effect of the interaction of CFR and early revascularization on outcomes, we performed an exploratory analysis of event-free survival stratified by

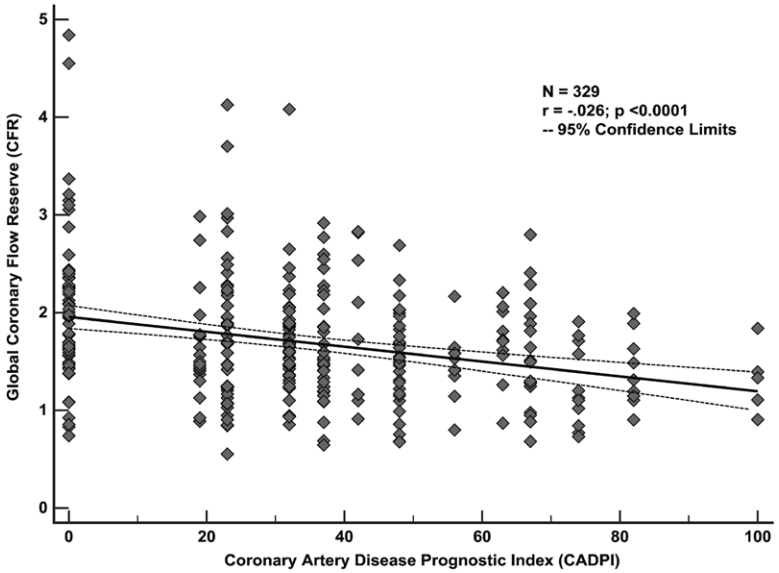
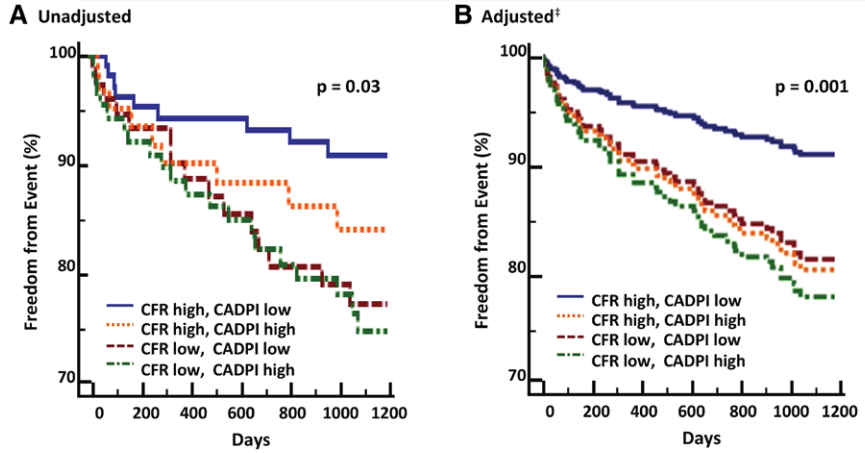


Figure 1. Association between coronary flow reserve (CFR) and extent and severity of angiographic disease. A significant but modest inverse correlation (r=–0.26; P<0.0001) was seen between CFR and coronary artery disease prognostic index (CADPI), a hierarchical score of angiographic disease, reflecting the role of CFR as an integrated measure of the effects of epicardial coronary artery disease, as well as diffuse atherosclerosis and associated microvascular dysfunction, on myocardial tissue perfusion. A wide range of CFR values was seen even among those subjects with CADPI of 0 (reflecting angiographically normal or nonobstructive [<50%] stenosis in the epicardial coronary arteries).

CFR and revascularization. Approximately half (53.8%) of primary end point events occurred in subjects who underwent early revascularization; of the 9 subjects meeting the clinical end point within 60 days of catheterization, 7 (77.8%) had undergone revascularization. Table III in the online-only Data Supplement displays the distribution of baseline characteristics by early revascularization type and shows that the major difference between groups was in the severity of CADPI (67 versus 37 for CABG compared with PCI; P>0.001).

Unadjusted and adjusted freedom from cardiovascular death or heart failure was significantly different for subgroups stratified by CFR and early revascularization (log-rank P=0.03; P=0.002 after adjustment for pretest clinical score, LVEF, LV ischemia, and CADPI). Subjects with high CFR, independently of revascularization, experienced lower rates of MACE, whereas those with low CFR who did not undergo revascularization experienced the highest rate of events (Figure 3A and 3B). In the subgroup of patients who underwent revascularization, there was no difference in event-free survival for those with high CFR who underwent CABG or PCI (log-rank P=0.76; adjusted P=0.61). Among patients with low CFR, however, only those who underwent CABG, compared with those who underwent PCI alone, experienced lower rates of events (log-rank P=0.02; adjusted P=0.01; Figure 3C and 3D). This is further illustrated in Figure 4, which shows that



	Total (N = 329)	Early Revascularization (%)	by PCI (%)
CFR high, CADPI low	106	38 (35.8)	34 (89.5)
CFR high, CADPI high	60	49 (81.7)	36 (73.5)
CFR low, CADPI low	74	35 (47.3)	34 (97.1)
CFR low, CADPI high	89	71 (79.8)	50 (70.4)

Figure 2. Freedom from cardiovascular death or heart failure admission according to coronary flow reserve (CFR) and angiographic score (coronary artery disease prognostic index [CADPI]). Freedom from cardiovascular death or heart failure admission differed significantly among subgroups stratified by CFR and CADPI, such that patients with low CFR, independently of angiographic disease score, experienced higher rates of events (overall P=0.03). In adjusted analysis, patients with low CFR experienced rates of events similar to those of patients with high CADPI, and those with low CFR or high CADPI showed the highest cumulative incidence of events (adjusted overall P=0.001). PCI indicates percutaneous coronary intervention.

*CFR denotes coronay flow reserve: high (≥1.6), low (<1.6).
†CADPI denotes coronary artery disease prognostic index: low (<37), high (≥37, reflects >70% stenosis in >1 epicardial artery).
‡Adjusted for pretest clinical score, left ventricular ejection fraction, left ventricular ischemia, and early revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
Early Revascularization denotes that within 90 days of noninvasive imaging.

Table 2. Association Between Coronary Flow Reserve, Luminal Angiographic Severity, and Clinical Events

Outcome	Univariable Model Hazard Ratio (95% CI)		Multivariable Model* Hazard Ratio (95% CI)	
	CFR†	CADPI‡	CFR†	CADPI‡
Cardiovascular death or heart failure§	2.17 (1.34–3.52)	1.10 (0.99–1.21)	2.02 (1.20–3.40)	1.17 (1.01–1.34)
All-cause death or heart failure§	1.91 (1.29–2.83)	1.05 (0.97–1.15)	1.64 (1.08–2.48)	1.15 (1.03–1.29)
Cardiovascular death, heart failure,§ or myocardial infarction¶	1.90 (1.23–2.93)	1.13 (1.03–1.24)	1.63 (1.02–2.59)	1.22 (1.08–1.38)

CI indicates confidence interval.

*Includes pretest clinical score, left ventricular ejection fraction, left ventricular ischemia, time-dependent revascularization with percutaneous coronary intervention or coronary artery bypass grafting within 90 days of noninvasive imaging, coronary flow reserve (CFR), and coronary artery disease prognostic index (CADPI). There is a significant interaction between CFR and revascularization with coronary artery bypass grafting (P=0.04 for cardiovascular death or heart failure; P=0.006 for cardiovascular death, heart failure, or myocardial infarction).

†CFR per −1 U.

‡CADPI per +10 U.

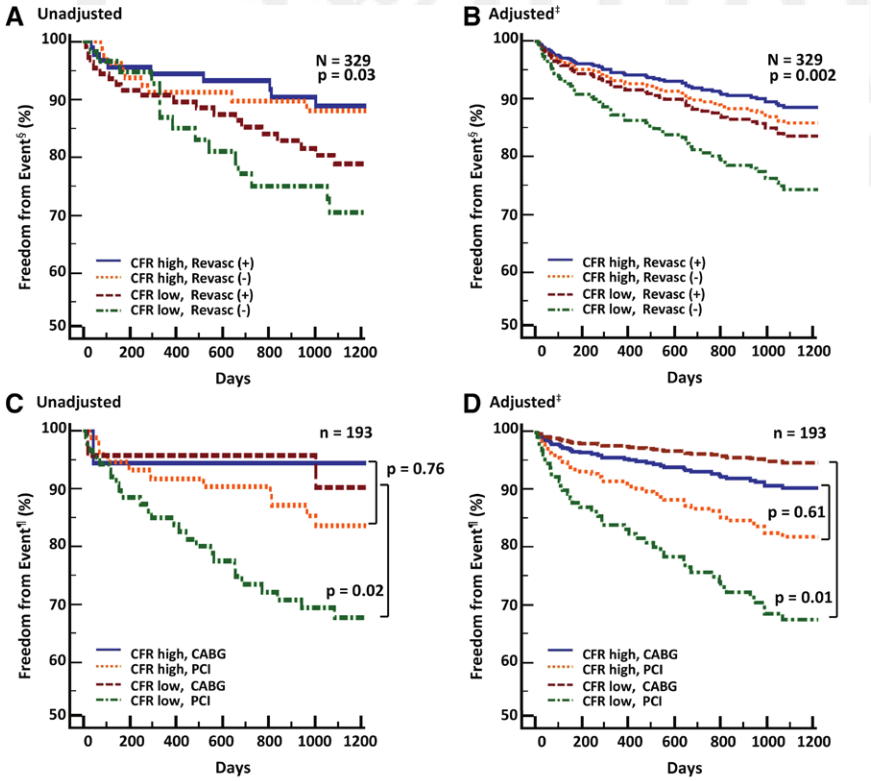
§Admission for heart failure.

¶Admission for myocardial infarction.

patients with low CFR who underwent CABG had adjusted annualized event rates that were similar to, and possibly better than, those with high CFR who underwent CABG. In contrast, patients with low CFR who underwent PCI showed event rates that were not statistically different from those with low CFR who did not undergo revascularization. In the patients with high CFR, there was no difference in event rates between those who did and did not undergo revascularization by either CABG or PCI.

Discussion

We demonstrated that, although global CFR is only modestly associated with the overall extent and severity of angiographic disease, both low CFR and high CADPI are independently associated with adverse clinical events. In addition, global CFR modified the effect of revascularization in this cohort, such that only patients with low CFR appeared to benefit from revascularization and only if the revascularization included CABG. Implied in these data is the possibility that invasive



*CFR denotes coronary flow reserve: high (≥1.6), low (<1.6).

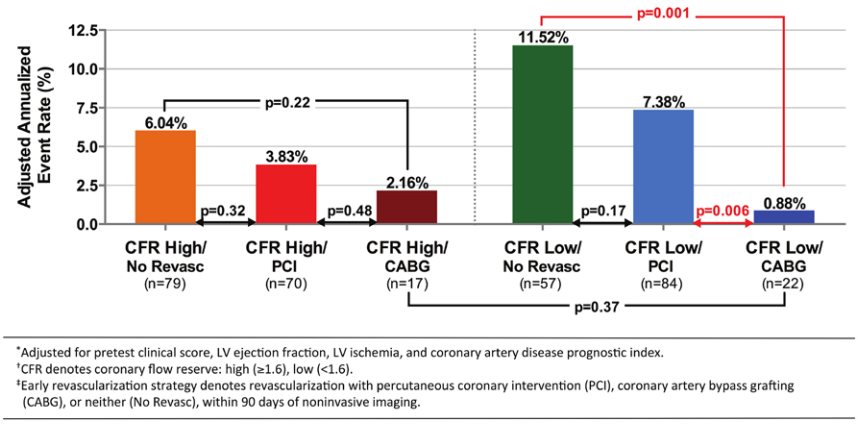
†Early revascularization (Revasc) denotes revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 90 days of noninvasive imaging.

‡Adjusted for pretest clinical score, LV ejection fraction, LV ischemia, and coronary artery disease prognostic index.

§Cardiovascular death or admission for heart failure.

¶All-cause death or admission for heart failure.

Figure 3. Freedom from events according to coronary flow reserve (CFR) and early revascularization (Revasc). Freedom from cardiovascular death or heart failure admission differed significantly among subgroups stratified by CFR and revascularization (overall log-rank P=0.03; adjusted P=0.002) **A** and **B**. Patients with high CFR, independently of revascularization, experienced lower rates of events, whereas those with low CFR who did not undergo revascularization experienced the highest rate of events. In the subgroup of patients who underwent revascularization (**C** and **D**), there was no difference in event-free survival among those with high CFR (log-rank P=0.76; adjusted P=0.61), but in those with low CFR, only those who also underwent coronary artery bypass grafting (CABG), vs percutaneous coronary intervention (PCI), experienced lower rates of events (log-rank P=0.02; adjusted P=0.01). LV indicates left ventricular.



*Adjusted for pretest clinical score, LV ejection fraction, LV ischemia, and coronary artery disease prognostic index.
†CFR denotes coronary flow reserve: high (≥1.6), low (<1.6).
‡Early revascularization strategy denotes revascularization with percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or neither (No Revasc), within 90 days of noninvasive imaging.

Figure 4. Adjusted annualized rates of cardiovascular death and heart failure admission among patients referred for coronary angiography by coronary flow reserve (CFR) and early revascularization (Revasc) strategy (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], or neither). No difference in event rates was seen in patients with high CFR (orange, red, maroon), regardless of revascularization strategy pursued. In patients with low CFR, those who underwent CABG (dark blue) had lower event rates than those who underwent PCI (light blue; *P*=0.006) or no revascularization (green; *P*=0.001) and had event rates similar to those with high CFR who underwent CABG (maroon). Annualized event rates were adjusted for pretest clinical score, left ventricular (LV) ejection fraction, LV ischemia, and coronary artery disease prognostic index.

revascularization in certain patients (ie, those with preserved CFR) may contribute to increased events. The apparent discrepancy between angiographic appearance of coronary lesions and their physiological significance has been attributed to limitations in the resolution of x-ray angiography[7,19,20] and its inadequacy to characterize microvascular disease or diffuse coronary atherosclerosis,[2,21] a nearly ubiquitous finding in autopsy and intravascular ultrasound studies of patients with CAD.[22,23] Thus, a stenosis that does not produce angina in one patient (with otherwise normal coronary arteries or outward remodeling or robust downstream collaterals) might result in severe functional limitation, chronic low-level ischemia, and myocardial remodeling in another (with diffuse atherosclerosis or microvascular disease). Furthermore, angina caused by a small versus a large ischemic area may carry a different prognosis and associated risk-benefit profile with revascularization such that angina itself may be an inadequate biomarker of risk.

The finding that global CFR is associated with events independently of angiographic score underscores the morbidity associated with diffuse atherosclerosis or microvascular disease. This has been illustrated in diabetic patients, who demonstrate impaired coronary vasoreactivity even in the absence of obstructive atherosclerosis[24] and in whom absence of myocardial ischemia on noninvasive testing does not necessarily identify a lower-risk cohort.[6,25] In contrast to diabetic patients without known CAD with preserved CFR (who demonstrate very low levels of risk), diabetic patients without known CAD with impaired CFR showed a risk of cardiac death comparable to, and possibly higher than, that for nondiabetic patients with known CAD.[6] The present study was not limited to diabetics (40.1% of cohort) and, together with previous findings,[6] suggests that impaired CFR may be a more powerful biomarker for diffuse atherosclerosis than diabetes mellitus alone.

These observations may be clinically relevant, particularly when it is considered that revascularization procedures based on anatomic thresholds have not reduced rates of adverse cardiovascular events in patients with stable ischemic heart disease in randomized, controlled trials comparing revascularization with guideline-directed medical therapy[8,9] or fractional flow reserve–guided PCI.[10] An alternative hypothesis generated from observational[15] and post hoc[26] analyses proposes that there may be a threshold of ischemia above which a revascularization strategy might result in improved cardiovascular outcomes. However, like angiographic severity, traditional semiquantitative measures of ischemia alone may be insufficient to risk-stratify patients potentially eligible for benefit from coronary revascularization.[2,27] Furthermore, the present study raises the possibility that the type of revascularization in this context may have profound impact on optimal management strategy.

Indeed, contemporary multicenter randomized clinical trials comparing outcomes of CABG and PCI in subjects with multivessel CAD have suggested benefit in major adverse cardiovascular events with CABG,[28] particularly in patients with diabetes mellitus.[9,29,30] In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, the benefit of CABG, relative to PCI, on outcomes was independent of the Synergy Between PCI With TAXUS and Cardiac Surgery (SYNTAX) score[30] (reflecting overall coronary lesion complexity), which may not be as sensitive as CFR to identify diffuse, downstream disease, particularly among diabetics. A better understanding of the relationship between diffuse coronary vascular dysfunction and CAD comorbid conditions, including diabetes mellitus and dyslipidemia, may guide new, more effective approaches for global cardiovascular risk reduction that may achieve some of the therapeutic benefit derived from more "complete revascularization" with CABG. These findings thus identify diffuse atherosclerosis and microvascular dysfunction as potentially relevant targets for aggressive therapeutic intervention.

Exactly how impaired CFR is associated with increased clinical risk independently of angiographic score and precisely how it modifies the effect of revascularization cannot be determined from this study. Low-level inflammation in the coronary microvasculature has been implicated as a potential driver of both coronary vasomotor dysfunction[31] and myocardial dysfunction and remodeling in heart failure with preserved ejection fraction.[32] Abnormal CFR in patients with heart failure correlates with diastolic load and high-sensitivity troponin release.[33] Furthermore, the observation that chronic circulating levels of high-sensitivity troponins are associated with increased

incidence of cardiovascular death or heart failure (but not acute coronary syndromes) in patients with stable CAD and preserved LVEF[17,18] highlights the potential interplay of chronic coronary vasomotor dysfunction and subclinical myocardial injury in the pathway to diastolic dysfunction and heart failure outcomes.

This study must be interpreted in the context of its single-center observational design, in which subjects were patients clinically referred for PET myocardial perfusion imaging and subsequently referred for invasive coronary angiography. CFR results were not available to referring clinicians and thus did not affect downstream management decisions regarding catheterization or additional therapies. We included patients undergoing both ^{82}rubidium and ^{13}N-ammonia myocardial perfusion PET imaging. Although we have previously published data documenting comparable MBF and CFR estimates using these 2 radiopharmaceuticals,[13] extrapolation of these results to imaging with other PET tracers, including ^{15}O-water and ^{18}F-flurpiridaz (neither of which is approved by the Food and Drug Administration), will require future studies. Our relatively modest sample size limits extensive subgroup (ie, sex, diabetes mellitus, revascularization) analysis for outcomes and may be underpowered to detect more subtle differences in outcomes between subgroups. We excluded patients with a reduced LVEF at the time of PET to focus on the outcomes of those without already severely impaired cardiac structure. In addition, we did not assess nonfatal stroke outcomes and intentionally avoided repeat revascularization outcomes. Despite inherent limitations with unmeasured confounding and cautions about drawing causal inferences, this work is the first to link the complementary but distinct associations of functional and anatomic coronary abnormalities with clinically meaningful cardiovascular outcomes in a high-risk, real-world patient population.

Conclusions

Global CFR showed limited correlation with the extent and severity of angiographic disease, was associated with MACE independently of angiographic disease score, and modified the effect of revascularization on outcomes. Low CFR or high CADPI together identified patients at the highest risk of events. A significant interaction was seen between CFR and revascularization strategy, such that patients with low CFR who underwent CABG, but not PCI alone, experienced event rates comparable to those with preserved CFR independently of revascularization. Diffuse atherosclerosis and reduced global CFR may play a role in the pathophysiological abnormalities leading to increased risk of cardiovascular death or heart failure and may affect the outcomes of revascularization. Prospective studies are needed to evaluate the ability of CFR to reclassify subsets of patients at differing levels of clinical risk (and potential for benefit) regardless of the presence of epicardial coronary obstruction on invasive angiography or ischemia on semiquantitative measures of relative myocardial perfusion imaging.

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CLINICAL PERSPECTIVE

Increasing evidence suggests that global atherosclerotic disease burden and resultant ischemia, even absent obstructive epicardial lesions, are important contributors to overall cardiovascular risk, especially when functional outcomes such as cardiovascular death and heart failure are considered. Although luminal coronary angiography is a cornerstone of modern cardiovascular care, it is limited in its ability to identify diffuse atherosclerosis and small-vessel disease, and this may help to explain why anatomically guided revascularization procedures have not resulted in improved outcomes in patients with stable ischemic heart disease in randomized, controlled trials comparing revascularization with guideline-directed medical therapy. Coronary flow reserve (CFR) is an integrated measure of focal, diffuse, and small-vessel coronary artery disease that assays the complex sequelae of ischemic insults in the heart and identifies patients at risk for cardiac death. This study demonstrated that (1) although global CFR is only modestly associated with the overall extent and severity of angiographic disease, both low CFR and high angiographic disease score are independently associated with adverse clinical events, and (2) global CFR modified the effect of revascularization, such that only patients with low CFR appeared to benefit from revascularization in this cohort, and only if the revascularization included coronary artery bypass grafting. As such, the present study raises the possibility that the type of revascularization for certain patients (ie, with preserved versus impaired CFR) may have profound implications for optimal management strategy. In addition, these findings identify diffuse atherosclerosis and microvascular dysfunction as potentially relevant targets for aggressive therapeutic intervention and global cardiovascular risk reduction.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. CAD Prognostic Index*

Extent of CAD	Prognostic Weight (0-100)
No CAD ≥50%	0
1 VD 50-74%	19
>1 VD 50-74%	23
1 VD (75%)	23
1 VD (≥95%)	32
2 VD	37
2 VD (both ≥95%)	42
1 VD, ≥95% proximal LAD	48
2 VD, ≥95% LAD	48
2 VD, ≥95% proximal LAD	56
3 VD	56
3 VD, ≥95% in at least one	63
3 VD, 75% proximal LAD	67
3 VD, ≥95% proximal LAD	74
Left main 75%	82
Left main ≥95%	100

* Index is hierarchical and patients are assigned to most severe category applicable.[11]

CAD denotes coronary artery disease; VD, vessel disease; and LAD, left anterior descending artery.

Supplemental Table 2. Patients Meeting Clinical Endpoint*

Outcome	**No. of Patients (%) (N = 329)**
Cardiovascular death or heart failure admission	64 (19.5)
All-cause death or heart failure admission	90 (27.4)
Cardiovascular death or admission for heart failure or myocardial infarction	74 (22.5)
Cardiovascular death	31 (9.4)
All-cause death	60 (18.2)

*Median (IQR) of follow-up time was 3.1 (1.7-4.3) years.

Supplemental Table 3. Baseline Characteristics of Patients with Early Revascularization

Characteristic	Overall (n=193)	Early Revascularization[§] PCI (n=154)	CABG (n=39)	P[*]
Demographic characteristics				
Age[†], y (IQR)	68 (60-76)	68 (61-79)	65 (56-71)	0.07
Female sex (%)	73 (37.8)	61 (39.6)	12 (30.8)	0.36
White race (%)	152 (78.8)	118 (76.6)	34 (87.2)	0.19
Body mass index[†], kg/m^2	29.8 (26.6-34.5)	29.8 (26.7-34.7)	29.6 (26.3-33.1)	0.56
Pretest clinical score[†‡], %	64.4 (34.7-87.7)	64.6 (37.4-87.1)	64.4 (25.2-90.9)	0.71
Medical history				
Myocardial infarction (%)	73 (37.8)	63 (40.9)	10 (25.6)	0.10
Percutaneous coronary intervention (%)	70 (36.3)	61 (39.6)	9 (23.1)	0.06
Peripheral arterial disease (%)	13 (6.7)	10 (6.5)	3 (7.7)	0.73
Diabetes mellitus (%)	74 (38.3)	63 (40.9)	11 (28.2)	0.20
Hypertension (%)	175 (90.7)	141 (91.6)	34 (87.2)	0.37
Dyslipidemia (%)	151 (78.2)	124 (80.5)	27 (69.2)	0.13
Current smoker (%)	19 (9.8)	14 (9.1)	5 (12.8)	0.55
Chronic obstructive lung disease (%)	26 (13.5)	23 (15.0)	3 (7.7)	0.30
Renal hemodialysis (%)	5 (2.6)	4 (2.6)	1 (2.6)	0.99
Medications				
Antiplatelet therapy (%)	157 (81.4)	126 (81.8)	31 (79.5)	0.82
Statin (%)	144 (74.6)	117 (76.0)	27 (69.2)	0.41
Beta-blocker (%)	140 (72.5)	116 (75.3)	24 (61.5)	0.11
Angiotensin inhibitor (%)	90 (46.6)	73 (47.4)	17 (43.6)	0.72
Nitroglycerin (%)	39 (20.2)	29 (18.8)	10 (25.6)	0.37
Diuretic (%)	69 (35.8)	59 (38.3)	10 (25.6)	0.19
Insulin (%)	32 (16.6)	26 (16.9)	6 (15.4)	0.99
Noninvasive imaging parameters				
Left ventricular ejection fraction[†], %	57 (50-64)	57 (50-64)	56 (50-64)	0.69
Left ventricular scar[†], %	0 (0-4.4)	0 (0-5.9)	0 (0-2.9)	0.36
Left ventricular ischemia[^], %	13.2 (7.4-19.1)	11.8 (7.4-19.1)	13.2 (7.4-22.1)	0.49
Rest myocardial blood flow[†], ml/g/min	1.0 (0.8-1.2)	0.9 (0.7-1.1)	1.0 (0.8-1.3)	0.20
Stress global myocardial blood flow[†], ml/g/min	1.5 (1.0-1.9)	1.5 (1.0-1.9)	1.5 (1.1-2.0)	0.91
Coronary flow reserve[†]	1.5 (1.2-1.9)	1.5 (1.2-1.9)	1.5 (1.1-1.8)	0.20
Rubidium-82 radiopharmaceutical, %	169 (87.6)	136 (88.3)	33 (84.6)	0.59
Invasive angiography				
Coronary artery disease prognostic index[†¶]	37 (32-56)	37 (32-48)	67 (42-82)	>0.001

[*] P-value is for comparison between groups, and is based on the Fisher's-exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

[†] Continuous variables are presented as medians (interquartile ranges).

[‡] Pretest clinical score is the pretest probability of >70% stenosis in ≥1 major coronary artery on angiography.[12]

[§] Early revascularization is defined as within 90 days of noninvasive imaging. Three patients who underwent early percutaneous coronary intervention (PCI) followed by early coronary artery bypass grafting (CABG) are listed under CABG.

[¶] Coronary artery disease prognostic index (CADPI) is a hierarchical index (0-100) assigning prognostic weights to increasing percent stenoses (50-100%) in one-, two-, or three-vessel classification, with higher weights for proximal left anterior descending or left main artery involvement. CADPI 0 (<50% stenoses), 37 (>70% stenosis in >1 major epicardial coronary artery).[11]