Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Prognostic Value of Modified Coronary Flow Capacity Derived From [^{15}O]H_2O Positron Emission Tomography Perfusion Imaging

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BACKGROUND: Coronary flow capacity (CFC) is a measure that integrates hyperemic myocardial blood flow and coronary flow reserve to quantify the pathophysiological impact of coronary artery disease on vasodilator capacity. This study explores the prognostic value of modified CFC derived from [^{15}O]H_2O positron emission tomography perfusion imaging.

METHODS: Quantitative rest/stress perfusion measurements were obtained from 1300 patients with known or suspected coronary artery disease. Patients were classified as having myocardial steal (n=38), severely reduced CFC (n=141), moderately reduced CFC (n=394), minimally reduced CFC (n=245), or normal flow (n=482) using previously defined thresholds. The end point was a composite of death and nonfatal myocardial infarction.

RESULTS: During a median follow-up of 5.5 (interquartile range, 3.7–7.8) years, the end point occurred in 153 (12%) patients. Myocardial steal (hazard ratio [HR], 6.70 [95% CI, 3.21–13.99]; $P<0.001$), severely reduced CFC (HR, 2.35 [95% CI, 1.16–4.78]; $P=0.018$), and moderately reduced CFC (HR, 1.95 [95% CI, 1.11–3.41]; $P=0.020$) were associated with worse prognosis compared with normal flow, after adjusting for clinical characteristics. Similarly, in the overall population, increased resting myocardial blood flow (HR, 3.05 [95% CI, 1.68–5.54]; $P<0.001$), decreased hyperemic myocardial blood flow (HR, 0.68 [95% CI, 0.52–0.90]; $P=0.007$) and decreased coronary flow reserve (HR, 0.55 [95% CI, 0.42–0.71]; $P<0.001$) were independently associated with adverse outcome. In a model adjusted for the combined use of perfusion metrics, modified CFC demonstrated independent prognostic value (overall $P=0.017$).

CONCLUSIONS: [^{15}O]H_2O positron emission tomography–derived resting myocardial blood flow, hyperemic myocardial blood flow, coronary flow reserve, and CFC are prognostic factors for death and nonfatal myocardial infarction in patients with known or suspected coronary artery disease. Importantly, after adjustment for clinical characteristics and the combined use of [^{15}O]H_2O positron emission tomography perfusion metrics, modified CFC remained independently associated with adverse outcome.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery disease ■ myocardial perfusion imaging ■ positron emission tomography ■ prognosis

Myocardial perfusion imaging in patients with coronary artery disease (CAD) identifies those at risk for adverse cardiovascular events.[1,2] Current guidelines recommend perfusion imaging to assess the presence and extent of myocardial ischemia to select patients in whom revascularization may

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CLINICAL PERSPECTIVE

Positron emission tomography myocardial perfusion imaging in patients with coronary artery disease allows for the quantification of absolute myocardial blood flow and can identify those at risk for adverse cardiovascular events. The integration of quantitative hyperemic myocardial blood flow and coronary flow reserve into coronary flow capacity (CFC) was proposed to provide a complementary measure capturing all relevant coronary flow characteristics with the aim to enhance interpretation of the pathophysiological impact of focal coronary lesions, diffuse atherosclerotic disease and microvascular dysfunction on vasodilator capacity. The current study explores the prognostic value of modified regional CFC derived from [15O]H_2O positron emission tomography perfusion imaging in patients with known or suspected coronary artery disease. We found that resting myocardial blood flow, hyperemic myocardial blood flow, coronary flow reserve, and modified CFC were all prognostic factors for death and nonfatal MI, independent of clinical characteristics and cardiovascular risk factors. After adjusting for clinical characteristics and the combined use of [15O]H_2O positron emission tomography perfusion metrics, modified CFC remained independently associated with adverse patient outcome. The present study shows that modified CFC may provide incremental prognostic value in patients referred for guideline-directed, noninvasive risk assessment using myocardial perfusion imaging with [15O]H_2O positron emission tomography. Future studies are needed to explore the value of prospectively obtained CFC to improve risk stratification and guide therapeutic and revascularization decision-making in patients evaluated for obstructive and nonobstructive coronary artery disease.

Nonstandard Abbreviations and Acronyms

CAD	coronary artery disease
CFC	coronary flow capacity
CFR	coronary flow reserve
MBF	myocardial blood flow
MI	myocardial infarction
PET	positron emission tomography

be considered in addition to optimal medical therapy.[3,4] Positron emission tomography (PET) myocardial perfusion imaging allows for the quantification of absolute myocardial blood flow (MBF), which can improve risk stratification over relative perfusion imaging.[2] The independent prognostic value of impaired hyperemic MBF (hMBF) and coronary flow reserve (CFR) has been demonstrated in several large PET cohorts.[5–8] Additionally, the coronary flow capacity (CFC) concept was introduced by integrating hMBF and CFR, providing a complementary measure capturing all relevant coronary flow characteristics aiming to enhance interpretation of the pathophysiological impact of coronary atherosclerotic disease on vasodilator capacity.[9,10] CFC was developed using ^{82}Rb PET imaging but can be derived from any functional modality that allows quantification of coronary blood flow.[9] As such, CFC has been adapted to several invasive and noninvasive functional techniques.[11–14] Gould et al[15,16] showed incremental prognostic value of ^{82}Rb PET–derived CFC over clinical characteristics and other PET perfusion metrics. Interestingly, studies using intracoronary Doppler- and thermodilution-derived flow measurements to calculate CFC reported similar findings.[11,13] Recently, we extrapolated the application of CFC to [15O]H_2O PET perfusion imaging in a coronary revascularization cohort study.[12] We found that an increase in modified CFC after revascularization was associated with improved patient outcome. However, the number of events was limited and only patients undergoing coronary revascularization were included. To date, comprehensive studies exploring the prognostic value of [15O]H_2O PET-derived CFC in patients evaluated for stable ischemic heart disease have not been conducted. Therefore, this study explores the prognostic value of modified CFC derived from [15O]H_2O PET perfusion imaging in a large clinical cohort of patients with known or suspected CAD.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

A total of 2254 consecutive patients with known or suspected CAD who underwent [15O]H_2O PET perfusion imaging at the Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, and the Turku PET Center, Turku University Hospital between 2007 and 2020 were considered for inclusion in the study. Patients who underwent a stress-only perfusion imaging protocol (n=826) were excluded, which resulted in a remaining sample size of 1428 patients. Poor image quality or technical issues precluded analysis of resting and hyperemic MBF values in 32 patients. Of the remaining 1396 patients, 96 (7%) were lost to follow-up, resulting in a final study population of 1300 patients. The index PET was included in the present study in case of multiple PET examinations during the study period. The treatment strategy after PET imaging was left to the discretion of the referring physician. Early revascularization was defined as a revascularization guided by the initial diagnostic work-up, including PET perfusion results (within 3–6 months after PET imaging, depending on the waiting period for revascularization therapy). This study complied with the declaration of Helsinki and was approved by the institutional Medical Ethics Committees of the Amsterdam University Medical Centers and

the Hospital District of Southwest Finland. All participants provided written informed consent unless waived by the local ethics committee.

[15O]H2O PET Perfusion Imaging and Analysis

Patients underwent [15O]H2O PET perfusion imaging using a hybrid PET/computed tomography device (Gemini TF 64 [647 patients, 50%]; Ingenuity TF 128 [462 patients, 36%]; Philips Healthcare, Best, the Netherlands, and GE Discovery VCT or GE D690 [191 patients, 15%]; General Electric Medical Systems, Waukesha, Wisconsin). Patients were advised to refrain from products containing caffeine or xanthine for at least 24 hours before scanning. The detailed scanning protocol has been previously described.[17,18] In short, images were acquired during dynamic perfusion scans, first at rest and subsequently during adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced maximum vasodilator stress, commencing simultaneously with the injection of [15O]H2O as perfusion tracer. A low-dose computed tomography scan was performed for scatter and attenuation correction before or directly after both resting and stress PET sequences. In-house developed software (Amsterdam University Medical Centers: Cardiac VUer; Turku University Hospital: Carimas) was used to generate parametric images of MBF expressed in $ml \cdot min^{-1} \cdot g^{-1}$ of perfusable myocardial tissue by using a basis function implementation of the single-tissue compartment model previously described by Iida et al., with corrections for partial volume effects (using the perfusable tissue fraction) and spillover.[18–20] The software extracted the arterial input function directly from the dynamic PET scan images.[18,19] Absolute perfusion indices derived from the parametric images were evaluated for the 3 vascular regions (left anterior descending coronary artery, right coronary artery, and circumflex coronary artery) according to the standardized 17-segment model of the American Heart Association.[21] CFR was defined as the ratio of stress to resting MBF. To account for the individual variation in hemodynamic conditions and left ventricular (LV) workload, the resting MBF was additionally corrected for the rate-pressure product (RPP; resting MBF×mean RPP of all patients/RPP in the individual patient).[22] The stress total perfusion deficit (TPD) was calculated by dividing the number of segments with hyperemic MBF≤2.3 $mL \cdot min^{-1} \cdot g^{-1}$ (an established [15O]H2O PET perfusion imaging threshold for patients with suspected obstructive CAD) by 17 (the number of LV segments).[17] Correspondingly, the number of segments with CFR below the previously described ischemic threshold of ≤2.5 was divided by the total number of LV segments to calculate the TPD for CFR as a percentage of the LV.[17] TPD percentage was used as a continuous measure to assess the effect on patient outcome. Previously described thresholds for [15O]H2O PET perfusion imaging were used for categorization of vascular regions into 5 modified color-coded CFC groups by combining regional hMBF and CFR values: myocardial steal (CFR<1), severely reduced CFC (hMBF≤1.50 $mL \cdot min^{-1} \cdot g^{-1}$ and 1.00<CFR≤1.50), moderately reduced CFC ([1.50 $mL \cdot min^{-1} \cdot g^{-1}$<hMBF≤2.30 $mL \cdot min^{-1} \cdot g^{-1}$ and CFR≤2.50] or [hMBF≤2.30 $mL \cdot min^{-1} \cdot g^{-1}$ and 1.50<CFR≤2.50]), minimally reduced CFC ([2.30 $mL \cdot min^{-1} \cdot g^{-1}$<hMBF≤3.01 $mL \cdot min^{-1} \cdot g^{-1}$ and CFR≤2.95] or [hMBF≤3.01 $mL \cdot min^{-1} \cdot g^{-1}$ and 2.5<CFR≤2.95]), and normal flow (hMBF>3.01 $mL \cdot min^{-1} \cdot g^{-1}$ or CFR>2.95).[12]

Clinical Outcome Assessment

Clinical follow-up data was obtained by observers blinded to PET imaging results using national registry databases, standardized telephone interviews, and longitudinal electronic health records. The study end point was a composite of all-cause death and nonfatal myocardial infarction (MI). The follow-up period started at PET scan acquisition. Deaths and periprocedural MIs related to early revascularization were not incorporated in the outcome analyses. Events were adjudicated according to contemporary guidelines.[3]

Statistical Analysis

We performed the statistical analysis using SPSS version 28.0 (IBM SPSS Statistics, Armonk, NY). Categorical variables are reported as numbers with percentages, whereas continuous variables are displayed as mean±SD or median with interquartile ranges according to normality of the data distribution. We used the χ^2 test to compare categorical variables and the Mann-Whitney *U* test or independent samples *t* test to compare continuous variables, as appropriate. To calculate the prognostic effect of PET perfusion parameters, the lowest regional value for hMBF, CFR, and modified CFC, and the highest regional value for resting MBF were included for each subject. Kaplan-Meier curves were plotted to compare event-free survival across the modified CFC categories using the log-rank test to analyze differences in event rates over time. We evaluated the independent association between individual PET perfusion indices and the occurrence of the end point by adding a single value for each perfusion parameter (originating from 1 of the 3 vascular regions) separately in different Cox proportional hazards regression analyses including clinical characteristics and cardiovascular risk factors. The perfusion variables CFR and modified CFC were calculated for each of the 3 vascular regions by using matched hMBF and resting MBF originating from the same region, after which the lowest regional CFR/CFC value was used in the multivariable outcome models. Furthermore, we compared the predictive value of modified CFC within the 3 lowest CFC categories to a comparable sample size of patients with the lowest regional hyperemic MBF and CFR values. Finally, a multivariable Cox proportional hazards regression analysis was performed with adjustments for clinical characteristics, CAD risk factors, and the combined use of [15O]H2O PET perfusion metrics. We included a single value of the lowest region for hMBF, CFR, and modified CFC per patient to identify vulnerable patients for future adverse events by evaluating the function of the coronary circulation through [15O]H2O PET myocardial perfusion parameters, which were compared to determine their independent prognostic value in predicting the occurrence of the composite end point death/nonfatal MI. The improvement in prognostic performance gained by adding [15O]H2O PET perfusion values to a risk prediction model including clinical characteristics and CAD risk factors was assessed using the likelihood ratio test with χ^2 results. Furthermore, Harrell's C statistics were calculated (Stata version 14.0 software, StataCorp) to compare the discriminative function of a prognostic perfusion model with versus without modified CFC. Quantitative hyperemic MBF and CFR showed a strong correlation (r=0.78), yet assessment of collinearity (tolerance 0.40, variance inflation factor 2.50) indicated that this did not preclude concomitant addition of these

flow markers to the same outcome model.[8] All analyses were adjusted for the following clinically relevant patient characteristics and CAD risk factors: age, sex, body mass index, diabetes, hypertension, hypercholesterolemia, family history of CAD, prior revascularization, prior MI, early revascularization with coronary artery bypass grafting (CABG), early revascularization with percutaneous coronary intervention (PCI), the extent of obstructive epicardial CAD, and LV ejection fraction. To account for the timing of early revascularization relative to the occurrence of the composite end point, early revascularization was treated as a time-dependent covariate in the multivariable Cox proportional hazards models. For resting MBF, an additional Cox regression analysis was performed incorporating adjustments for the RPP, heart rate, systolic blood pressure, and pulse pressure. A 2-sided level of $P<0.05$ was considered statistically significant.

RESULTS

Study Population

Baseline characteristics are presented in Table 1. Mean age was 61±10 years, and 835 (64%) patients were male. Early revascularization was performed in 513 patients (39%), consisting of 446 (87%) PCIs and 67 (13%) CABG surgeries. One patient suffered an event before early revascularization was performed. For this patient, early revascularization was set to zero (ie, no revascularization). During a median follow-up of 5.5 (interquartile range, 3.7–7.8) years, the end point occurred in 153 (12%) patients, including 87 (7%) deaths and 66 (5%) nonfatal MIs.

[15O]H2O PET Perfusion Metrics

By combining absolute hMBF and CFR, 38 (3%), 141 (11%), 394 (30%), 245 (19%), and 482 (37%) patients were stratified as having myocardial steal, severely reduced CFC, moderately reduced CFC, minimally reduced CFC and normal flow, respectively. Figure 1 shows the mean PET perfusion indices stratified by the occurrence of the end point. Modified CFC was lower in patients with an end point ($P<0.001$). Table 2 lists the mean [15O]H2O PET perfusion values according to the 5 modified CFC groups, whereas the baseline characteristics for each modified CFC group are presented in Table S1. In addition, Figure 2 depicts the integration of hMBF and CFR in a 2-dimensional, color-coded CFC graph, illustrating the distribution of events across the 5 modified CFC categories.

Prognostic Value of [15O]H2O PET Perfusion Imaging

Kaplan-Meier estimates stratified for the modified CFC categories indicated a decrease in event-free survival related to the 3 lowest CFC groups compared with normal flow (log-rank $P<0.001$ for all; Figure 3). Cox proportional hazards regression analysis adjusted for clinical characteristics and CAD risk factors showed that myocardial steal (hazard ratio [HR], 6.70 [95% CI, 3.21–13.99]; $P<0.001$), severely reduced CFC (HR, 2.35 [95% CI, 1.16–4.78]; $P=0.018$) and moderately reduced CFC (HR, 1.95 [95% CI, 1.11–3.41]; $P=0.020$) were independently associated with an increased risk of death/nonfatal MI (Table 3). In similar analyses, higher resting MBF (HR, 3.05 [95% CI, 1.68–5.54]; $P<0.001$, per unit increase), lower hMBF (HR, 0.68 [95% CI, 0.52–0.90]; $P=0.002$, per unit increase), and lower CFR (HR, 0.55 [95% CI, 0.42–0.71]; $P<0.001$, per unit increase) were independently associated with worse outcome. Resting MBF remained independently associated with adverse patient outcome after adjusting for the RPP, heart rate, systolic blood pressure, and pulse pressure (HR, 2.06 [95% CI, 1.08–3.90]; $P=0.027$). Figures S1 through S4 show the results of the adjusted Cox proportional hazards regression analyses including the individual PET perfusion metrics, clinical characteristics, and CAD risk factors.

Prognostic Value of the Combined Use of PET Perfusion Metrics

Table 3 shows the results of the multivariable Cox proportional hazards regression analysis used to explore the prognostic value of all [15O]H2O PET perfusion parameters after adjustment for clinical characteristics and CAD risk factors. Addition of the TPD, hMBF, and CFR to a model including clinical covariates resulted in a significant improvement in prognostic performance ($P<0.001$). The sequential addition of modified CFC to the perfusion model further improved risk stratification to predict the end point ($P=0.028$; Figure 4). Similarly, assessment of Harrell C statistic showed improved prognostic discrimination after addition of modified CFC to the multivariable analysis adjusted for clinical covariates and the combined use of [15O]H2O PET perfusion metrics (0.759 versus 0.755). In this combined perfusion model, modified CFC remained independently associated with the occurrence of the end point (overall $P=0.017$; Table 3; Table S2). Furthermore, we found that reduced modified CFC (n=573, comprising the lowest 3 CFC categories) was an independent predictor of adverse outcome in addition to reduced hyperemic MBF (HR, 3.02 [95% CI, 1.71–5.32]; $P<0.001$ versus HR, 1.16 [95% CI, 0.67–2.01]; $P=0.606$) and CFR (HR, 2.25 [95% CI, 1.34–3.75]; $P=0.002$ versus HR, 1.72 [95% CI, 1.03–2.87]; $P=0.038$), using a similar sample size of patients with the lowest regional perfusion values (Table S3). Early CABG was more often performed in patients with lower modified CFC (0.2% for normal flow, 3% for minimally reduced CFC, 8% for moderately reduced CFC, 16% for severely reduced

Table 1. Baseline Characteristics

	Overall study population (N=1300)	Patients without death/MI (n=1147)	Patients with death/MI (n=153)
Demographics			
Male sex	835 (64)	730 (64)	105 (69)
Age, y	61±10	61±10	65±10
BMI, kg/m^2	27±4	27±4	27±4
Cardiovascular risk factors			
Hypertension	667 (51)	577 (50)	90 (59)
Hypercholesterolemia	621 (48)	537 (47)	84 (55)
Diabetes	266 (21)	214 (19)	52 (34)
Smoking	352 (27)	307 (27)	45 (29)
Family history of CAD	640 (49)	570 (50)	70 (46)
Cardiac history			
Prior revascularization	405 (31)	353 (31)	52 (34)
Prior MI	272 (21)	236 (21)	36 (24)
LVEF, %			
≥55	998 (77)	888 (77)	110 (72)
45–54	169 (13)	152 (13)	17 (11)
30–44	98 (8)	79 (7)	19 (12)
<30	29 (2)	23 (2)	6 (4)
Medication			
Antiplatelet therapy	1059 (82)	925 (81)	134 (88)
β-blocker	843 (65)	732 (64)	111 (73)
ACE inhibitor/ARB	583 (45)	493 (43)	90 (59)
Statin	944 (73)	825 (72)	119 (78)
Calcium channel blockers	327 (25)	278 (24)	48 (31)
Symptoms			
Typical angina	449 (35)	388 (34)	61 (40)
Atypical angina	428 (33)	382 (33)	46 (30)
Nonspecific chest discomfort	403 (31)	360 (31)	43 (28)
Early revascularization			
PCI	446 (34)	384 (34)	62 (41)
CABG	67 (5)	60 (5)	7 (5)
Epicardial CAD			
No obstructive CAD	425 (33)	398 (35)	27 (18)
Single-vessel disease	454 (35)	396 (35)	58 (38)
Two-vessel disease	210 (16)	180 (16)	30 (20)
Three-vessel disease	99 (8)	79 (7)	20 (13)

Mean±SD/n (%). The number of obstructively diseased vessels was assessed using computed tomography coronary angiography or invasive coronary angiography. In 192 patients without prior CAD and no additional information available on ventricular function, the LVEF was considered normal (≥55%). In Turku, LVEF ≥50% was considered normal (n=79). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

CFC, and 26% for myocardial steal; Table S1). A significant interaction was observed between CFR and early revascularization with CABG (*P*=0.045; Table S2). Kaplan-Meier estimates stratified according to early revascularization with CABG or PCI among patients within the 3 lowest modified CFC groups showed improved event-free survival for patients undergoing early revascularization with CABG compared with PCI (log-rank *P*=0.046; Figure S5).

DISCUSSION

This study assessed the prognostic value of [15O]H_2O PET-derived CFC to predict the occurrence of death and nonfatal MI in patients with known or suspected CAD. Myocardial steal, severely reduced CFC, and moderately reduced CFC were associated with an increased risk of adverse events during a median follow-up of 5.5 years, independent of clinical characteristics and CAD risk factors. Similarly, increased resting MBF, decreased hMBF, and decreased CFR were associated with adverse outcome. In a prognostic model adjusted for the combined use of [15O]H_2O PET perfusion metrics, modified CFC remained an independent prognostic factor for events.

Prognostic Value of PET Perfusion Imaging

The prognostic value of quantitative PET myocardial perfusion imaging in patients evaluated for ischemic heart disease is well established.[5–8] Multiple studies consistently demonstrated that impaired stress perfusion and CFR are associated with an elevated risk of future adverse events, independent of clinical covariates. In accordance, we found that reduced hMBF and CFR were both associated with death and nonfatal MI after adjusting for clinical characteristics and cardiovascular risk factors. Interestingly, increased resting MBF also demonstrated independent prognostic value for the occurrence of events. Although this finding has not been described for [15O]H_2O PET perfusion imaging, the association between increased basal flow and worse prognosis has been previously reported.[7,23] van de Hoef et al[23] found increased mortality risk in patients with impaired coronary flow velocity reserve in unobstructed coronary arteries, which resulted from elevated basal flow rather than decreased hyperemic flow. Similarly, Gupta et al[7] documented an elevated annual cardiovascular mortality risk of 1.7% in patients with impaired CFR and preserved hMBF values, denoting increased resting MBF. The association between elevated resting flow and adverse patient outcome is likely attributed to risk factors such as hypertension, diabetes, and increased arterial stiffness related to hardened calcific arteries in older patients, resulting in an increase in resting LV workload and myocardial oxygen demand.[24–27] Still, in accordance with prior work by Gupta et al,[7] we found that increased resting MBF remained independently associated with the composite end point after adjusting for clinical risk

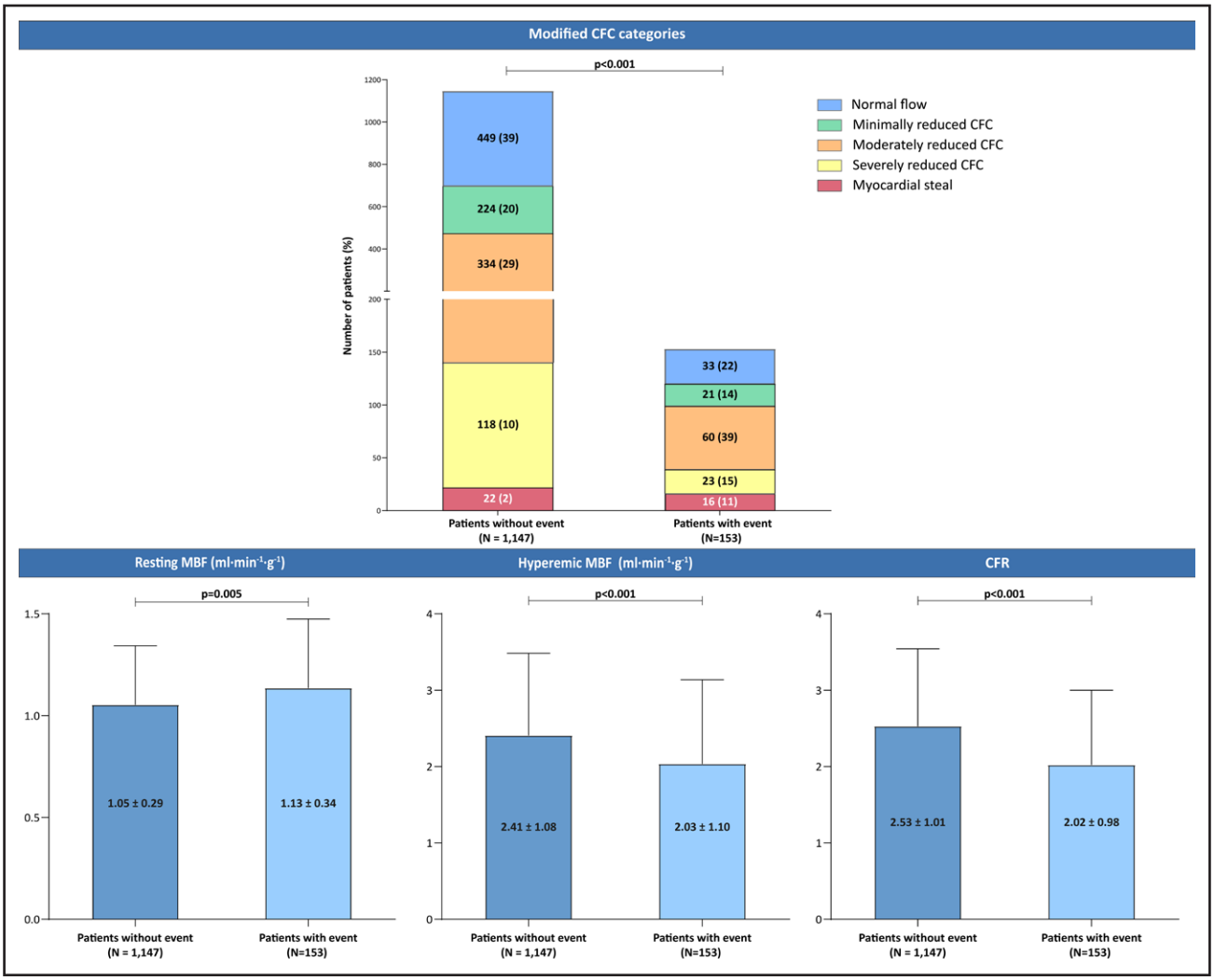

Figure 1. Perfusion indices stratified to patients with and without the end point.
This figure illustrates the number of patients stratified to the 5 modified coronary flow capacity (CFC) groups for the patients with and without an event during follow-up. A significant difference in modified CFC distribution was observed between the patients with vs without the composite end point. In addition, the bar graphs show that resting myocardial blood flow (MBF) was significantly higher, whereas hyperemic MBF and coronary flow reserve (CFR) were signficantly lower in patients with death/nonfatal myocardial infarction (MI) compared with patients without death/nonfatal MI.

factors and markers of increased myocardial workload.[7] This pathophysiological mechanism warrants further exploration, as this group of patients may benefit from intensified risk reduction therapy.

Association Between Modified CFC and Patient Outcome

Several studies compared hMBF and CFR to identify the most important prognostic predictor but reported discordant results.[6–8] Johnson and Gould[9] introduced CFC, arguing that integration of these physiological complementary perfusion metrics may augment the understanding of the impact of atherosclerotic burden and CAD severity on coronary vasodilator capacity by capturing all relevant coronary flow characteristics into 1 cross-modality parameter.[10,15] This is of even greater significance since the landmark ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) randomized over 5000 patients and found no evidence of superior outcome in patients with predefined moderate-to-severe ischemia undergoing coronary revascularization compared with optimal medical therapy, whereas Reynolds et al. demonstrated that the extent of atherosclerotic burden may be a stronger risk predictor compared with myocardial ischemia evaluation in a subsequent subanalysis.[28,29] These findings have recently been further extended in the POST-PCI trial (Pragmatic Trial Comparing Symptom-Oriented Versus Routine Stress Testing in High-Risk Patients Undergoing Percutaneous Coronary Intervention) illustrating that routine functional testing

Table 2. [15O]H2O PET Perfusion Measurements According to Modified CFC Categories

	[15O]H2O PET perfusion indices
Resting MBF (mL·min-1·g-1)	
Baseline CFC group (modified)	
Normal flow (n=482)	1.24±0.39
Minimally reduced CFC (n=245)	1.00±0.23
Moderately reduced CFC (n=394)	1.01±0.23
Severely reduced CFC (n=141)	1.09±0.28
Myocardial steal (n=38)	1.10±0.35
Hyperemic MBF (mL·min-1·g-1)	
Normal flow	3.40±0.96
Minimally reduced CFC	2.39±0.39
Moderately reduced CFC	1.67±0.33
Severely reduced CFC	1.10±0.22
Myocardial steal	0.89±0.30
CFR	
Normal flow	3.46±0.86
Minimally reduced CFC	2.44±0.36
Moderately reduced CFC	1.87±0.31
Severely reduced CFC	1.24±0.15
Myocardial steal	0.83±0.13

Mean±SD. CFC indicates coronary flow capacity; CFR, coronary flow reserve; MBF, myocardial blood flow; and PET, positron emission tomography.

after PCI did not reduce adverse outcome compared with standard care in a high-risk patient population.[30] The results of ISCHEMIA and POST-PCI require further confirmation with longer follow-up, yet have increased the interest in novel techniques to accurately quantify myocardial perfusion impairment to improve diagnostic accuracy and patient risk stratification.[31] In this context, the integration of quantitative hyperemic MBF and CFR into CFC may prove useful. The suggested incremental value of CFC is derived from the principle that either CFR or absolute hMBF values below established ischemic cutoffs do not necessarily indicate clinically pertinent pathophysiological impairment of the coronary vasodilator reserve. This was illustrated using several case examples representing different clinical scenarios of impaired or adequate vasodilator capacity in the setting of focal obstructive coronary stenosis, diffuse atherosclerotic disease, and microcirculatory dysfunction.[9,32] Subsequently, multiple studies confirmed the independent prognostic value of CFC using invasive and noninvasive flow quantification.[11,13,15] Consistent with the literature, our study shows increased risk for the occurrence of adverse events in patients with reduced modified CFC, independent of clinical characteristics, CAD risk factors, and obstructive CAD. This is in line with the concept that CAD and perfusion abnormalities are a continuum, illustrated by studies showing the association between nonobstructive CAD and impaired long-term cardiovascular prognosis.[33,34] The evidence of the continuity of coronary atherosclerotic plaque burden is corroborated by large coronary computed tomography angiography studies, including the randomized

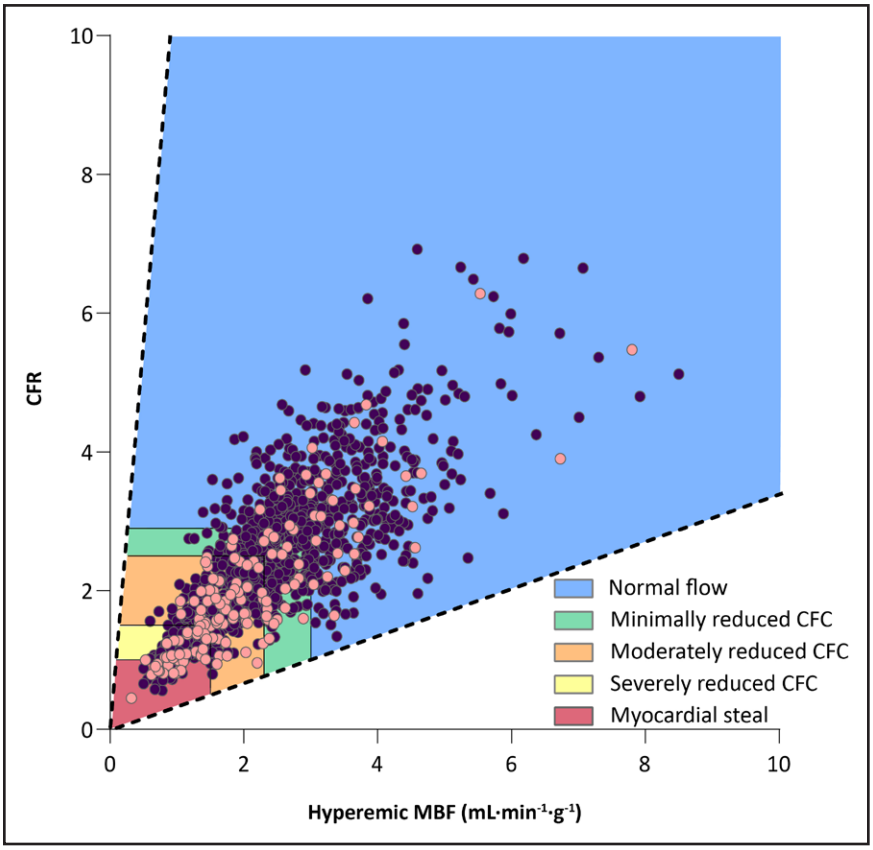

Figure 2. Coronary flow capacity (CFC) graph illustrating the distribution of events across the 5 modified CFC categories.
Hyperemic myocardial blood flow (MBF) and coronary flow reserve (CFR) plotted in a color-coded, 2-dimensional CFC graph capturing all relevant coronary flow characteristics. Events are stratified into 5 modified regional CFC categories: myocardial steal, severely reduced CFC, moderately reduced CFC, minimally reduced CFC, and normal flow. The vascular region with the lowest CFR was selected to plot the hyperemic MBF and CFR of the same region in this graph. The dots in the scatterplot represent patients with (red) and without (dark blue) an end point during follow-up.

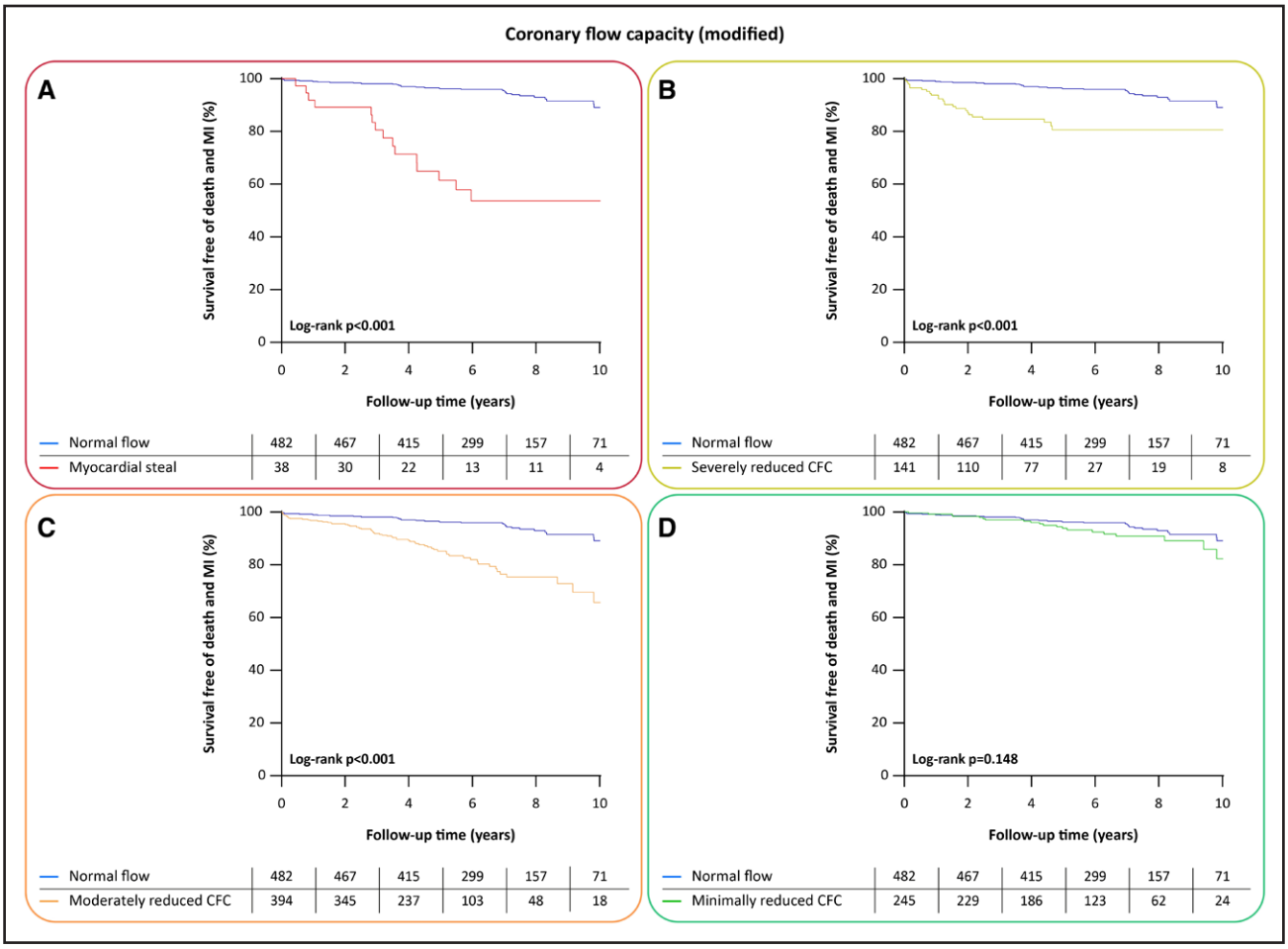

Figure 3. Kaplan-Meier curve stratified according to modified coronary flow capacity (CFC) categories.
Kaplan-Meier estimates illustrating event-free survival from death and nonfatal myocardial infarction (MI) stratified according to modified CFC classification. (**A**) Myocardial steal, (**B**) severely reduced CFC, and (**C**) moderately reduced CFC were associated with a decrease in event-free survival compared with normal flow (log-rank *P*<0.001 for all).

PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) and SCOT-HEART (The Scottish COmputed Tomography of the HEART) trials, showing the association between the extent of plaque and worse prognosis in patients with obstructive and nonobstructive coronary disease.[35–37] The present study provides evidence that modified CFC derived from [15O]H_2O PET perfusion imaging improves risk stratification in patients with known or suspected CAD.

Incremental Prognostic Value of Modified CFC

van de Hoef et al[11] adapted CFC for Doppler-based intracoronary flow measurements and reported a significant improvement in the prediction of adverse events for CFC over CFR alone. Furthermore, Hoshino et al[13] calculated CFC using thermodilution-derived flow metrics and demonstrated independent value of CFC in predicting major adverse cardiac events compared with CFR and fractional flow reserve. In agreement, we found that the addition of [15O]H_2O PET-derived CFC to a multivariable model including hMBF and CFR improved prognostic performance. These results reflect the outcomes of previous studies combining quantitative hMBF and CFR using binary thresholds, given that patients with concordantly impaired hMBF and CFR showed the highest risk of adverse events.[7,8,38] Importantly, in our study, the incremental prognostic value of modified CFC seems primarily driven by the identification of patients with myocardial steal, the lowest CFC category. This is congruent with previous observations reported by Gould et al,[15,16] who demonstrated that the identification of patients with the worst regional CFC could improve risk stratification in addition to the use of stress perfusion and CFR alone, pointing out that the risk of both individual metrics might be of an additive nature in these patients.

Limitations

Several limitations need to be addressed. First, this was an observational study in which modified CFC was retrospectively collected. Second, the extended enrollment

Table 3. Prognostic Value of [15O]H2O PET-Derived Perfusion Metrics

	Adjusted for clinical covariates*		Adjusted for clinical covariates and the combined use of PET perfusion metrics†	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CFC (modified)		<0.001		0.017
Minimally reduced CFC	0.86 (0.44–1.68)	0.654	0.69 (0.32–1.52)	0.362
Moderately reduced CFC	1.95 (1.11–3.41)	0.020	1.32 (0.61–2.84)	0.480
Severely reduced CFC	2.35 1.16–4.78)	0.018	1.18 (0.50–2.80)	0.706
Myocardial steal	6.70 (3.21–13.99)	<0.001	3.26 (1.40–7.62)	0.006
[15O]H2O PET perfusion metrics				
Resting MBF (mL·min-1·g-1)	3.05 (1.68–5.54)	<0.001	…	…
Hyperemic MBF (mL·min-1·g-1)	0.68 (0.52–0.90)	0.007	1.43 (0.89–2.28)	0.139
CFR	0.55 (0.42–0.71)	<0.001	0.83 (0.47–1.48)	0.533

Prognostic value of [15O]H2O PET perfusion metrics to predict the occurrence of death and nonfatal MI. BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CFC, coronary flow capacity; CFR, coronary flow reserve; HR, hazard ratio; LVEF, left ventricular ejection fraction; MBF, myocardial blood flow; MI, myocardial infarction; and PET, positron emission tomography.

*Clinical covariates in the Cox proportional hazards model include age, sex, BMI, diabetes, hypertension, hypercholesterolemia, family history of CAD, prior revascularization, prior MI, early revascularization with CABG, early revascularization with PCI, the extent of obstructive epicardial CAD and LVEF. Perfusion metrics were separately included in the model (Figures S1 through S4 show all included variables). For calculation of the HRs of the modified CFC groups, normal flow was used as a reference. For the other [15O]H2O PET perfusion metrics, HRs are based on a unity increase.

†Multivariable outcome model showing the prognostic value of [15O]H2O PET perfusion metrics to predict the occurrence of death and nonfatal MI adjusted for clinical covariates and the combined use of [15O]H2O PET perfusion indices. For calculation of the HRs of the modified CFC groups, the impact of each CFC category was compared with the average effect of subsequent categories. For the other [15O]H2O PET perfusion metrics, HRs are based on a unity increase. Table S2 presents all included covariates.

period may have resulted in differences with respect to cardiovascular risk management and risk reduction therapy over time. Third, in contrast to other nuclear imaging tracers such as ^{82}Rb, $^{13}NH_3$, and ^{99m}Tc, $[^{15}O]H_2O$ is freely diffusible and extracted linear to perfusion from the arterial blood pool by the myocardium.[39] As the tracer does

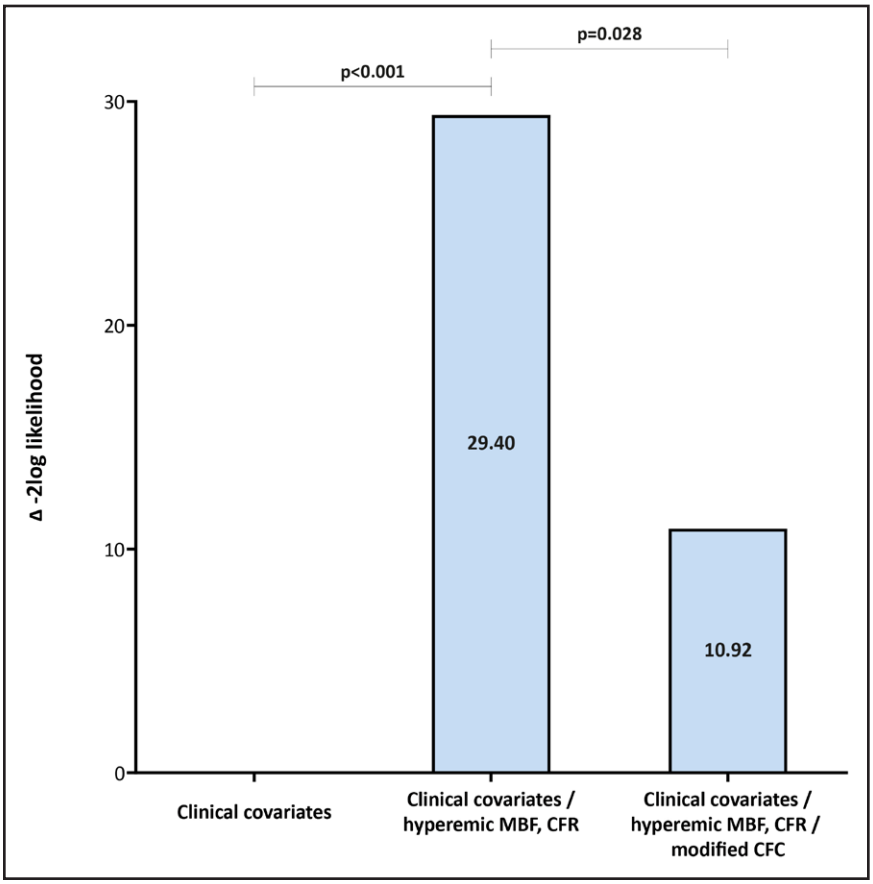

Figure 4. Incremental prognostic value of modified coronary flow capacity (CFC).
Incremental prognostic value of [15O]H2O positron emission tomography perfusion metrics for the occurrence of the composite endpoint in addition to clinical covariates (age, gender, BMI, diabetes, hypertension, hypercholesterolemia, family history of coronary artery disease (CAD), prior revascularization, prior myocardial infarction, early revascularization with coronary artery bypass grafting, early revascularization with percutaneous coronary intervention, the extent of obstructive epicardial CAD and left ventricular ejection fraction). Risk stratification improved after addition of total perfusion deficit, hyperemic myocardial blood flow (MBF), coronary flow reserve (CFR) and subsequently modified CFC to the outcome model.

not accumulate within the myocardium, LV function, and volumes are not routinely obtained using [15O]H_2O PET perfusion imaging.[39] Last, the present study calculated regional [15O]H_2O PET-derived CFC by using established thresholds that have been designed according to the original CFC concept but that requires further verification.[12] Furthermore, the present study used the lowest regional myocardial perfusion value to identify vulnerable patients for future adverse events, which has the advantage of facilitated interpretation and reproducibility of study findings.[8,14] However, this strategy has the inherent limitation that not all regional perfusion values are utilized to predict the occurrence of the composite end point. Johnson and Gould[9] used a more sophisticated, granular approach and calculated CFC for a total of 1344 pixels of the left ventricle, allowing for a more detailed measure of the regional size-severity pathophysiological classification of CAD.

Conclusions

CFC captures all relevant coronary flow characteristics and has been proposed to enhance the understanding of the pathophysiological impact of coronary atherosclerotic disease on vasodilator capacity. In the present study, [15O]H_2O PET-derived resting MBF, hMBF, CFR, and CFC were associated with the occurrence of death and nonfatal MI, independent of clinical characteristics, and cardiovascular risk factors. After adjusting for clinical characteristics and the combined use of [15O]H_2O PET perfusion metrics, modified CFC remained independently associated with adverse patient outcome.

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Supplemental Material

Figures S1–S5
Tables S1–S3

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