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Coronary Flow Reserve and Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis

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ABSTRACT

BACKGROUND The prognostic impact of microvascular status in patients with high fractional flow reserve (FFR) is not clear.

OBJECTIVES The goal of this study was to investigate the implications of coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) in patients who underwent FFR measurement.

METHODS Patients with high FFR (>0.80) were grouped according to CFR (≤2) and IMR (≥23 U) levels: group A, high CFR with low IMR; group B, high CFR with high IMR; group C, low CFR with low IMR; and group D, low CFR with high IMR. Patient-oriented composite outcome (POCO) of any death, myocardial infarction, and revascularization was assessed. The median follow-up was 658 days (interquartile range: 503.8 to 1,139.3 days).

RESULTS A total of 313 patients (663 vessels) were assessed with FFR, CFR, and IMR. Correlation ($r = 0.201$; $p < 0.001$) and categorical agreement (kappa value = 0.178; $p < 0.001$) between FFR and CFR were modest. Low CFR was associated with higher POCO than high CFR ($p = 0.034$). There were no significant differences in clinical and angiographic characteristics among groups. Patients with high IMR with low CFR had the highest POCO ($p = 0.002$). Overt microvascular disease ($p = 0.008$), multivessel disease ($p = 0.033$), and diabetes mellitus ($p = 0.033$) were independent predictors of POCO. Inclusion of a physiological index significantly improved the discriminant function of a predictive model (relative integrated discrimination improvement 0.467 [$p = 0.037$]; category-free net reclassification index 0.648 [$p = 0.007$]).

CONCLUSIONS CFR and IMR improved the risk stratification of patients with high FFR. Low CFR with high IMR was associated with poor prognosis. (Clinical, Physiological and Prognostic Implication of Microvascular Status; NCT02186093) (J Am Coll Cardiol 2016;67:1158–69) © 2016 by the American College of Cardiology Foundation.

Epicardial coronary artery stenosis is not a prerequisite for ischemic heart disease. Although it has not been established that microvascular coronary disease is independent of macrovascular disease (1–3), clinical studies show that microvascular disease is an independent predictor of poor clinical outcomes in patients with acute myocardial infarction (MI) (4,5).

The pressure-derived fractional flow reserve (FFR) index is a standard method for evaluating the functional significance of epicardial coronary artery stenosis, and clinical outcomes of FFR-guided

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percutaneous coronary intervention (PCI) are better than those of angiography-guided PCI or medical treatment (6–8). However, clinical events occur even in patients with high FFR (6). Coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) may provide additional diagnostic and prognostic insights for patients with ischemic heart disease, but the clinical implications of CFR and IMR measurements in patients who have undergone FFR measurement remain unclear.

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We investigated clinical, angiographic, and hemodynamic characteristics of patients with high FFR and evaluate the prognostic implications of abnormal CFR and IMR in these patients.

METHODS

PATIENT POPULATION. Between April 2009 and September 2013, consecutive patients who underwent clinically indicated invasive coronary angiography and had FFR, CFR, and IMR measurements for ≥1 coronary artery with intermediate stenosis (40% to 70% by visual assessment) were enrolled from 4 Korean university hospitals (Seoul National University Hospital, Inje University Ilsan Paik Hospital, Keimyung University Dongsan Medical Centre, and Ulsan University Hospital). FFR was measured to identify functionally significant stenosis in accordance with current guidelines (9,10). CFR and IMR were measured as part of routine clinical practice or for research purposes. Patients with hemodynamic instability, left ventricular dysfunction, elevated cardiac enzyme levels, or evidence of acute MI were excluded. All patients gave informed consent, and institutional review board approval was obtained per current regulations. The study protocol was in accordance with the Declaration of Helsinki.

CORONARY ANGIOGRAPHY AND QUANTITATIVE ANALYSIS. Coronary angiography was performed by using standard techniques. Angiographic views were obtained after administration of intracoronary nitrate (100 or 200 μg). All angiograms and coronary physiological data were analyzed at a core laboratory in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Percent diameter stenosis, minimum lumen diameter, reference vessel size, and lesion length were measured. Gensini and SYNTAX scores were measured to quantify patients' macrovascular disease burden (11).

CORONARY PHYSIOLOGICAL MEASUREMENTS. All measurements were obtained after diagnostic angiography (12). When PCI was performed with FFR guidance, pre-interventional physiological indices were used for analysis. Measurement protocols for FFR, CFR, and IMR were standardized among the 4 participating centers. A 5- to 7-F guide catheter without side holes was used to engage the coronary artery, and a pressure temperature sensor-tipped guidewire (St. Jude Medical, St. Paul, Minnesota) was introduced. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200 μg) was administered before each measurement. To derive resting mean transit time (T_{mn}), a thermodilution curve was obtained by using 3 injections of 4 ml of room temperature saline. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg/min) via a peripheral or central vein. Hyperemic proximal aortic pressure (Pa), distal arterial pressure (Pd), and hyperemic T_{mn} were measured during sustained hyperemia. The guidewire was then pulled back to the guide catheter, and the presence of pressure drift was checked. FFR was calculated as the lowest average of 3 consecutive beats during stable hyperemia. CFR was calculated by resting T_{mn}/hyperemic T_{mn}. The uncorrected IMR was calculated by Pd × T_{mn} during hyperemia. All IMR values were corrected by using Yong's formula (corrected IMR [IMR_{corr}] = Pa × T_{mn} × ([1.35 × Pd/Pa] − 0.32) (12).

Reproducibility testing for IMR measurements was performed at the beginning of the registry after standardization of the procedure. IMR measurements were repeated after a 5-min interval in each of 60 patients (15 consecutive patients from each center). Both measurements showed significant correlation ($r = 0.957$; $p < 0.001$), and the intraclass correlation coefficient was 0.991 (95% confidence interval [CI]: 0.984 to 0.994), suggesting excellent reproducibility for the IMR measurement in the study cohort (Online Figure 1).

CUTOFF VALUES AND CLASSIFICATION OF PATIENTS. Cutoff values were FFR ≤0.80 (low FFR) and CFR ≤2 (low CFR), as previously described (3,6). High IMR was defined as values ≥75th percentile of IMR_{corr} in the study population. For our study, high IMR was defined as IMR_{corr} ≥23 U. Patients with high FFR (>0.80) were grouped according to CFR and IMR values as follows: high CFR with low IMR (group A), high CFR with high IMR (group B), low CFR

ABBREVIATIONS AND ACRONYMS

CFR = coronary flow reserve
FFR = fractional flow reserve
HR = hazard ratio
IMR = index of microcirculatory resistance
IMR_{corr} = index of microcirculatory resistance corrected according to Yong's formula
IQR = interquartile range
MI = myocardial infarction
Pa = proximal aortic pressure
PCI = percutaneous coronary intervention
Pd = distal arterial pressure
POCO = patient-oriented composite outcome
T_{mn} = mean transit time

with low IMR (group C), and low CFR with high IMR (group D).

PATIENT FOLLOW-UP. Clinical data were obtained at outpatient clinic visits or by telephone and/or medical questionnaires. Medical records were reviewed for clinical events and adjudicated by an external clinical event committee. The vital status of all patients was crosschecked by using the Korean health system's unique identification numbers, which allowed the occurrence of mortality to be confirmed even in patients who were lost to follow-up. Primary outcome was the patient-oriented composite outcome (POCO) of all-cause mortality, any MI, and any revascularization. Secondary outcomes were individual components of POCO. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiac unless an undisputable noncardiac cause was present. Fourteen patients (4.2%) were lost to follow-up; the vital status of these patients, however, was assessed as previously described. The median duration of follow-up was 658.0 days (interquartile range [IQR]: 503.8 to 1,139.3 days).

STATISTICAL ANALYSIS. Categorical variables are presented as numbers and relative frequencies (percentages); continuous variables are presented either as mean ± SD or median with IQR according to their distributions, which were checked by using the Kolmogorov-Smirnov and Levene tests. Data were analyzed on a per-patient basis for clinical characteristics and outcomes and on a per-vessel basis for other factors. Of the 424 patients, 111 (26.2%) showed discordant classification in 4 quadrant models according to either FFR and CFR or CFR and IMR. Patients with >1 interrogated vessel and different quadrant model classifications were excluded from the per-patient analysis, including the comparison of clinical outcomes. Kaplan-Meier analysis was used to calculate the cumulative incidence of primary and secondary clinical outcomes, and the log-rank test or the Breslow test was used to compare between-group differences. In addition, Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs to compare between-group differences. Firth-penalized Cox proportional hazards regression was used for the separation problem (13,14).

For per-vessel analyses, a generalized estimating equation was used to adjust intrasubject variability among vessels from the same patient. Estimated means and 95% CIs were presented as summary statistics. A generalized estimating equation procedure with pairwise comparison was used to compare per-vessel variables in the 4-quadrant classification. No post hoc adjustment was performed. Linear regression analysis was used to estimate the correlation coefficient (Pearson or Spearman, according to the normality of the variables) between quantitative variables. Per-vessel comparisons of cumulative incidence of POCO in the high-FFR population with inclusion of excluded patients and lesions that showed discordant classification among multiple interrogated vessels were performed to check the robustness of the results from the per-patient analysis. For this analysis, except for death, the clinical outcomes (MI and revascularization) were separately coded as vessel-specific outcomes and compared among the 4 groups on a per-vessel basis and adjusted for patient effect by using the marginal Cox proportional hazards regression model (15). For the reproducibility testing of IMR measurements, the difference between the 2 IMR values was analyzed with the Wilcoxon signed-rank test and the Spearman correlation coefficient. The intraclass correlation coefficient, reflecting relative intraobserver variability, was used to assess agreement between the 2 IMR values. A Cox proportional hazards regression model was used to identify independent predictors of POCO among patients with high FFR. The improvement in discriminant function of the model with or without incorporation of the physiological index was compared by using the category-free net reclassification index and integrated discrimination improvement. The covariates used in multivariate analysis were selected with the criterion of $p < 0.1$. SPSS version 18.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and R programming language version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

RESULTS

CHARACTERISTICS OF PATIENTS AND TARGET VESSELS. Table 1 displays the clinical, angiographic, and physiological characteristics of the study patients. Risk factors were similar between patients in the high- and low-FFR groups, except for a higher proportion of men and hypercholesterolemia among patients with low FFR. Most patients (84.2%) presented in stable condition.

Anatomical severity of epicardial coronary stenoses was generally intermediate, with a mean stenosis diameter of 41.0 ± 17.2%. Mean FFR was 0.85 ± 0.09; FFR was ≤0.8 in 147 vessels (22.2%). Mean CFR was

TABLE 1 General Characteristics of Study Population and Target Vessels

	Total	High FFR	Low FFR	p Value	High FFR		
					High CFR	Low CFR	p Value
Per-patient analysis	313	230/313 (73.5)	83/313 (26.5)		183/230 (79.6)	47/230 (20.4)	
General characteristics							
Age, yrs	61.2 ± 9.7	61.8 ± 9.9	63.3 ± 9.0	0.216	61.0 ± 9.8	64.6 ± 9.7	0.030
Male	206 (65.8)	140 (60.9)	66 (79.5)	0.002	112 (61.2)	28 (59.6)	0.838
BMI, kg/m^2	24.7 ± 3.0	24.6 ± 2.9	24.9 ± 3.3	0.383	24.6 ± 3.0	24.8 ± 2.7	0.627
Clinical presentation				0.025			0.743
Stable angina	152 (48.6)	103 (44.8)	49 (59.0)		83 (45.4)	20 (42.6)	
Unstable angina	49 (15.7)	37 (16.1)	12 (14.5)		31 (16.9)	6 (12.8)	
Atypical chest pain	69 (22.0)	60 (26.1)	9 (10.8)		45 (24.6)	15 (31.9)	
Silent ischemia	43 (13.7)	30 (13.0)	13 (15.7)		24 (13.1)	6 (12.8)	
Cardiovascular risk factors							
Hypertension	189 (60.4)	133 (57.8)	56 (67.5)	0.124	105 (57.4)	28 (59.6)	0.786
Diabetes mellitus	90 (28.8)	67 (29.1)	23 (27.7)	0.807	54 (29.5)	13 (27.7)	0.804
Hypercholesterolemia	195 (62.3)	135 (58.7)	60 (72.3)	0.028	111 (60.7)	24 (51.1)	0.234
Current smoker	50 (16.0)	36 (15.7)	14 (16.9)	0.796	31 (16.9)	5 (10.6)	0.289
Obesity (BMI >25 kg/m^2)	135 (43.1)	98 (42.6)	37 (44.6)	0.756	80 (43.7)	18 (38.3)	0.503
Family history	50 (16.0)	34 (14.8)	16 (19.3)	0.338	30 (16.4)	4 (8.5)	0.174
Previous MI	12 (3.8)	8 (3.5)	4 (4.8)	0.585	8 (4.4)	0	0.145
Previous PCI	86 (27.5)	58 (25.2)	28 (33.7)	0.136	47 (25.7)	11 (23.4)	0.748
Multivessel disease	141 (45.0)	86 (37.4)	55 (66.3)	<0.001	69 (37.7)	17 (36.2)	0.846
SYNTAX score	7.0 (0.0–14.5)	5.0 (0.0–11.0)	14.0 (9.0–20.0)	<0.001	5.0 (0.0–11.0)	6.0 (0.0–12.0)	0.905
Gensini score	17.0 (8.5–33.0)	12.3 (6.5–25.5)	36.0 (19.0–52.0)	<0.001	12.0 (6.5–24.5)	16.5 (8.0–28.5)	0.341
Per-vessel analysis	663	516/663 (77.8)	147/663 (22.2)		382/516 (74.0)	134/516 (26.0)	
Measured vessel location				<0.001			0.142
Left anterior descending artery	378 (57.0)	255 (49.4)	123 (83.7)		187 (49.0)	68 (50.7)	
Left circumflex artery	137 (20.7)	127 (24.6)	10 (6.8)		88 (23.0)	39 (29.1)	
Right coronary artery	148 (22.3)	134 (26.0)	14 (9.5)		107 (28.0)	27 (20.1)	
Quantitative coronary angiography							
Reference diameter, mm	2.99 ± 0.61	3.04 (3.00–3.10)	2.81 (2.72–2.90)	<0.001	3.06 (3.00–3.13)	3.00 (2.89–3.07)	0.106
Diameter stenosis, %	41.0 ± 17.2	36.8 (32.4–38.2)	55.6 (53.0–58.1)	<0.001	36.7 (35.1–38.3)	37.1 (34.5–39.6)	0.790
Lesion length, mm	11.8 ± 7.9	10.9 (10.2–11.5)	15.2 (13.5–16.8)	<0.001	10.9 (10.2–11.6)	10.8 (9.6–11.9)	0.849
Coronary physiological parameters							
FFR	0.85 ± 0.93*	0.91 (0.90–0.91)	0.73 (0.72–0.74)	<0.001	0.91 (0.90–0.91)	0.91 (0.90–0.92)	0.656
CFR	2.81 ± 1.02†	2.88 (2.78–2.97)	2.48 (2.32–2.64)	<0.001	3.34 (3.25–3.42)	1.57 (1.52–1.61)	<0.001
IMR, U	16.0 (12.5–22.4)	20.2 (19.3–21.1)	18.9 (17.2–20.6)	0.200	19.9 (19.0–20.9)	21.0 (19.0–23.0)	0.347
IMR$_{corr}$, U	15.7 (12.0–21.6)	20.5 (19.5–21.5)	17.2 (15.7–18.8)	<0.001	20.3 (19.1–21.4)	21.1 (19.1–23.1)	0.452

Values are n, N/n (%), mean ± SD, n (%), median (interquartile ranges), or estimated mean (95% confidence interval) (per-vessel analysis). Generalized estimating equation model or maximum likelihood chi-square tests were used for overall and between-group comparisons in the per-vessel analysis. *FFR—median: 0.86 (interquartile range: 0.80 to 0.91). †CFR—median: 2.69 (interquartile range: 2.0 to 3.54).

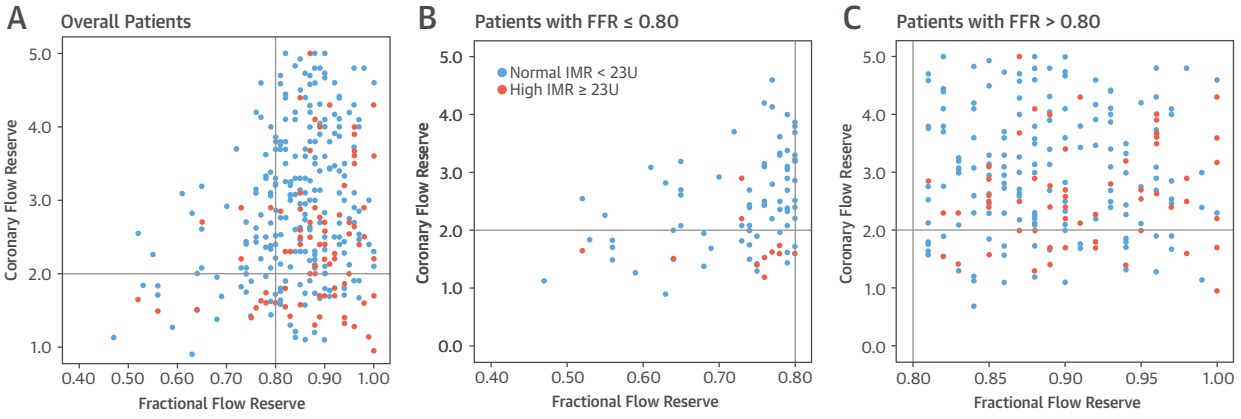
BMI = body mass index; CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microcirculatory resistance; IMR$_{corr}$ = corrected index of microcirculatory resistance with Yong's formula (IMR$_{corr}$ = Pa × T$_{mn}$ × ([1.35 × Pd/Pa] − 0.32), where Pa indicates proximal aortic pressure, T$_{mn}$ indicates mean transit time, and Pd indicates distal arterial pressure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

2.81 ± 1.02 (median: 2.69; IQR: 2.0 to 3.54); CFR was ≤2 in 190 vessels (28.7%). Median unadjusted IMR was 16.0 U (IQR: 12.5 to 22.4 U) and median IMR$_{corr}$ was 15.7 U (IQR: 12.0 to 21.6 U). Compared with the high-FFR group, the low-FFR group had more severe stenosis, higher SYNTAX and Gensini scores, and lower CFR. However, IMR$_{corr}$ was higher in the high-FFR group, compared with the low-FFR groups.

Figure 1 shows the population distribution according to FFR and CFR cutoff values, overall and in patients with low and high FFR. There was a modest correlation between FFR and CFR (r = 0.201; $p < 0.001$). Categorical agreement of FFR and CFR was low (kappa = 0.178; $p < 0.001$), and 98 patients (31.3%) reported discordant results. The distributions of IMR$_{corr}$ values were different across each quadrant classification, and IMR$_{corr}$ was highest in patients with high FFR and low CFR (mean: 21.1; 95% CI: 19.2 to 23.2 U; $p < 0.001$).

HIGH AND LOW CFR IN PATIENTS WITH HIGH FFR. There was no difference in clinical characteristics between high-FFR patients with high CFR and

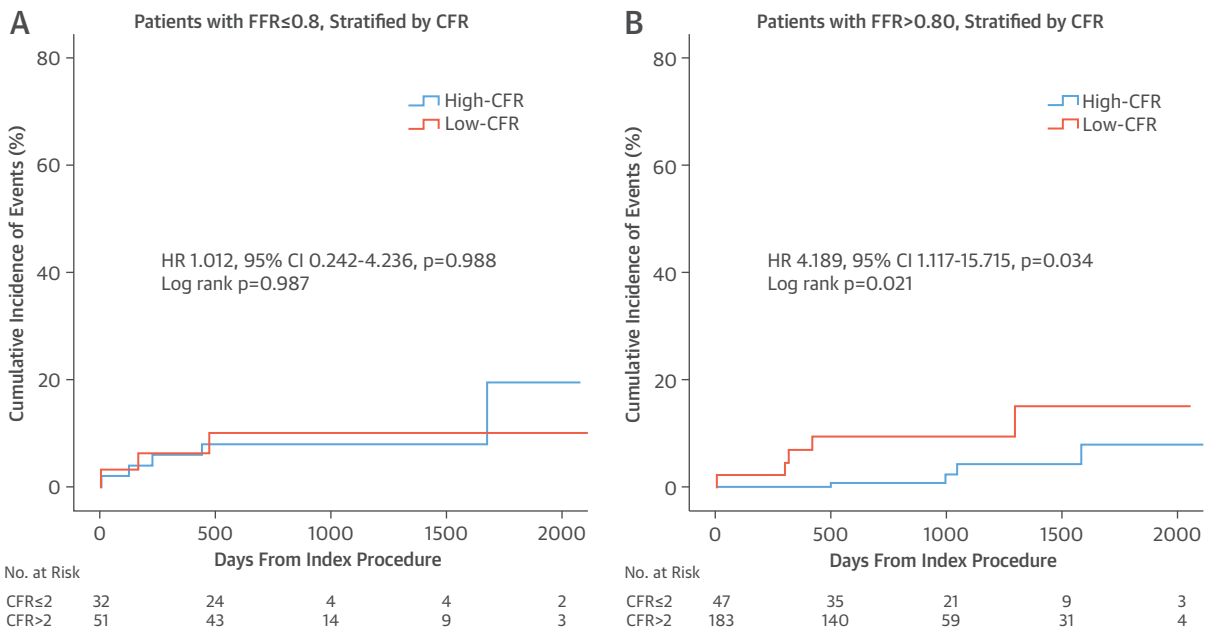
FIGURE 1 Distribution of Patients According to FFR and CFR



The **red dots** represent patients with a high index of microcirculatory resistance (IMR) (≥23 U). All IMR values were adjusted with Yong's formula ($IMR_{corr} = Pa \times T_{mn} \times ([1.35 \times Pd/Pa] - 0.32)$, where Pa indicates proximal aortic pressure, T_{mn} indicates mean transit time, and Pd indicates distal arterial pressure. **(A)** Overall population, **(B)** patients with fractional flow reserve (FFR) ≤0.80, and **(C)** patients with FFR >0.80. CFR = coronary flow reserve.

low CFR, other than age. Angiographic lesion severity did not differ between the 2 groups (mean percent diameter stenosis 36.7% vs. 37.1% for high and low CFR, respectively, p = 0.790; mean lesion length 10.9 mm vs. 10.8 mm, p = 0.849; median Gensini score 12.0 vs. 16.5, p = 0.341; and median SYNTAX score 5.0 vs. 6.0, p = 0.938). FFR values were similar between patients in the high- and low-CFR groups (0.91 [IQR: 0.90 to 0.92] vs. 0.91 [IQR: 0.90 to 0.91], p = 0.656) (Table 1). Among patients with high FFR,

FIGURE 2 Impact of CFR on Cumulative Incidence of POCO



(A) Cumulative incidence of patient-oriented composite outcome (POCO) in patients with low FFR (≤0.80) according to CFR values. **(B)** Cumulative incidence of POCO in patients with high FFR (>0.80) according to CFR values. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

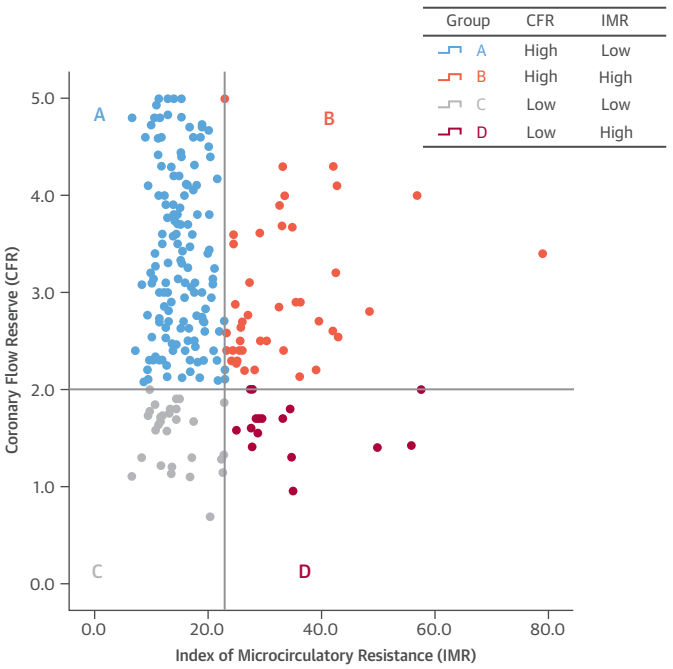
those with high IMR had a greater body mass index, a lower proportion of multivessel disease, and lower SYNTAX and Gensini scores than did those with low IMR. Other cardiovascular risk factors and severity of epicardial lesion were similar between the groups (Online Table 1).

Figure 2 displays the clinical outcomes among patients with high or low FFR according to CFR. In patients with low FFR, POCO did not differ between the high- and low-CFR groups (HR: 1.012; 95% CI: 0.242 to 4.236; p = 0.988; log-rank p = 0.987). Conversely, in patients with high FFR, those with low CFR had a significantly higher POCO rate compared with those with high CFR (HR: 4.189; 95% CI: 1.117 to 15.715; p = 0.034; log-rank p = 0.021). The difference in POCO rate was driven mainly by a higher revascularization rate in the low-CFR group (Online Table 2).

CLINICAL OUTCOMES DIVIDED ACCORDING TO CFR AND IMR. To distinguish among heterogeneous populations in patients with high FFR, patients were divided into 4 groups according to CFR and IMR_{corr} values (**Figure 3**, **Table 2**). Of patients with high FFR, 61.3% had normal CFR and IMR_{corr} (group A), 18.3% had high CFR despite high IMR_{corr} (group B), 13.5% had low CFR despite low IMR_{corr} (group C), and 7.0% had low CFR and high IMR (group D). The distribution of cardiovascular risk factors and angiographic lesion severity was similar among all groups, and there was no difference in FFR values. IMR_{corr} was highest in group D, and CFR was lowest in group C. In group B, CFR was preserved despite high IMR_{corr} because the resting T_{mn} was higher than in the other groups (1.20 s [95% CI: 1.10 to 1.31] vs. 0.60 s [95% CI: 0.57 to 0.63]; p < 0.001). In group C, low CFR was mainly due to a resting T_{mn} lower than in the other groups (0.31 s [95% CI: 0.29 to 0.34] vs. 0.80 s [95% CI: 0.76 to 0.85]; p < 0.001).

The cumulative incidences of POCO were 9.5%, 0%, 7.0%, and 27.9% for groups A, B, C, and D, respectively (Breslow p value for overall comparison = 0.002). Group D had a significantly higher risk of POCO than group A (HR: 5.623; 95% CI: 1.234 to 25.620; p = 0.026) (**Figure 4**). Because group B had no POCO events, the Firth-penalized Cox regression model was used to calculate the HR of group B, compared with group A, and produced the same result as the original analysis (Online Figure 2). The primary factor influencing the higher POCO rate in group D was the high rate of all-cause death or MI as well as any revascularization (**Table 3**). The revascularization event was due to the progression of atherosclerosis, which was documented by both angiography and FFR.

FIGURE 3 4 Patterns of Microvascular Status According to CFR and IMR Among Patients With High FFR



To differentiate potentially heterogeneous populations in patients with high FFR, 4 patterns of microvascular status were classified according to CFR and IMR_{corr} values. Abbreviations as in **Figure 1**.

A multivariate model without a physiological index found that multivessel disease (HR: 3.254; 95% CI: 1.082 to 9.787; p = 0.033) and diabetes mellitus (HR: 2.828; 95% CI: 1.088 to 7.349; p = 0.033) were independent predictors of POCO (**Table 4**). When low CFR and high IMR were added to the model, the presence of low CFR with high IMR_{corr} was the most powerful independent predictor for POCO in patients with high FFR (HR: 4.914; 95% CI: 1.541 to 15.663; p = 0.007). A model using a physiological index revealed significantly improved discriminant function (relative integrated discrimination improvement 0.467 [p = 0.037]; category-free net reclassification index 0.648 [p = 0.007]). Sensitivity analysis excluding 5 patients who underwent PCI despite a high FFR altered none of the aforementioned results. In addition, per-vessel analysis with inclusion of patients and lesions that showed discordant classification among multiple interrogated vessels also revealed a significantly higher risk of POCO in group D compared with group A (HR: 4.929; 95% CI: 1.458 to 16.65; p = 0.010), consistent with the results from the per-patient analysis.

TABLE 2 Angiographic Characteristics and Physiological Differences in Patients With High FFR, According to Microvascular Function

	Group A (CFR >2 and IMR <23 U)	Group B (CFR >2 and IMR ≥23 U)	Group C (CFR ≤2 and IMR <23 U)	Group D (CFR ≤2 and IMR ≥23 U)	p Value
Per-patient analysis (n = 230)	141 (61.3)	42 (18.3)	31 (13.5)	16 (7.0)	
Age, yrs	60.2 ± 9.9	63.9 ± 7.1	65.6 ± 9.7	62.6 ± 9.9	0.017
Male	90 (63.8)	22 (52.4)	18 (58.1)	10 (62.5)	0.591
BMI, kg/m^2	24.3 ± 2.9	25.4 ± 3.1	24.6 ± 2.5	25.2 ± 3.3	0.161
Hypertension	78 (55.3)	27 (64.3)	18 (58.1)	10 (62.5)	0.747
Diabetes mellitus	44 (31.2)	10 (23.8)	8 (25.8)	5 (31.3)	0.784
Hypercholesterolemia	88 (62.4)	23 (54.8)	17 (54.8)	7 (43.8)	0.434
Current smoker	25 (17.7)	6 (14.3)	3 (9.7)	2 (12.5)	0.687
Obesity (BMI >25 kg/m^2)	57 (40.4)	23 (54.8)	11 (35.5)	7 (43.8)	0.326
Family history of CAD	23 (16.3)	7 (16.7)	3 (9.7)	1 (6.3)	0.548
Previous MI	6 (4.3)	2 (4.8)	0	0	0.541
Previous PCI	40 (28.4)	7 (16.7)	9 (29.0)	2 (12.5)	0.263
Multivessel disease	57 (40.4)	12 (28.6)	14 (45.2)	3 (18.8)	0.163
SYNTAX score	6.0 (0.0–13.0)*	2.0 (0.0–7.0)†	8.0 (0.0–16.0)	0.0 (0.0–7.8)	0.014
Gensini score	12.0 (6.5–25.5)	11.3 (5.0–18.8)	20.5 (9.0–37.0)	9.3 (4.8–19.5)	0.114
Per-vessel analysis (n = 516)	283 (54.8)	99 (19.2)	94 (18.2)	40 (7.8)	
Angiographic characteristics					
Reference diameter	3.02 (2.95–3.09)	3.18 (3.03–3.34)‡	2.91 (2.80–3.01)*	3.12 (2.92–3.32)	0.017
Diameter stenosis, %	36.8 (34.9–38.6)	36.4 (33.4–39.4)	38.7 (35.6–41.9)	33.2 (28.3–38.1)	0.343
Lesion length, mm	10.9 (10.1–11.8)	10.7 (9.4–12.4)	10.9 (9.4–12.4)	10.4 (8.6–12.2)	0.961
Coronary physiological parameters					
FFR	0.91 (0.90–0.91)	0.92 (0.91–0.93)	0.90 (0.89–0.91)	0.92 (0.90–0.94)	0.150
CFR	3.38 (3.28–3.48)‡,§	3.21 (3.06–3.36)‡,§	1.56 (1.50–1.62)*,†	1.59 (1.50–1.67)*,†	<0.001
Resting T_{mn}, s	0.68 (0.65–0.72)*,‡	1.20 (1.10–1.31)†,‡,§	0.31 (0.29–0.34)*,†,§	0.67 (0.61–0.74)‡,§	<0.001
Hyperemic T_{mn}, s	0.20 (0.20–0.21)*,§	0.39 (0.37–0.42)†,‡	0.20 (0.19–0.22)*,§	0.42 (0.37–0.47)†,‡	<0.001
IMR_{corr}, U	15.5 (15.1–16.0)*,‡,§	33.5 (31.2–35.9)†,‡	15.5 (14.7–16.3)*,§	34.0 (30.5–37.6)†,‡	<0.001

Values are n (%), mean ± SD (per-patient analysis), or estimated mean (95% confidence interval) (per-vessel analysis). Generalized estimating equation model or maximum likelihood chi-square tests were used for overall and between-group comparisons in the per-vessel analysis. *p < 0.05 compared with group B. †p < 0.05 compared with group A. ‡p < 0.05 compared with group C. §p < 0.05 compared with group D.

CAD = coronary artery disease; other abbreviations as in Table 1.

DISCUSSION

In this study, patients with low CFR had poorer clinical outcomes than those with high CFR despite an absence of significant differences in clinical or angiographic characteristics. Measurement of CFR and IMR in patients with high FFR provided information regarding the microvascular system that was not evident by clinical or angiographic characteristics (**Central Illustration**). Patients with low CFR and high IMR_{corr} had poorer clinical outcomes than patients in other groups. Independent prognostic factors in patients with high FFR were the presence of low CFR with high IMR_{corr}, diabetes mellitus, and multivessel disease. These findings suggest that the integration of CFR and IMR with FFR may improve risk stratification for patients with high FFR.

CLINICAL IMPLICATIONS OF CFR IN PATIENTS WITH HIGH FFR. Although FFR-guided PCI has been shown to improve patient outcomes (6,7,16,17), and FFR is now the gold standard invasive method for assessing the functional significance of coronary artery stenosis (9), further improvement in the diagnosis and treatment of patients with high FFR is possible. In the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) II study, 14.6% of the registry arm (FFR >0.80 and deferral of PCI) experienced persistent angina, and 9.0% of these patients experienced clinical events during the 2-year follow-up period (6).

Previous studies suggest that measurement of CFR could aid risk stratification for patients with high FFR. Meuwissen et al. (18) reported that among patients with FFR ≥0.75, those with abnormal Doppler-derived CFR had a higher 1-year event rate than those with normal coronary flow velocity reserve. In our study, among patients with high FFR, patients with low CFR also had poorer clinical outcomes than patients with high CFR. Because the 2 groups had no differences in angiographic characteristics or FFR, the difference in CFR seems to be due to the difference in microvascular status. However, patients with high IMR_{corr} were widely distributed between the high- and low-CFR groups, and there was no difference in IMR_{corr}

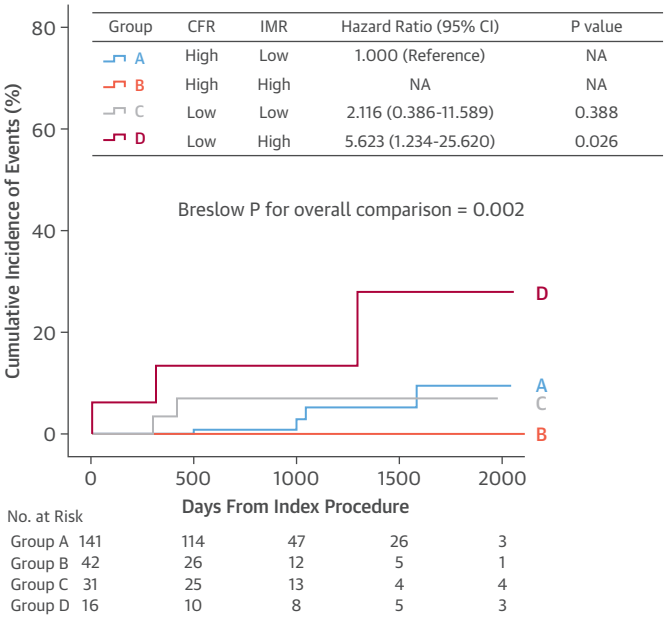
between the 2 groups (Figure 1). These results suggest the presence of heterogeneous populations and that classification according to CFR levels alone cannot characterize the differences between these patients.

DISCORDANCE BETWEEN CFR AND IMR. As with FFR, thermodilution-derived CFR (or Doppler-derived CFR) is also used to determine the functional significance of epicardial coronary stenosis. In patients with no significant epicardial stenosis, CFR and IMR are commonly used to assess microvascular status. However, because CFR represents the flow ratio between hyperemic and resting conditions, and IMR represents microvascular resistance in a hyperemic condition, some patients may have discordant results. Although several studies have focused on the relationship between FFR and CFR, the clinical relevance of IMR and CFR in patients with high FFR is unclear. In our study, 45.0% of the total population had no abnormality in FFR, CFR, or IMR, and 61.3% of the patients with high FFR had no abnormality in either CFR or IMR. When 230 patients with high FFR were stratified according to CFR and IMR, 73 (31.7%) had discordant classifications using CFR or IMR. Clinical and angiographic characteristics other than age did not differ between concordant and discordant patients (Online Table 3) and were similar among the 4 groups when classified according to IMR and CFR (Table 2).

Of discordant patients, group B patients were considered to have high microvascular resistance with preserved flow reserve. The resting T_{mn} was higher in group B than in other groups, suggesting relatively lower resting coronary flow in these patients. Clinical outcomes of this group were not different from the concordant normal group A patients. These results align with a previous report in which low resting and hyperemic flow along with preserved CFR were not associated with myocardial ischemia (19).

Group C patients had a high resting flow with normal microvascular resistance. In our study, CFR was lowest in these patients, mainly due to a lower resting T_{mn} than in other groups. When comparing resting hemodynamic values among the 4 groups, group C patients had a significantly higher resting heart rate than other groups (Online Table 4), and resting heart rate (per increase of 10 beats/min; odds ratio: 0.923; 95% CI: 0.988 to 0.997; $p < 0.001$) was the only independent predictor of resting T_{mn}. Previously, van de Hoef et al. (20) studied long-term outcomes of 157 patients with intermediate stenosis who were evaluated with FFR and CFR, and they found that patients with high FFR and low CFR ($n = 10$) had a higher 10-year major adverse cardiovascular event rate than patients with high FFR and high CFR ($n = 78$; relative risk: 2.8; 95% CI: 1.8 to 4.6; $p < 0.001$).

FIGURE 4 **Clinical Outcomes According to Patterns of Microvascular Status Defined According to CFR and IMR Among Patients With High FFR**



The cumulative incidence of patient-oriented composite outcomes was compared among 4 groups divided according to CFR and IMR. All IMR values were adjusted with Yong's formula (IMR_{corr}). NA = not available; other abbreviations as in Figures 1 and 2.

Another study from van de Hoef et al. (21) found that a low reference vessel CFR (≤2.7) was associated with higher all-cause mortality than a normal reference vessel CFR (>2.7) in stable patients ($n = 178$) during a 12-year follow-up period. In both studies, low CFR was due to high resting flow velocity or low resting resistance, not low hyperemic flow velocity.

In our study, group C had a numerically higher, albeit not statistically significant, POCO rate than group A. This finding could be attributed to the difference in patient characteristics among the studies or to the heterogeneous mechanisms of low CFR. Because high resting coronary flow can reflect various conditions, including disturbed autoregulatory processes in coronary circulation (21), intraindividual variability in resting condition (22), or uncontrolled blood pressure or heart rate (19), clinical outcomes could depend on different mechanisms of low CFR in these patients. The dependence of CFR on resting T_{mn} or resting hemodynamic conditions may be a weakness of this parameter, as it is not always easy to define and maintain true resting conditions in a cardiac catheterization laboratory.

MICROVASCULAR DISEASE AND ITS PROGNOSTIC IMPLICATION. Group D patients (7.0% of patients) in our study were regarded as having overt

TABLE 3 Clinical Outcomes of Patients With High FFR According to CFR and IMR

	Group A (CFR >2 and IMR <23 U)	Group B (CFR >2 and IMR ≥23 U)	Group C (CFR ≤2 and IMR <23 U)	Group D (CFR ≤2 and IMR ≥23 U)	p Value
Per-patient analysis (n = 230), n (%)	141 (61.3)	42 (18.3)	31 (13.5)	16 (7.0)	
All-cause death or MI	9.5	0	0	13.5	0.001
Target vessel revascularization	0	0	3.7	0	0.106
Nontarget vessel revascularization	0	0	3.4	16.7	0.082
Any revascularization	7.0	0	7.0	16.7	0.009
Patient-oriented composite outcome*	9.5	0	7.0	27.9	0.002

Values are n (%) or %. The cumulative incidences of clinical outcomes were presented as Kaplan-Meier estimates during the median follow-up of 658.0 days (interquartile range: 503.8–1,139.3 days). p values were log-rank or Breslow p value in survival analysis. *Included all-cause mortality, any MI, and any revascularization.
Abbreviations as in Table 1.

microvascular disease. These patients seemed to have both high microvascular resistance and impaired flow reserve. Among the 4 groups, IMR_{corr} was highest in this group. Although the proportion of patients with high FFR who had overt microvascular disease was small, group D had the poorest clinical outcomes during follow-up. The presence of overt microvascular disease was an independent prognostic factor in patients with high FFR. In addition, the presence of overt microvascular disease had additive prognostic value aside from clinical risk factors, with significantly improved discriminant function of the prediction model. These results suggest that the invasive physiological assessment for microvascular disease combined with CFR and IMR can identify patients at high risk for future cardiovascular events among those with high FFR.

TABLE 4 Independent Predictors of Patient-Oriented Composite Outcomes Among Patients With High FFR

	Hazard Ratio	95% CI	p Value
Model 1			
Multivessel disease	3.254	1.082–9.787	0.033
Diabetes mellitus	2.828	1.088–7.349	0.033
Current smoking	0.773	0.218–2.739	0.690
Hypercholesterolemia	0.893	0.325–2.450	0.826
Acute coronary syndrome	0.237	0.031–1.833	0.168
Model 2 (model 1 + low CFR and high IMR)			
Low CFR and high IMR	4.914	1.541–15.663	0.007
Multivessel disease	3.639	1.238–10.699	0.019
Diabetes mellitus	2.714	1.050–7.016	0.039
Current smoking	0.928	0.257–3.354	0.910
Hypercholesterolemia	0.859	0.304–2.424	0.774
Acute coronary syndrome	0.162	0.019–1.359	0.094

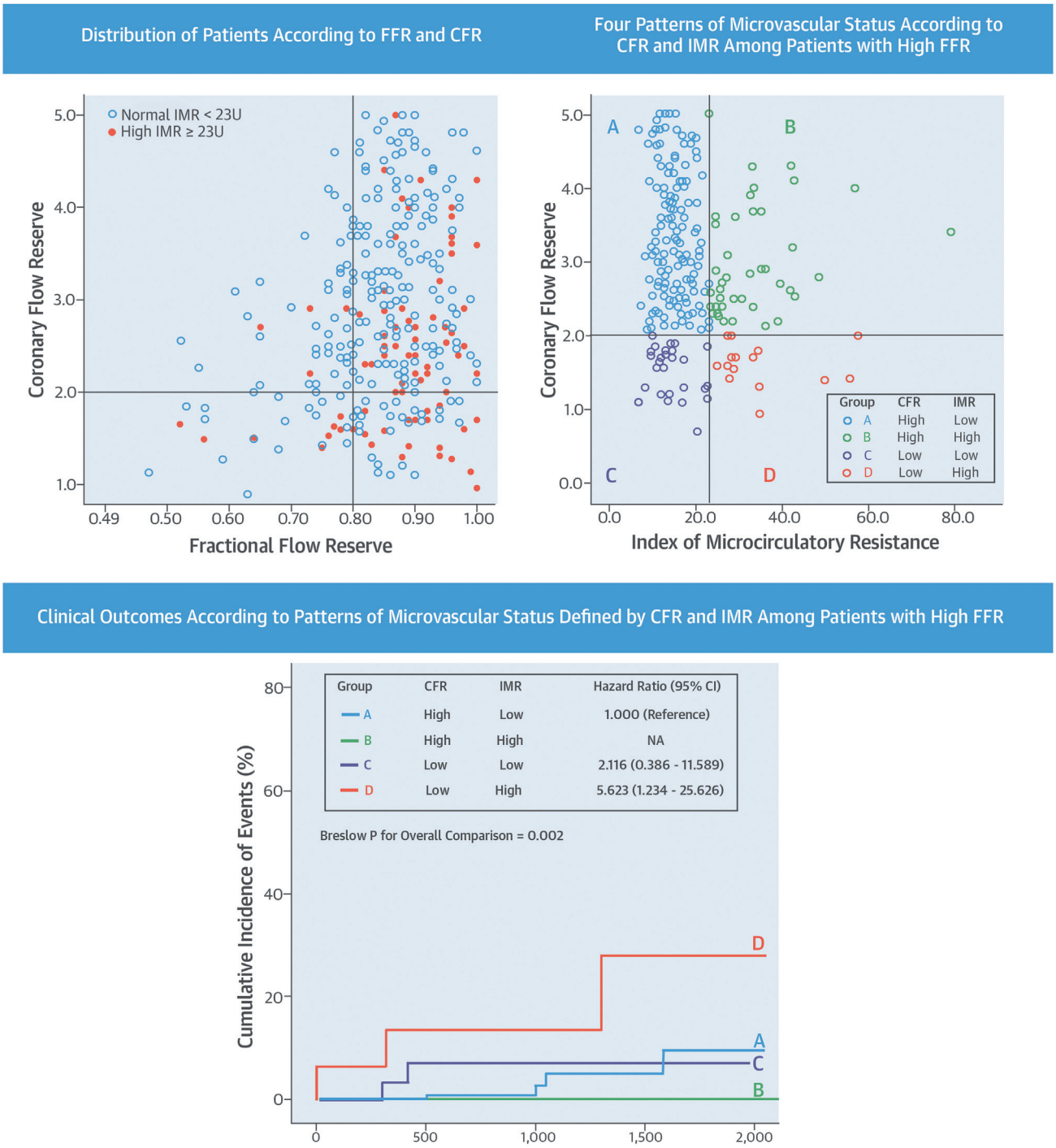
Patient-oriented composite outcomes included all-cause mortality, any MI, and any revascularization. The C-index of models was 0.755 (95% confidence interval [CI]: 0.675–0.835) and 0.824 (95% CI: 0.740–0.909) for models 1 and 2, respectively (p for difference = 0.314). The relative integrated discrimination improvement of model 2 was 0.467 (p = 0.037), and the category-free net reclassification index was 0.648 (p = 0.007).
Abbreviations as in Table 1.

Previous studies have shown that microvascular disease is associated with higher risk of cardiovascular events in patients without flow-limiting epicardial stenosis (23–26). Several mechanisms have been proposed to explain this outcome. In addition to myocardial ischemia, microvascular disease is reportedly associated with endothelial dysfunction and inflammatory activity that precedes intimal thickening, lipid deposition in the macrovascular system, and coronary vasomotor dysfunction (24,27–30). In 1 study, coronary microvascular dysfunction in patients with nonobstructive coronary artery disease was associated with higher levels of serum high-sensitivity C-reactive protein and a higher frequency of thin-cap fibroatheroma (23).

In our study, the higher POCO rate in group D resulted from higher rates of cardiac death and revascularization compared with the other groups. Previously, a long-term follow-up study by van de Hoef et al. (21) presented the excess risk of all-cause mortality in patients with low reference vessel CFR. Conversely, the results of the FAME II registry cohort suggested revascularization was the main cause of clinical events in patients with high FFR (>0.8), although the incidence was much lower than in those with FFR ≤0.80 and those randomized to the optical medical treatment group (6). In another study by van de Hoef et al. (20), the higher clinical event rate in the low-CFR and high-FFR group was mainly due to a higher revascularization rate, especially during the early follow-up period. Although patients in group D in our study exhibited an excess risk of death and revascularization, discrepancies among the previous studies and the relatively small number of patients in group D warrant further research to clarify the mechanism of microvascular disease and its association with accentuated atherosclerotic progression and cardiac death.

CLINICAL IMPLICATIONS. In clinical practice, if a target lesion's FFR is low, macrovascular disease

CENTRAL ILLUSTRATION **CFR and IMR in Patients With High FFR: Clinical Relevance**



Lee, J.M. et al. J Am Coll Cardiol. 2016; 67(10):1158–69.

Distribution of patients according to fractional flow reserve (FFR) and coronary flow reserve (CFR). There was a modest correlation between FFR and CFR, and categorical agreement of FFR and CFR was low (kappa = 0.178; $p < 0.001$). The distributions of index of microcirculatory resistance (IMR) values were different across each quadrant classification, and IMR was highest in patients with high FFR and low CFR. Four patterns of microvascular status according to CFR and IMR among patients with high FFR. There were no significant differences in clinical and angiographic characteristics and FFR values among the 4 groups. Clinical outcomes according to patterns of microvascular status defined according to CFR and IMR among patients with high FFR. The group with overt microvascular disease (low CFR with high IMR [group D]) exhibited a significantly higher incidence of adverse cardiovascular events compared with other groups. These results suggest that invasive physiological assessment for microvascular disease with CFR and IMR can be helpful to identify patients at high risk for future cardiovascular events among those with high FFR. NA = not applicable.

should be treated by using the appropriate revascularization method, according to the guideline (9). Our study showed that comprehensive physiological assessment using both CFR and IMR to stratify high-FFR patients could differentiate patterns of microvascular status among these patients with functionally insignificant macrovascular disease. Although the medication of choice for overt microvascular disease is unclear, the treatment goal for patients with normal resistance and relatively high resting flow or overt microvascular disease differs because the mechanism of limited CFR is inherently different.

STUDY LIMITATIONS. We included patients with no evidence of acute MI; therefore, our findings cannot be applied to patients with acute MI (1,4). In addition, an intravascular imaging assessment (e.g., intravascular ultrasound) that could differentiate between diffuse atherosclerotic narrowing and pure microvascular disease was not available. However, because there was no difference in any of the angiographic parameters among high-FFR patients, the proportion of patients with diffuse atherosclerotic narrowing could have been minimal in our study population.

We did not integrate coronary wedge pressure to adjust IMR values. However, IMR values corrected by using Yong's formula were used to minimize the influence of collateral flow because it was not practical to measure wedge pressure in patients with intermediate stenosis. Although we used IMR_{corr} values, it should be noted that the difference between IMR and IMR_{corr} was almost negligible and using IMR did not alter any of the original results.

Because a well-validated cutoff value for IMR is not yet established, we used the 75th percentile of the IMR as the cutoff to define high IMR. Further study is warranted, however, to determine the IMR cutoff value that has independent prognostic impact.

Of the original population of 424 enrolled patients, 111 (26.2%) were excluded from the analysis because they showed discordant classification according either to FFR and CFR or to CFR and IMR across the different interrogated vessels. The clinical significance of these discordant results within individual patients requires further investigation.

Although both thermodilution-derived CFR and Doppler-derived CFR conceptually present the same ratio of resting and hyperemic coronary flow, the thermodilution technique uses the surrogate of coronary flow velocity. Previous studies suggested a close correlation between thermodilution- and Doppler-derived CFR measurements (31,32).

We primarily focused on anatomical lesion severity and not on angiographic flow or perfusion. It may be helpful to measure Thrombolysis In Myocardial Infarction frame count in both resting and hyperemic conditions to investigate whether this index can be a surrogate for microvascular status. Also, the overall follow-up period was approximately 3 years, but the median follow-up duration (658.0 days; IQR: 503.8 to 1139.3 days) was too short to explore the long-term clinical impact of overt microvascular disease.

Investigators were not blinded to the physiological indices, and this factor might have influenced the management strategy for these patients. In addition, the results of noninvasive tests were not available in our study. Even though the validated physiological indices indicated the presence or absence of myocardial ischemia, this relationship could not be reaffirmed by using noninvasive test results. Finally, because this study was not a randomized controlled trial, inherent limitations of residual confounding factors should be considered.

CONCLUSIONS

Integration of microvascular assessment by using CFR and IMR with FFR can provide additional information on coronary circulation and improve the risk stratification of patients with high FFR. The presence of overt microvascular disease (low CFR with high IMR) was an independent prognostic factor in patients with high FFR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Measurement of FFR has become a standard approach to evaluation of the functional significance of epicardial coronary artery stenosis, but ischemic events can occur even in patients with high FFR. Assessment of CFR and an IMR provides additional information about vascular resistance in those with high FFR that correlates with clinical outcomes.

TRANSLATIONAL OUTLOOK: Further studies are needed to clarify clinical settings in which functional microvascular assessments by measurement of CFR and IMR can improve risk stratification and guide therapy for patients with ischemic heart disease and high FFR.

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KEY WORDS coronary artery disease, coronary flow reserve, fractional flow reserve, index of microcirculatory resistance, microvascular function

APPENDIX For supplemental figures and tables, please see the online version of this article.