ORIGINAL RESEARCH

Clinical Relevance of Functionally Insignificant Moderate Coronary Artery Stenosis Assessed by 3-Vessel Fractional Flow Reserve Measurement

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***Background*—**Understanding of the risk conferred by functionally insignificant lesions in multiple coronary vessels is limited. We investigated the prognostic implications of coronary artery disease (CAD) based on 3-vessel fractional flow reserve (FFR).

***Methods and Results*—**A total of 1,136 patients underwent FFR measurement in the 3 major epicardial arteries. We defined vessels with "Moderate CAD" as vessels with FFR, 0.81 to 0.87. Patients were classified into Group 1: No apparent CAD (FFR>0.87 in all 3-vessels); Group 2: Single-vessel moderate CAD; Group 3: Multivessel moderate CAD; and Group 4: Functionally significant CAD (FFR≤0.80) in any vessel. The primary end point was 2-year major adverse cardiac events, a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization. Forty-three percent of patients had moderate CAD (Group 2: 403/1136, 35.5%; Group 3: 84/1136, 7.4%). The 2-year risk of major adverse cardiac events was not significantly different between patients with single-vessel moderate CAD and no apparent CAD (2.6 versus 2.6%; HR, 1.1; 95% confidence interval, 0.4%–2.8%; *P*=0.89). However, patients with multivessel moderate CAD were at significantly higher risk than Group 1 (7.4 versus 2.6%; hazard ratio, 3.3; 95% confidence interval, 1.1%–9.8%; *P*=0.03). The risk of major adverse cardiac events in patients with multivessel moderate CAD was comparable to that of patients with functionally significant CAD (hazard ratio, 1.2; 95% confidence interval, 0.5%–3.0%; *P*=0.67). In a multivariable regression model, multivessel moderate CAD was an independent predictor of greater risk of 2-year major adverse cardiac events.

***Conclusions*—**Global physiologic assessment with FFR measurement of 3 vessels can identify multivessel moderate CAD. The prognostic implication of multivessel moderate CAD appears comparable to that of functionally significant CAD.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01621438. **(*J Am Heart Assoc*. 2018;7: e008055. DOI: 10.1161/JAHA.117.008055.)**

Key Words: coronary artery disease • fractional flow reserve • multivessel coronary artery disease • physiology/function • prognosis

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Accompanying Tables S1 through S4 and Figure S1 are available at http://jaha.ahajournals.org/content/7/4/e008055/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Information about the risk conferred by functionally insignificant lesions in multiple coronary vessels is limited.
- We investigated the prognostic implications of the severity and extent of physiologically defined coronary artery disease (CAD) by measuring fractional flow reserve in 3 vessels.
- The current study focused on the prognosis of patients who have moderate CAD (fractional flow reserve 0.81–0.87), especially those with multivessel moderate CAD.
- Patients with multivessel moderate CAD had a significantly higher risk of major adverse cardiac events than those with single-vessel moderate CAD or no apparent CAD.
- Patients with multivessel moderate CAD had a risk of major adverse cardiac events similar to that of patients with functionally significant CAD.

What Are the Clinical Implications?

- The number of vessels with physiologically defined moderate CAD may have prognostic implications.
- The physiologic index, fractional flow reserve, reflects the risk continuum of coronary atherosclerosis, and the scope of fractional flow reserve can be extended beyond an individual coronary vessel to the atherosclerotic burden of the whole coronary tree.

In the assessment of epicardial coronary stenosis, fractional flow reserve (FFR) is now regarded as a reference standard method to evaluate the functional significance of a stenosis.[1,2] Clinical outcomes of FFR-guided percutaneous coronary intervention (PCI) were reported to be better than those of angiography-guided PCI or medical treatment.[3–5] Although a FFR>0.80 indicates that there is no ischemia caused by epicardial coronary stenosis,[6] clinical events still occur in patients with high FFR and deferred revascularization.[3,7]

A growing body of evidence suggests that FFR has prognostic value beyond the single cutoff value of 0.80. A recent study of deferred lesions showed a gradual trend of decreasing event rates from the FFR strata of 0.76 to 0.80 to the strata of 0.81 to 0.85.[8] Studies based on angiography and coronary computed tomography angiography showed that the extent of nonobstructive disease has prognostic implications (coronary artery disease [CAD]).[8–10] However, information about the influence of the extent of physiologically defined "moderate" CAD is limited.

The current study sought to explore the prognostic implication of patients with functionally insignificant CAD affecting single or multiple vessels.

Methods

The data and analytic methods that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Selection

This study is a post hoc analysis of the 3V FFR-FRIENDS study (3-vessel fractional flow reserve for the assessment of total physiologic atherosclerotic burden and its clinical impact in patients with coronary artery disease, NCT01621438).[11] The 3V FFR-FRIENDS study was an observational, prospective, multinational, and multicenter study to investigate the prognostic implications of a new physiologic index, the total sum of FFR values of the 3 vessels (3V-FFR). The current study is a post hoc analysis of that entire study population and was not prespecified in the study protocol of the 3V FFR-FRIENDS study. The 3V FFR-FRIENDS study included consecutive patients who underwent successful FFR measurement in all 3 major epicardial coronary arteries at 12 centers in 3 countries (Korea, China, and Japan). Patients with depressed left ventricular systolic function (ejection fraction <35%), ST-elevation myocardial infarction within 72 hours, previous coronary artery bypass graft surgery, chronic kidney disease, abnormal epicardial coronary flow (Thrombolysis in myocardial infarction flow <3), or patients who received planned coronary artery bypass graft surgery after diagnostic angiography were excluded. The study protocol was approved by the Institutional Review Board (IRB approval number: H-1203-087-402) or Ethics Committee of each participating center and all patients provided written informed consent before they were enrolled in the study. A detailed rationale for sample size calculations for the 3V FFR-FRIENDS is presented in Data S1.

Quantitative Coronary Angiography and Angiographic Analysis

Coronary angiography was performed using standard techniques and angiographic views were obtained after intracoronary administration of nitrate (100 or 200 μg). Quantitative coronary angiography was performed at a core laboratory that was blinded to other variables. The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score was calculated to quantify the angiographic disease extent and severity in each patient.[12,13]

FFR Measurement and Procedures

All FFR measurements were performed after diagnostic angiography. A 5–7 Fr guide catheter was used to engage the coronary artery, and a pressure sensor guide wire (St. Jude Medical, St. Paul, MN) was positioned at the distal

segment of a target vessel. Continuous intravenous infusion of adenosine or ATP was used to induce hyperemia. Hyperemic proximal aortic pressure and distal coronary arterial pressure were measured during sustained hyperemia and FFR was calculated as the mean of distal coronary arterial pressure/proximal aortic pressure during hyperemia. Intracoronary nitroglycerine (100 or 200 μg) was administered before each FFR measurement. In the presence of significant drift, the study protocol required re-equalization and re-measurement of FFR.

For lesions with significantly low per-vessel FFR (≤0.80), PCI was recommended based on the current guideline. When indicated, PCI was performed using current standard techniques with second-generation drug-eluting stents. The treating physician made decisions about PCI. In patients who underwent PCI, the study protocol required post-PCI FFR measurement, and post-PCI FFR was used for per-vessel classification in the current analysis.

Definitions of Per-Vessel and Per-Patient Classifications

For the per-vessel level classification based on FFR, target vessels were classified as either functionally significant (FFR ≤0.80) or insignificant (FFR >0.80) vessels. The functionally insignificant vessels were further classified as either vessels with moderate CAD (FFR 0.81–0.87) or no apparent CAD (FFR >0.87) (Figure 1) according to the lowest quartile value of FFR (0.87). Patients were classified according to extent of CAD into 4 groups as follows: Group 1: No apparent CAD (FFR >0.87 in all 3 vessels); Group 2: Moderate CAD (FFR 0.81–0.87) in a single vessel; Group 3: Moderate CAD (FFR 0.81–0.87) in multiple vessels; and Group 4: Functionally significant CAD (FFR ≤0.80) in any vessel.

Follow-Up of Patients, Outcome Measurements, and Adjudication of Clinical Events

Clinical data were obtained at outpatient clinic visits or by telephone interview. An independent clinical event committee, which was unaware of clinical, angiographic, and physiologic data, adjudicated all events. The primary outcome was any major adverse cardiac event (MACE) by 2 years after FFR, including cardiac death, any myocardial infarction, or any ischemia-driven revascularization. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of myocardial infarction.[14] All deaths were considered cardiac unless an undisputable noncardiac cause was present. Ischemia-driven revascularization was defined as a revascularization procedure with at least 1 of the following: (1) Recurrence of angina, (2) Positive noninvasive test, or (3) Positive invasive physiologic test.

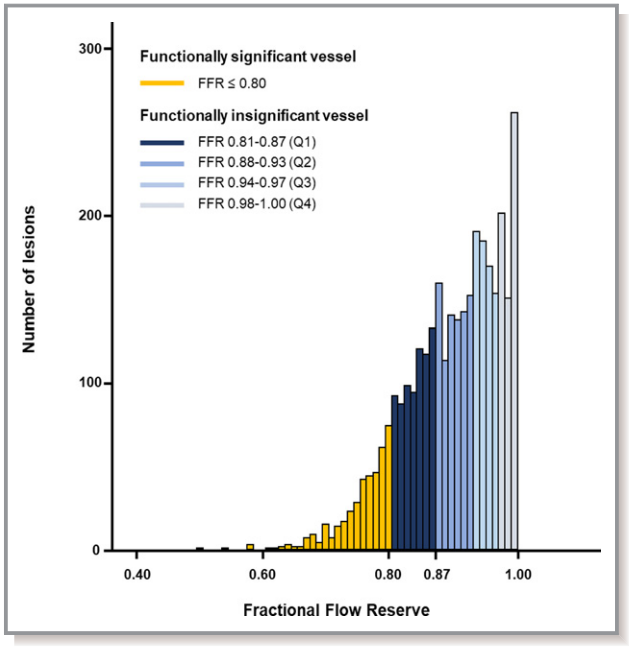

Figure 1. Distribution of per-vessel fractional flow reserve. The histogram depicts the frequency of vessels by FFR values. Among the total 3298 vessels, 12.3% were functionally significant (FFR ≤0.80, yellow bars). The functionally insignificant vessels (87.7%, 2891/3298) are further categorized into quartiles and depicted as bars filled with graded saturation (blue). The darkest blue bars represent vessels in the lowest quartile (FFR 0.81–0.87) defined as moderate CAD in this study. CAD indicates coronary artery disease; FFR, fractional flow reserve.

Statistical Analysis

The primary hypothesis of this study was that the presence of moderate CAD (FFR 0.81–0.87) and its extent would significantly affect the risk of 2-year MACE. For this, the analysis was performed for 3 groups of vessels classified with the per-vessel FFR value (functionally significant, moderate CAD, and no apparent CAD) and for 4 groups of patients classified according to the severity and extent of CAD. Event rates were calculated based on Kaplan–Meier censored estimates, and survival curves between groups were compared using the log-rank test.

Cox proportional hazards regression analysis was used to examine the associations between covariables and the 4 patient groups described above and MACE. Previously known risk factors and variables that were distributed significantly differently among the 4 groups were included in univariable Cox regression analyses (Table S1). For continuous variables, the linearity assumption was assessed graphically using Martingale residuals. SYNTAX score and age were converted to categorical values because they did not fulfill the linearity assumption. Crude and multivariable adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were computed by univariable and multivariable Cox regression analyses. Variables associated with time to MACE in the univariable Cox

regression analyses (Wald test $P<0.10$) were included in a multivariable Cox regression model. The multivariable Cox regression model included age, male sex, smoking status, presentation with acute coronary syndrome, high SYNTAX score (≥8), and the 4-group categorical variable based on FFR measurement of 3 vessels. C-statistics with 95% CI were calculated to validate the discriminant function of the model.

Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables as means and SDs. All probability values were 2-sided, and P values <0.05 were considered statistically significant. The SPSS version 20.0 (SPSS Inc, Chicago, IL), STATA version 12 (SAS Institute, Inc, Cary, NC), and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) statistical packages were used for statistical analyses.

Results

Patient Characteristics of 4 Groups According to the Extent of CAD

In the parent study, 1136 patients were admitted for coronary angiography and underwent FFR measurements of all 3 major coronary arteries. Baseline characteristics and treatment strategies are presented in Table 1. The mean age of the study cohort was 61.9±9.8 years and 73.5% of the patients were male. Hypertension was diagnosed in 60.7% of the patients, 32% had diabetes mellitus, and 22.4% of patients were admitted because of acute coronary syndrome. Among the 3298 interrogated vessels, 572 vessels were revascularized and 2726 vessels were deferred. Among the deferred vessels, 314 vessels (11.5%) were deferred despite vessel-specific FFR ≤0.80. Among these 314 vessels, PCI was deferred because of insignificant angiographic stenosis (reverse mismatch) (185 vessels, 58.9%), diffuse disease without focal stenosis (48 vessels, 15.3%), no angiographic progression since previous angiography (31 vessels, 9.9%), negative results of noninvasive tests (17 vessels, 5.4%), small myocardial territory (15 vessels, 4.8%), or for other reasons (17 vessels, 5.4%).

Among the 1136 patients, 26.6% (302/1136) were classified as no apparent CAD (Group 1), 35.5% (403/1136) as moderate CAD (FFR 0.81–0.87) in a single vessel (Group 2), 7.4% (84/1136) as multivessel moderate CAD (FFR 0.81–0.87) (Group 3), and 30.5% (347/1136) as functionally significant disease in any of the 3 major epicardial arteries

Table 1. Clinical and Lesion Characteristics

	Overall	Group 1	Group 2	Group 3	Group 4	*P* Value
			Moderate CAD (FFR 0.81–0.87)			
		No Apparent CAD	Single Vessel	Multiple Vessels	Functionally Significant CAD	
Patients, n (%)	1136 (100)	302 (26.6)	403 (35.5)	84 (7.4)	347 (30.5)	
Age, y, mean±SD	61.9±9.8	62.1±10.2	62.1±10.0	61.2±10.0	61.6±9.2	0.80
Male, n (%)	835 (73.5)	201 (66.6)	307 (76.2)	64 (76.2)	263 (75.8)	0.017
Cardiovascular risk factors						
Hypertension, n (%)	689 (60.7)	175 (57.9)	242 (60.0)	54 (64.3)	218 (62.8)	0.54
Diabetes mellitus, n (%)	363 (32.0)	76 (25.2)	143 (35.5)	29 (34.5)	115 (33.1)	0.027
Hypercholesterolemia, n (%)	597 (52.6)	154 (51.0)	218 (54.1)	40 (47.6)	185 (53.3)	0.66
Current smoking, n (%)	327 (28.8)	84 (27.8)	115 (28.5)	21 (25.0)	107 (30.8)	0.69
Clinical presentations, n (%)						0.35
Acute coronary syndrome	254 (22.4)	59 (19.6)	88 (21.8)	19 (22.6)	88 (25.4)	
Stable angina/elective	882 (77.6)	243 (80.4)	315 (78.2)	65 (77.4)	259 (74.6)	
Index of CAD burden						
SYNTAX score, mean±SD	8.2±6.8	5.6±5.8	7.5±5.9	9.9±7.4	11.0±7.5	<0.001
3-Vessel FFR, mean±SD	2.70±0.14	2.83±0.05	2.74±0.06	2.62±0.06	2.55±0.13	<0.001
Discharge medication						
Aspirin, n (%)	891 (79.3)	226 (74.8)	317 (78.7)	70 (83.3)	288 (83.0)	0.058
Dual anti-platelet therapy, n (%)	657 (57.8)	156 (51.7)	229 (56.8)	54 (64.3)	218 (62.8)	0.020
Statin, n (%)	998 (87.9)	255 (84.4)	358 (88.8)	72 (85.7)	313 (90.2)	0.12

Values are mean±SD, or n (%). CAD, coronary artery disease; FFR, fractional flow reserve; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery.

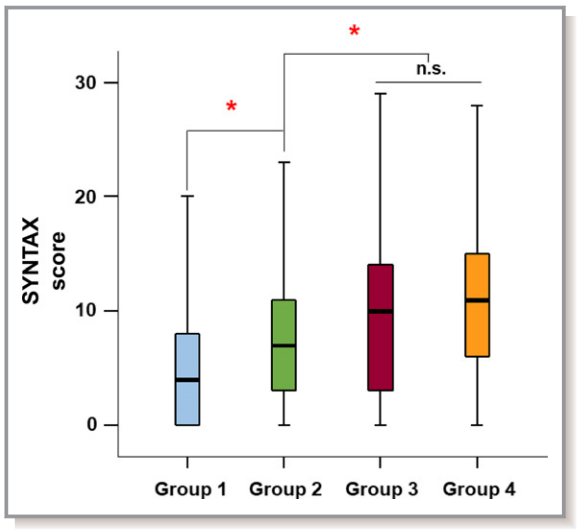

Figure 2. Distribution of SYNTAX score among the 4 patient groups. The box plots with whiskers depict distribution of SYNTAX score among the 4 patient groups including interquartile range, median, and minimum to maximum values, within 1.5 times the interquartile range. *P<0.05 for between-group comparisons; n.s. indicates not significant; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery.

(Group 4). Table 1 summarizes the comparison of baseline characteristics among the 4 patient groups. More patients in Groups 3 and 4 were prescribed anti-platelet therapy at discharge. During the 2-year follow-up, the use of antiplatelet therapy decreased among the whole study population. At discharge, 87.9% were prescribed a statin. The frequency of statin use did not change significantly during the 2-year follow-up (Table S2). Otherwise, clinical characteristics among the 4 groups did not differ significantly.

A significant trend of increasing SYNTAX score (P<0.001 for trend) was observed from Group 1 to Group 4. Between-group comparisons found that Group 3 had significantly higher SYNTAX scores than Group 2 (2.4±0.8, P=0.012), whereas the difference of SYNTAX score between Groups 4 and 3 was insignificant (1.1±0.8, P=0.54) (Table 1 and Figure 2)

Comparison of Clinical Outcomes Among 4 Patient Groups According to the Extent of CAD

Figure 3 presents the comparison of 2-year MACE rates among the 4 patient groups. The risk of 2-year MACE of Group 1 (patients with no apparent CAD) and Group 2 (patients with single-vessel moderate CAD [FFR 0.81–0.87]) was not significantly different (2.6 versus 2.6%; HR, 1.1; 95% CI, 0.4%–2.8%; P=0.89). However, Group 3 (patients with multivessel moderate CAD [FFR 0.81–0.87]) had a significantly higher risk of MACE than Group 1 (7.4 versus 2.6%; HR, 3.3; 95% CI, 1.1%–9.8%; P=0.032). The 2-year MACE risk of Group 3 was similar to Group 4 (patients with any functionally significant CAD) (7.4 versus 8.0%; HR, 1.0; 95% CI, 0.4%–2.4%; P=0.98) (Table 2 and Figure 3). Between-group differences in MACE risk were mainly driven by significant differences in the rates of ischemia-driven revascularization events (Table 2). Among patients with ischemia-driven revascularization, 25 patients (62.5%) presented with acute coronary syndrome: 9 patients had aggravated angina with progression of the coronary stenosis, and the remaining 6 underwent revascularization because of positive noninvasive tests during follow-up.

Table 3 presents the independent predictors of 2-year MACE according to multivariable regression analysis. The independent predictors included age (>70 years), SYNTAX score (>8), presentation with acute coronary syndrome, and patient group based on FFR measurements of the 3 vessels. The relatively higher risk of MACE in Groups 3 and 4 than in Group 1 was consistently observed in multivariable-adjusted regression models. Moderate CAD (FFR 0.81–0.87) in multiple vessels (Group 3) was independently associated with greater risk of 2-year MACE (HR, 3.3; 95% CI, 1.0%–10%; P=0.043) than in Group 1. The 2-year risk of MACE in patients with multivessel moderate CAD (FFR 0.81–0.87) (Group 3) was comparable to that of patients with functionally significant CAD (Group 4) (HR, 1.2; 95% CI, 0.5%–3.0%; P=0.67). When 3V FFR was added to the multivariable Cox regression model, the high-risk patient group with multivessel moderate CAD (FFR 0.81–0.87) or any functionally significant CAD (FFR ≤0.80) was still associated with increased risk of 2-year MACE (HR, 2.3; 95% CI, 1.0%–5.3%; P=0.043) (Table 4).

Vessels with functionally significant stenosis (FFR ≤0.80) had the highest risk of 2-year ischemia-driven revascularization relative to vessels with no apparent CAD (HR, 9.5; 95% CI, 4.0%–22%; P<0.001), or moderate CAD (FFR 0.81–0.87) (HR, 3.2; 95% CI, 1.4%–7.7%; P=0.008). Vessels with moderate CAD (FFR 0.81–0.87) were associated with moderately greater risk of ischemia-driven revascularization than vessels with no apparent CAD (HR, 2.9; 95% CI, 1.1%–7.8%; P=0.031) (Figure S1).

Clinical Outcomes in High-Risk Subgroups and Anatomically Nonobstructive CAD

In patients with diabetes mellitus, the 2-year risk of MACE was higher in patients with moderate CAD (FFR 0.81–0.87) in multivessels (Group 3) (HR, 11.7; 95% CI, 0.4%–2.5%; P=0.028) than in Group 1; the risk of patients in Group 2 was similar to that of Group 1 (HR, 1.1; 95% CI, 0.1%–11.7%; P=0.96). In patients with acute coronary syndrome, the pattern of 2-year risk of MACE was similar to that of the whole study population. In the high-risk subgroups of diabetes mellitus or acute coronary syndrome, Group 3 had significantly higher risk of MACE than Group 1 (HR, 4.8; 95% CI, 1.2%–20.2%; P=0.031), and those risks were comparable to

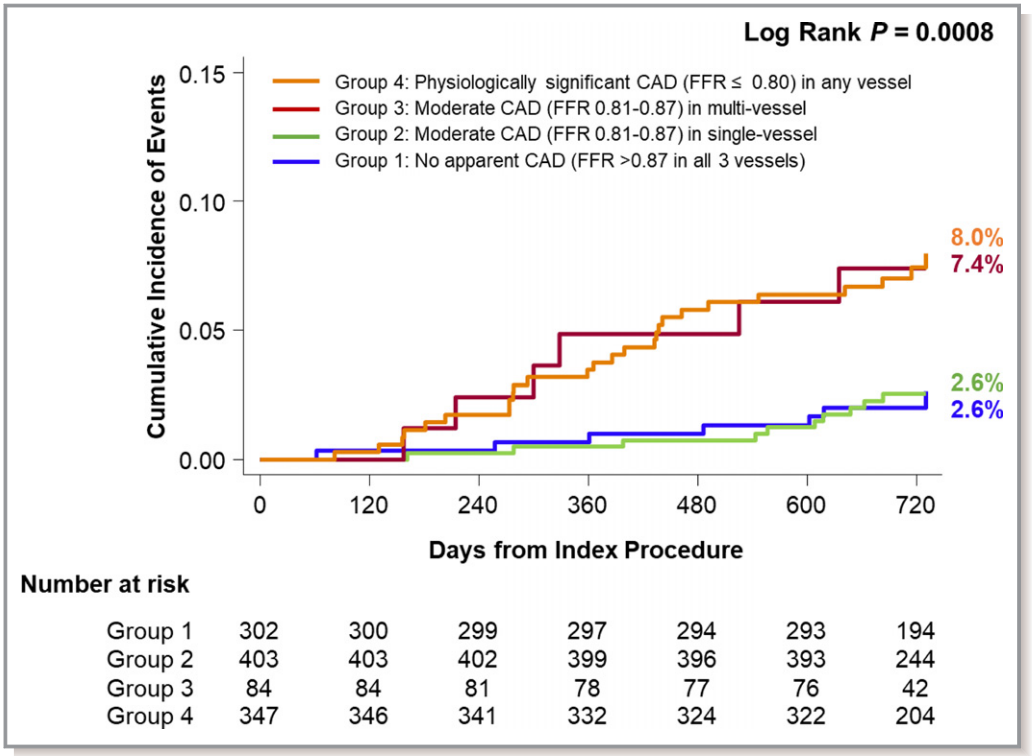

Figure 3. Comparison of 2-year MACE among the 4 groups. Cumulative incidence of (MACE) in each group is shown. CAD indicates coronary artery disease; FFR, fractional flow reserve; MACE, major adverse cardiac events.

those of Group 4 (HR, 1.2; 95% CI, 0.5%–3.3%; *P*=0.68) (Figure 4). In a subgroup of patients without anatomically obstructive CAD (% DS in all coronary vessels <50%), the 2-year risk of MACE was higher in patients with multivessel moderate CAD (FFR 0.81–0.87) (Group 3) than in Group 1 (HR, 12.0; 95% CI, 2.2%–65.5%; *P*=0.004) (Figure 4).

Table 2. Cumulative Rates of Clinical Outcomes Among 4 Groups

2-Year Clinical Outcome	N	Events (Rate*)	HR	95% CI	*P* Value
Major adverse cardiac events†	1136	49 (4.6)			
Group 1: No apparent CAD	302	7 (2.6)	1		
Group 2: Moderate CAD (FFR 0.81–0.87) in a single vessel	403	10 (2.6)	1.1	0.4 to 2.8	0.892
Group 3: Moderate CAD (FFR 0.81–0.87) in multiple vessels	84	6 (7.4)	3.3	1.1 to 9.8	0.032
Group 4: Functionally significant CAD	347	26 (8.0)	3.3	1.4 to 7.7	0.005
Ischemia-driven revascularization	1136	40 (3.8)			
Group 1: No apparent CAD	302	4 (1.7)	1		
Group 2: Moderate CAD (FFR 0.81–0.87) in a single vessel	403	8 (2.1)	1.5	0.5 to 5.0	0.509
Group 3: Moderate CAD (FFR 0.81–0.87) in multiple vessels	84	6 (7.4)	5.8	1.6 to 20.5	0.006
Group 4: Functionally significant CAD	347	22 (6.9)	4.9	1.7 to 14.3	0.003
Cardiac death or myocardial infarction	1136	20 (1.9)			
Group 1: No apparent CAD	302	5 (1.7)	1		
Group 2: Moderate CAD (FFR 0.81–0.87) in a single vessel	403	5 (1.3)	0.75	0.2 to 2.6	0.647
Group 3: Moderate CAD (FFR 0.81–0.87) in multiple vessels	84	1 (1.3)	0.77	0.1 to 6.6	0.810
Group 4: Functionally significant CAD	347	9 (2.9)	1.62	0.5 to 4.8	0.386

CAD indicates coronary artery disease; CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio.
*Two-year cumulative incidence rate (%) was estimated by Kaplan–Meier failure function.
†Major adverse cardiac events are composite of cardiac death, myocardial infarction, and ischemia-driven revascularization.

Table 3. Independent Predictors of 2-Year MACEs in Multivariable Cox Regression Analysis

Variables*	Adjusted HR (95% CI)	*P* Value†
Age >70 y	2.0 (1.1–3.9)	0.033
Male	1.88 (0.8–4.4)	0.140
Current smoker	1.5 (0.8–2.8)	0.189
Acute coronary syndrome	2.3 (1.3–4.2)	0.026
High SYNTAX score (≥8)	1.8 (1.0–3.5)	0.059
Groups with 3-vessel FFR measurement		0.015
Group 1: No apparent CAD	1 (reference)	
Group 2: Moderate CAD (FFR 0.81–0.87) in a single vessel	1.0 (0.4–2.8)	0.991
Group 3: Moderate CAD (FFR 0.81–0.87) in multiple vessels	3.3 (1.0–10)	0.043
Group 4: Functionally significant CAD	2.7 (1.1–6.7)	0.030

C-index of the multivariable Cox regression model was 0.73 (95% CI, 0.66%–0.80%). CAD indicates coronary artery disease; CI, confidence interval; HR, hazard ratio; FFR, fractional flow reserve; MACEs, major adverse cardiac events; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery.
*All the covariables included in the multivariable Cox regression model are presented.
†By multivariable Cox regression analysis.

Discussion

This study focused on the prognostic implications of the severity and extent of physiologically defined CAD based on FFR measurements of all 3 major coronary arteries. The main findings can be summarized as follows. Patients with multivessel moderate CAD (FFR 0.81–0.87) had a significantly higher risk of MACE than those with single-vessel moderate CAD (FFR 0.81–0.87) or no apparent CAD. Patients with multivessel moderate CAD (FFR 0.81–0.87) had a risk of MACE similar to patients with functionally significant CAD. These findings persisted in a multivariable regression model and were more prominent in the clinically high-risk subsets and in patients without anatomically obstructive CAD.

Table 4. Independent Predictors of 2-Year MACEs in Multivariable Cox Regression Analysis Including 3V-FFR as a Continuous Predictor

Variable*	HR	95% CI	*P* Value
Age >70 y	2.00	1.05–3.83	0.036
Male	1.84	0.79–4.27	0.158
Current smoker	1.50	0.80–2.79	0.205
High SYNTAX score (≥8)	1.76	0.92–3.36	0.087
Acute coronary syndrome	2.33	1.29–4.22	0.005
3V FFR (per 0.05 decrease)† as continuous predictor	1.04	0.92–1.18	0.507
High-risk patient group: Group 3 and 4‡	2.33	1.03–5.30	0.043

C-index of the multivariable Cox regression model was 0.73 (95% CI, 0.66%–0.80%). CAD indicates coronary artery disease; CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; MACEs, major adverse cardiac events; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery; 3V-FFR , total sum of FFR values of the 3 vessels.
*All the covariables included in the multivariable Cox regression model are presented.
†3V-FFR is the sum of FFR measurements of all 3 major epicardial coronary arteries.
‡Group 3, multivessel moderate CAD (FFR 0.81–0.87); Group 4, any functionally significant CAD (FFR≤0.80).

Risk Beyond Per-Vessel FFR Value 0.8

The risk of CAD extends beyond the FFR cutoff value of 0.80, and moderate CAD can contribute to the risk of an individual patient. In the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation)-2 substudy by Barbato et al,[15] the per-vessel 2-year MACE rate was significantly higher in vessels with moderate CAD (FFR value of 0.78–0.86, defined by the second quartile) than in those with FFR closer to normal (FFR value of 0.87–1.00, defined by the highest quartile) (HR, 3.4; 95% CI, 1.9%–6.2%, $P<0.001$). In the current study, moderate CAD was defined as the vessels within the lowest quartile of FFR values (0.81–0.87) among functionally insignificant coronary vessels. The risk of 2-year per-vessel ischemia-driven revascularization was higher in vessels with moderate CAD (FFR 0.81–0.87) than in vessels with no apparent CAD (FFR 0.87–1.0) (HR, 3.0; 95% CI, 1.4%–6.4%; $P=0.006$). When the criteria of Barbato et al[15] were applied to our study, the risk of 2-year ischemia-driven revascularization was also greater in vessels with FFR of 0.78 to 0.86 than in those with a FFR of 0.87 to 1.00 (HR, 3.3; 95% CI, 1.7%–6.7%, $P=0.001$). We observed a continuous association between the risk of ischemia-driven revascularization and lower FFR value in coronary arteries with FFR >0.80 (Table S3). In addition, the continuous association between the risk of 2-year MACE in patients with lower 3-vessel FFR measurements was consistently observed in patients without any coronary artery with functionally significant CAD (FFR ≤0.80) (Table S4). Considered together, these findings indicate that coronary arteries with moderate CAD could have prognostic implications.

Per-Vessel Versus Per-Patient Risk Assessment

To comprehensively evaluate the long-term risk of CAD in an individual patient, the risk of all 3 epicardial coronary arteries needs to be taken into consideration. Previous studies[16,17] demonstrate that a substantial proportion of late events occur in nontarget lesions and that CAD burden confers a significant risk for plaque progression. In the BASKET-PRO (Basel Stent Kosten-Effektivitäts Trial -Progression of CAD) study,[18] 37.1% of late clinical events occurred in the nontarget vessels.

The current study focused on the outcomes of patients with multivessel moderate CAD (FFR 0.81–0.87) because FFR measurement in all 3 epicardial coronary arteries enabled the

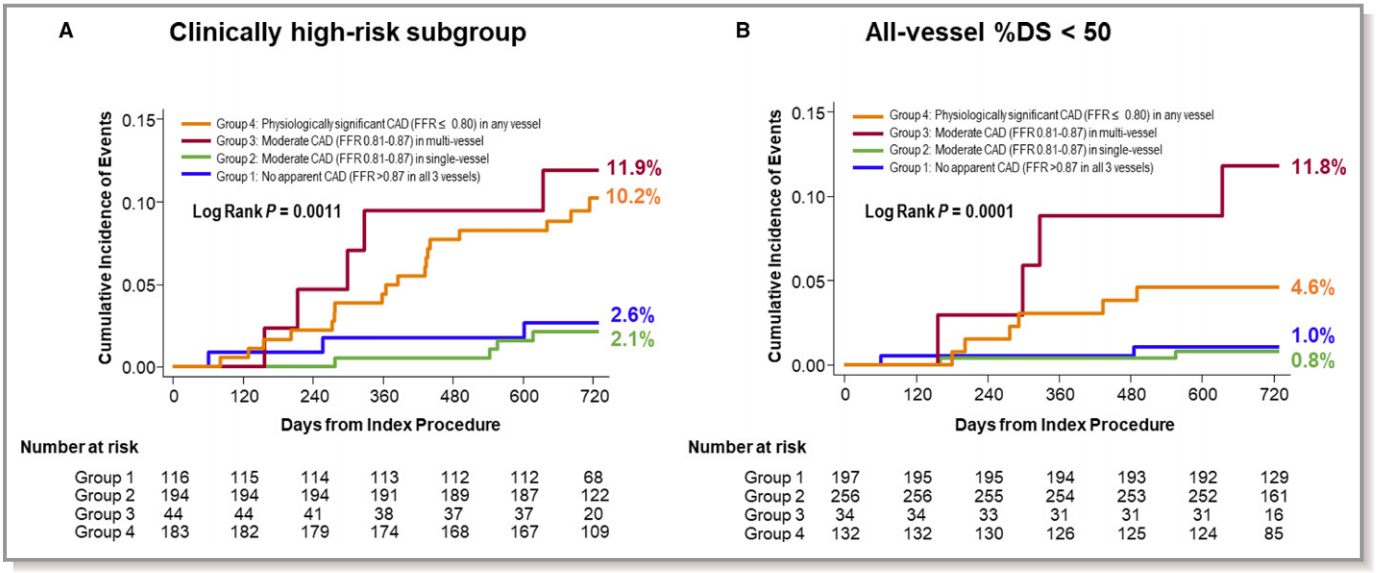

Figure 4. Comparison of 2-year MACE among the 4 groups, restricted to subgroups. The clinical outcomes of 4 patient groups are compared in patient subgroups with (A) clinically high-risk (diabetes mellitus or acute coronary syndrome) and (B) anatomically nonobstructive CAD with all coronary vessels % DS <50%. Cumulative incidences of major adverse cardiac events (MACE) patients are presented. CAD indicates coronary artery disease; DS, diameter stenosis; FFR, fractional flow reserve.

evaluation of the aggregated risk of CAD. Based on per-patient risk assessment, patients with moderate CAD (FFR 0.81–0.87) in a single vessel (Group 2) and multivessel (Group 3) experienced substantially different outcomes. The patients with multivessel moderate CAD (FFR 0.81–0.87) had significantly higher per-patient indices of disease burden, such as 3V-FFR and SYNTAX score. Because pathological progression of CAD involves incremental expansion of the total atherosclerotic volume that occurs in 2 dimensions (both the extent and the stenotic severity),[19] Group 3 may represent patients at a more advanced stage of atherosclerosis in terms of disease extent, compared with Group 2. It was interesting in our study that despite the incremental difference in per-patient anatomical and physiologic disease burden between Groups 1 and 2, clinical outcomes of these 2 groups did not differ. This result suggests that a certain anatomical or physiologic threshold determines clinical outcomes.

Implication of the Extent of Nonobstructive CAD

Several studies investigated the prognostic impact of the extent of anatomical nonobstructive disease evaluated by coronary angiography[9,20] or coronary computed tomography angiography.[8,21,22] In the CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) registry,[22] patients with 2- or 3-vessel involvement of nonobstructive (1–49% diameter stenosis) CAD on coronary computed tomography angiography had a 3-fold higher risk of all-cause mortality than normal subjects. Conversely, the risk of patients with 1-vessel involvement was similar to that of normal subjects.

Our study demonstrated that the extent of physiologically defined moderate CAD (FFR 0.81–0.87) may have prognostic implications. Although CAD of the individual coronary vessel was functionally insignificant, the risk associated with multivessel moderate CAD (FFR 0.81–0.87) was as high as the risk of patients who had functionally significant CAD. The prognostic implication of the high-risk group of multivessel moderate CAD or any functionally significant CAD was still observed in a multivariable regression model that included 3V-FFR as a continuous predictor (Table 4). This finding further supports the concept that the extent of disease can be a predictor of clinical outcome and opens the possibility of practical risk stratification of a patient for whom the measurement of FFR in all 3 vessels is not available.

This finding was more prominent in a subgroup of high-risk patients and in those without anatomically obstructive CAD. The risk of patients with single-vessel moderate CAD (FFR 0.81–0.87) was not significantly different from those without apparent CAD. These findings suggest that the physiologic index, FFR, reflects the risk continuum of coronary atherosclerosis, and further extends the scope of FFR beyond an individual coronary vessel to the atherosclerotic burden of the whole coronary tree.

Limitations

Some limitations of the current study should be considered. First, the patient group with multivessel moderate CAD (FFR 0.81–0.87) comprised a relatively small (84 of 1136 patients) portion of the study population and the difference of 2-year

MACE rates among the 4 groups was primarily driven by ischemia-driven revascularization. Second, we did not apply differential weights to the FFR values of different coronary arteries based on the volume of myocardium supplied by each vessel. Therefore, individual variance in coronary anatomy and subsequent difference in the prognostic impact between coronary arteries were not taken into account. Third, total plaque burden assessed by invasive imaging modalities was not available in this study.

Conclusion

The prognostic implication of multivessel moderate CAD (FFR 0.81–0.87) might be comparable to that of functionally significant CAD. Global physiologic assessment with FFR measurement in 3 vessels enables the identification of patients with multivessel moderate CAD (FFR 0.81–0.87) who might be at greater risk of long-term complications.

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Disclosures

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Sample Size Calculation of the 3V FFR-FRIENDS Study

The primary hypothesis of the 3V FFR-FRIENDS[1] study was that patients with low total sum of 3-vessel fractional flow reserve (3V-FFR) would experience a significantly higher 2-year MACE rate than those with high 3V-FFR. The estimated sample size of 1,136 patients was based on a two-sided chi square test with an alpha level of 0.05, a statistical power of 0.80, and a 5% drop-out rate, assuming 2-year rates of MACE, based on a previous study, of 12% in the low 3V-FFR group and 7% in the high 3V-FFR group.[2]

Table S1. Univariable Cox Regression Analysis of Association of Variables with 2-year MACE.

Characteristics	HR (95% CI)	Wald	*P*
Demographic			
Age > 70 years	1.7 (0.9-3.1)	2.83	0.093
Male	2.1 (0.9-4.6)	3.24	0.072
Comorbid Conditions			
Hypertension	0.9 (0.5-1.6)	0.22	0.64
Diabetes	1.0 (0.5-1.9)	0.00	0.98
Dyslipidemia	0.9 (0.5-1.5)	0.25	0.62
Current smoker	1.7 (0.9-3.0)	3.10	0.078
Clinical presentation			
Acute coronary syndrome	2.4 (1.4-4.4)	8.94	0.003
Anatomical and functional CAD burden			
High SYNTAX score (≥8)	2.6 (1.4-4.7)	9.43	0.002
Groups with 3V FFR measurement		15.10	0.002
Group 1: No apparent CAD	1 (reference)		
Group 2: Moderate CAD (FFR 0.81-0.87), single vessel	1.1 (0.4-2.8)	0.20	0.89
Group 3: Moderate CAD (FFR 0.81-0.87), multi vessel	3.3 (1.1-9.8)	4.58	0.032
Group 4: Functionally significant CAD	3.3 (1.4-7.7)	8.01	0.005

Abbreviations: CAD, coronary artery disease; CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; PCI, percutaneous coronary intervention.

* By univariable Cox regression

Table S2. Medication Changes during Follow-Up*

	Overall (1136)	Group 1 No apparent CAD (302)	Group 2 Moderate CAD 1-vessel (403)	Group 3 Moderate CAD 2 or 3-vessel (84)	Group 4 Functionally Significant CAD (347)	*P*-value†
Aspirin						<.001
At discharge	891 (79.3)	226 (74.8)	317 (78.7)	70 (83.3)	288 (83.0)	N/A
6 months	848 (74.7)	203 (67.2)	306 (75.9)	70 (83.3)	269 (77.5)	<.001
1 year	784 (69.3)	188 (62.7)	273 (67.7)	67 (80.7)	256 (74.0)	<.001
2 years	675 (59.5)	156 (51.7)	235 (58.3)	57 (67.9)	227 (65.6)	<.001
***P*-value‡**	0.004	Ref	0.119	0.002	0.002	
Dual anti-platelet therapy						<.001
At discharge	657 (57.8)	156 (51.7)	229 (56.8)	54 (64.3)	218 (62.8)	N/A
6 months	546 (48.1)	124 (41.1)	177 (43.9)	51 (60.7)	194 (55.9)	<.001
1 year	426 (37.6)	92 (30.7)	136 (33.8)	42 (50.6)	156 (45.1)	<.001
2 years	261 (23.0)	62 (20.5)	75 (18.7)	24 (28.6)	100 (28.9)	<.001
***P*-value‡**	<.001	Ref	0.355	0.003	<.001	
Statin						0.103
At discharge	998 (87.9)	255 (84.4)	358 (88.8)	72 (85.7)	313 (90.2)	
6 months	970 (85.4)	243 (80.5)	353 (87.6)	74 (88.1)	300 (86.5)	
1 year	949 (83.8)	236 (78.7)	342 (84.9)	75 (90.4)	296 (85.6)	
2 years	948 (83.6)	232 (76.8)	341 (84.8)	71 (84.5)	304 (83.9)	
***P*-value‡**	0.014	0.006	0.29	0.52	Ref	

Abbreviations: CAD, coronary artery disease.

***** Generalized estimating equations logistic regression models for repeated measures were used to assess the effect of time and patient group severity based on 3-vessel FFR measurements. No significant interaction between time and group severity was detected in the models for aspirin, dual anti-platelet and statin.

†*P*-value for Wald Chi-square test of the overall effect of time and for the difference between a time point and the preceding time point.

‡*P*-value for Wald Chi-square test of the overall effect of group severity and for the difference compared to the reference group.

Table S3. Univariable Cox Regression Analysis of Association of FFR with Per-Vessel Ischemia-Driven Revascularization Incidence.

Variable	HR	95% CI	*P*	Interaction *P*
FFR (per 0.05 decrease)*	1.4	1.23 - 1.60	<.001	
FFR (per 0.05 decrease) in Subgroups †				
No apparent CAD, FFR > 0.87	1.29	1.01 - 1.65	0.045	
Moderate CAD, FFR 0.81-0.87	1.28	0.97 - 1.69	0.080	0.63
Functionally significant CAD FFR ≤0.80	1.25	0.92 - 1.70	0.158	

Abbreviations: FFR, fractional flow reserve.

* From univariable Cox regression with FFR as a continuous variable in the whole study vessel.

† From univariable Cox regression with FFR as a continuous variable in the subgroup classified by FFR values.

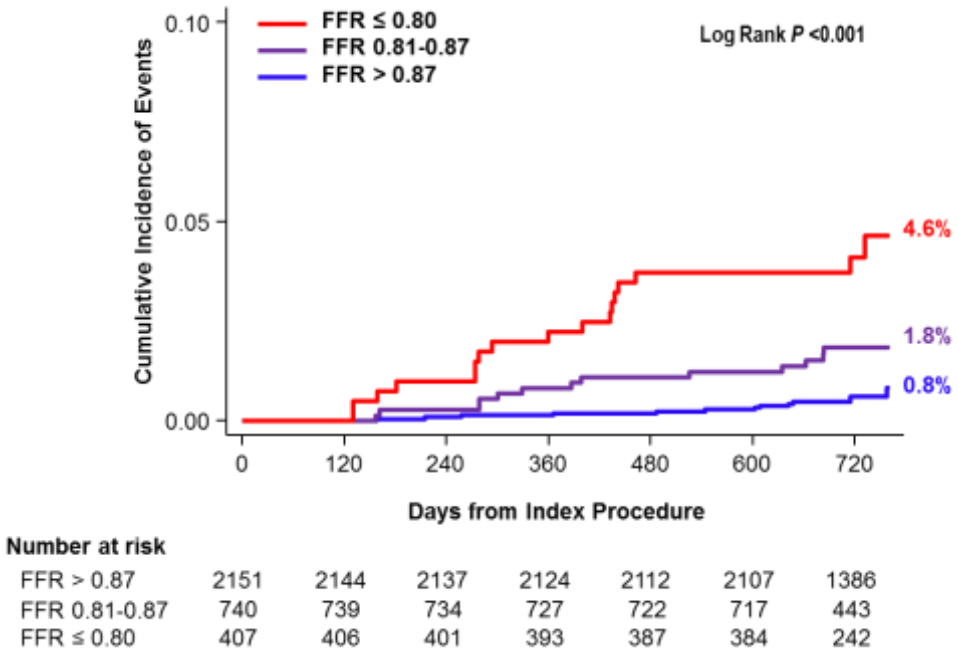
Table S4. Independent Predictors of 2-year Major Adverse Cardiac Events in Multivariable Cox Regression Analysis with 3V FFR as a Continuous Variable.

Variable	HR	95% CI	*P*	Interaction *P*
Age >70 years	1.86	0.97 - 1.23	0.059	
Male	1.74	0.75 - 4.05	0.200	
Current Smoker	1.5	0.80 - 2.78	0.208	
High SYNTAX score (≥8)	1.82	0.95 - 3.49	0.071	
Acute Coronary Syndrome	**2.37**	**1.32 - 4.29**	**0.004**	
3V FFR (per 0.05 decrease)*	**1.13**	**1.04 - 1.23**	**0.005**	
3V FFR (per 0.05 decrease) in patient subgroup†				
Group 1 to 3 (No Functionally significant CAD)	1.09	0.98 - 1.22	0.118	0.286
Group 4 (Any functionally significant CAD)	1.08	0.96 - 1.22	0.191	

* From multivariable Cox regression with 3V FFR as a continuous variable in the whole study population.

† From multivariable Cox regression with 3V FFR as a continuous variable in the subgroup classified by the presence of any major coronary artery with FFR ≤ 0.80.

Figure S1. Comparison of Per-Vessel Ischemia-Driven Revascularization Incidence among Vessel Groups Stratified by FFR.



Cumulative incidence of ischemia-driven revascularization in vessel groups stratified by per-vessel FFR (FFR ≤ 0.80: Functionally significant CAD; FFR 0.81-0.87: Moderate CAD; FFR > 0.87: No apparent CAD). The Kaplan-Meier estimated survival curves were compared using the log rank test.

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