JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 2, 2025

ORIGINAL RESEARCH

CORONARY

Prognostic Value of Coronary Angiography-Derived Index of Microcirculatory Resistance in Patients With Intermediate Coronary Stenosis

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ABSTRACT

BACKGROUND The association between coronary microcirculation and clinical outcomes in patients with intermediate stenosis remains unclear.

OBJECTIVES The aim of this study was to assess the prognostic significance of angiography-derived index of microcirculatory resistance (angio-IMR) in patients with intermediate coronary stenosis.

METHODS This post hoc analysis included 1,658 patients from the FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound for Clinical Outcomes in Patients with Intermediate Stenosis) trial, with angio-IMR measured in each vessel exhibiting intermediate stenosis. The primary endpoint was a patient-oriented composite outcome (POCO), a composite of all-cause death, myocardial infarction, or revascularization over a 2-year period.

RESULTS The median follow-up period was 24.8 months (Q1-Q3: 24.4-26.4 months). Over the 2-year follow-up period, patients with angio-IMR >25 exhibited a significantly higher POCO rate in both the percutaneous coronary intervention (PCI) group (35.06% [27 of 77] vs 7.2% [51 of 708]; $P < 0.001$) and the non-PCI group (17.95% [21 of 117] vs 4.23% [32 of 756]; $P < 0.001$). After adjusting for potentially related risk factors, angio-IMR >25 remained an independent predictor of the POCO in the PCI group (HR: 6.235; 95% CI: 3.811-10.203; $P < 0.001$) and the non-PCI group (HR: 5.282; 95% CI: 2.948-9.462; $P < 0.001$). The addition of angio-IMR demonstrated incremental prognostic value in both an angiographic risk factor model (C-index 0.710 [95% CI: 0.663-0.756] vs 0.615 [95% CI: 0.563-0.664] [$P < 0.001$]; net reclassification index 0.268 [95% CI: 0.191-0.362; $P < 0.001$]; integrated discrimination improvement 0.055 [95% CI: 0.030-0.108; $P < 0.001$]) and a clinical risk factor model (C-index 0.705 [95% CI: 0.658-0.751] vs 0.594 [95% CI: 0.544-0.644] [$P < 0.001$]; net reclassification index 0.268 [95% CI: 0.171-0.350; $P < 0.001$]; integrated discrimination improvement 0.057 [95% CI: 0.027-0.102; $P < 0.001$]).

CONCLUSIONS In individuals with intermediate coronary stenosis, elevated angio-IMR is linked to an adverse prognosis. Using angio-IMR significantly enhanced the capability to reclassify patients and accurately estimate the risk for the POCO. (JACC Cardiovasc Interv. 2025;18:171–183) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2024.10.017

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 2, 2025
JANUARY 27, 2025:171–183

ABBREVIATIONS AND ACRONYMS

Angio-IMR = angiography-derived index of microcirculatory resistance

CFR = coronary flow reserve

CMD = coronary microcirculatory dysfunction

FFR = fractional flow reserve

IDI = integrated discrimination improvement

IMR = index of microcirculatory resistance

IVUS = intravascular ultrasound

NRI = net reclassification index

PCI = percutaneous coronary intervention

POCO = patient-oriented composite outcome

QCA = quantitative coronary analysis

Intermediate coronary stenosis is commonly defined as a 40% to 70% stenosis of the epicardial coronary artery, assessed visually on angiography.[1,2] Nevertheless, coronary angiography has notable limitations, such as angle-limited images, subjective stenosis estimation, and an incomplete evaluation of the lesion, making it insufficient for guiding the treatment of intermediate stenosis alone. Therefore, the FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound for Clinical Outcomes in Patients with Intermediate Stenosis) trial investigated and compared 2 diagnostic tools, fractional flow reserve (FFR) and intravascular ultrasound (IVUS), as guidance in treating intermediate coronary stenosis. The findings of the FLAVOUR trial suggested that FFR guidance was noninferior to IVUS guidance concerning the composite primary outcome of death, myocardial infarction, or revascularization at 24 months.[3] However, despite the assessment of epicardial coronary dysfunction by FFR and IVUS, it is important to recognize that coronary microcirculatory dysfunction (CMD) can contribute to the clinical symptoms of patients with coronary intermediate stenosis.

Previous studies have highlighted the role of CMD in inducing angina pectoris, even in the absence of significantly severe epicardial coronary artery obstruction shown on angiography.[4,5] Additionally, various studies have emphasized the significance of coronary microcirculation in determining patient outcomes.[6,7] To address this, the concept of the index of microcirculatory resistance (IMR) was introduced by Fearon and colleagues[8-10] to invasively and quantitatively assess the status of microcirculation independent of the epicardial artery status. Substantial research has acknowledged the value of IMR in reflecting myocardial viability and left ventricular recovery after primary stenting for acute myocardial infarction, microvascular damage after ST-segment elevation myocardial infarction, and predicting adverse events in patients with stable coronary artery disease.[11-13] Lee et al[14] explored the prognostic value of coronary flow reserve (CFR) and IMR in patients with intermediate coronary stenosis and higher FFR. However, because of the limited clinical application of IMR, there remains a lack of large-scale research and sufficient data on the relationship between microcirculatory resistance and coronary intermediate stenosis.

Angiography-derived IMR (angio-IMR), being wire free and adenosine free, exhibited a noteworthy correlation and diagnostic accuracy in predicting IMR. Consequently, it has emerged as a promising alternative to invasive IMR for identifying coronary microvascular disorders in individuals presenting with acute and stable coronary syndromes.[15-20] In this study, we sought to assess the predictive validity of angio-IMR in patients with coronary intermediate stenosis under guidance with FFR or IVUS.

METHODS

PATIENT POPULATION AND STUDY DESIGN. This was a post hoc analysis of the FLAVOUR trial (NCT02673424), a multicenter randomized clinical trial designed to compare the clinical efficacy of FFR-guided percutaneous coronary intervention (PCI) with that of IVUS-guided PCI in patients with

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Manuscript received July 30, 2024; revised manuscript received September 26, 2024, accepted October 8, 2024.

intermediate coronary stenosis. The trial design, inclusion and exclusion criteria, and primary results have been reported previously.[3,21] The trial enrolled patients suspected of having ischemic heart disease, with at least 1 vessel showing intermediate stenosis (40%-70% stenosis by visual estimation). Exclusions from the angio-IMR analysis included patients diagnosed with ST-segment elevation myocardial infarction and those with severe vascular overlap or significant artifacts in angiographic images. Angio-IMR was measured retrospectively, both before and after intervention in PCI patients and only once at baseline in non-PCI patients before FFR or IVUS measurement. The FLAVOUR study protocol was approved by the ethics committee at each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for inclusion in the database for potential future research.

CORONARY ANGIOGRAPHIC PROCEDURES. In the FLAVOUR trial, coronary angiography and PCI were conducted using standard techniques. Quantitative coronary analysis (QCA) was performed at a core laboratory (Seoul National University Hospital QCA Core Laboratory). FFR measurement and IVUS image acquisition were carried out postrandomization using a standard technique, as previously described.[3,22] The quantitative coronary angiographic, FFR, and IVUS image data used in the present study were consistent with the data previously reported in the main trial.

ANGIO-IMR MEASUREMENTS. In this study, angio-IMR was retrospectively computed by 3 experienced analysts who were blinded to clinical information and outcome data in an external academic core laboratory using AccuIMR version 1.0 software (ArteryFlow Technology) (**Figure 1**). Briefly, angio-IMR can be derived from angiographic images in 3 key steps.[20,23,24] First, the image features, including the centerlines and the boundary lines of the coronary arteries, were detected and extracted. Next, the 3-dimensional centerlines of the arteries were reconstructed by pairing 2 different angiographic views with projections >25° apart. This allowed the overall 3-dimensional reconstruction of coronary arteries. Subsequently, the mean blood flow velocity was estimated using the equation of vessel length divided by mean transport time. Mean transport time was derived by selecting 2 TIMI frames as the starting and ending frames and tracking the time of the contrast media along the path. The pressure drop was then derived on the basis of anatomical information from 2 angiographic views, and mean blood flow was estimated according to the TIMI frame count as an input boundary condition. A specific computational fluid dynamics method was subsequently applied to calculate the pressure drop along the selected vessel segment. Finally, angio-IMR was obtained using the following 2 formulas:

$$\text{Angio-IMR} = (P_{a,\text{hyp}} - \Delta P_{\text{hyp}}) \cdot L / V_{\text{hyp}}$$

or

$$\text{Angio-IMR} = P_{a,\text{hyp}} \cdot \text{angio-FFR}_{\text{hyp}} \cdot L / V_{\text{hyp}}$$

where L is the length of the target vessel, V_{hyp} is the mean blood flow velocity at hyperemia, and angio-FFR_{hyp} is the angiograph-derived FFR value, which can also be calculated in similar ways as previously described.[25,26]

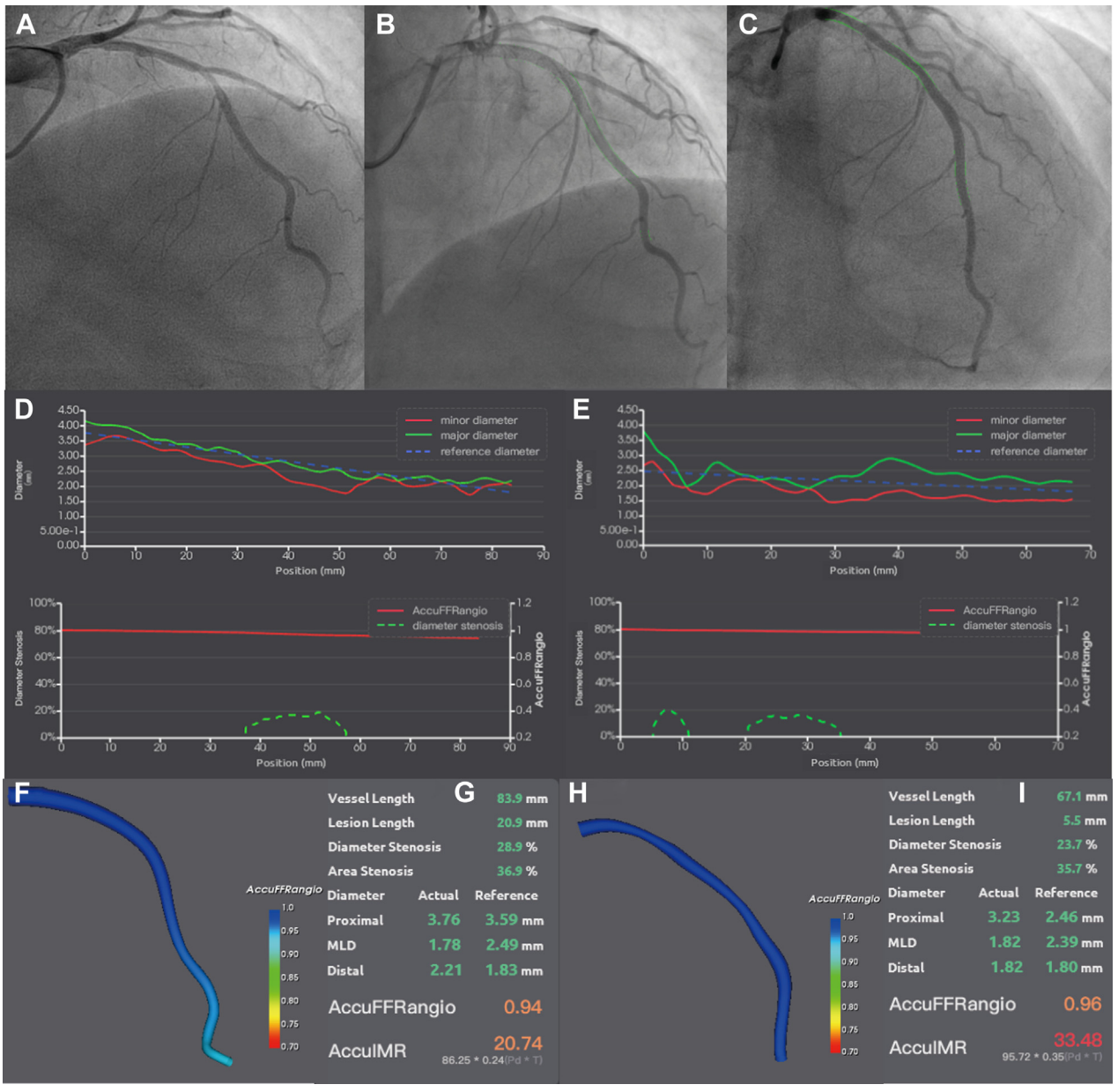
We used the final angio-IMR to represent the status of microcirculation in patients from both the PCI and non-PCI groups. The final angio-IMR is defined as the post-PCI angio-IMR value for patients in the PCI group and the baseline angio-IMR value for patients in the non-PCI group.

CLINICAL ENDPOINTS AND PATIENT FOLLOW-UP. The primary endpoint was the patient-oriented composite outcome (POCO), which included all-cause death, any myocardial infarction, and any revascularization. Secondary outcomes included the individual components of the POCO. In the FLAVOUR trial, all clinical events were defined according to the Academic Research Consortium, including the addendum to the definition of myocardial infarction. Unless a noncardiac cause was indisputable, all deaths were considered cardiac deaths. Follow-up was conducted through clinical visits or telephone interviews, with 14 patients (0.84%) lost to follow-up. The median follow-up period was 24.8 months (Q1-Q3: 24.4-26.4 months).

STATISTICAL ANALYSIS. All categorical variables are presented as numbers and frequencies (proportions), while continuous variables are reported as mean ± SD or median (Q1-Q3) according to distribution, which was assessed using the Kolmogorov-Smirnov test and visual inspection of Q-Q plots and histograms. Categorical variables were compared using the chi-square test, and continuous variables were analyzed using Student's *t*-test or the rank sum test, depending on the distribution. Data were analyzed both on a per patient and a per vessel basis.

We used a cutoff of 25 in our analyses to investigate the prognostic value of angio-IMR, as reported by several studies examining IMR values in healthy populations.[27-30] Kaplan-Meier analysis was used to

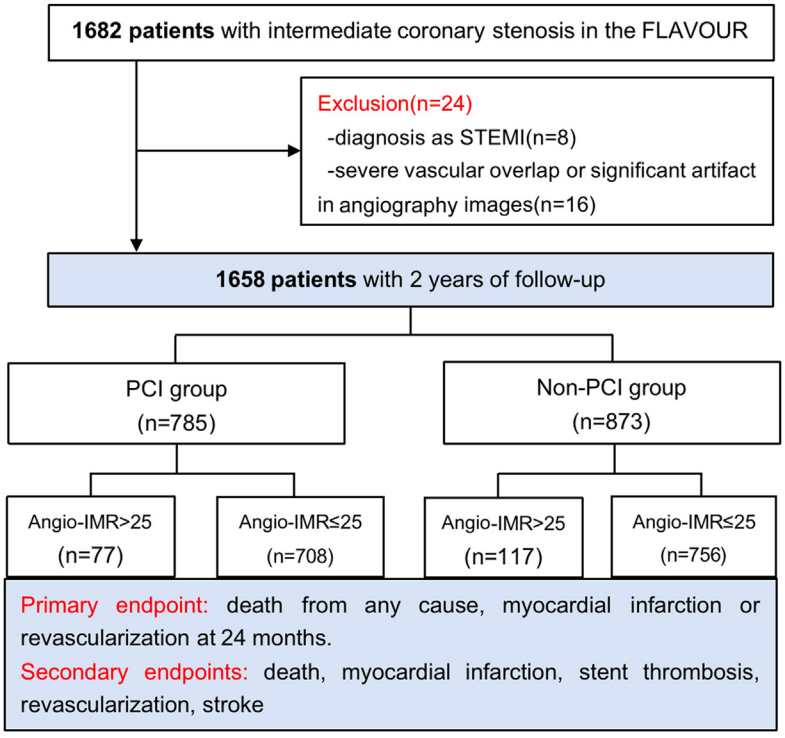
FIGURE 1 Computation of Angio-IMR From Coronary Angiography



(A, B) Coronary angiography of the same vessel at baseline and after percutaneous coronary intervention (PCI). (C) Coronary angiography of a vessel unoperated with PCI. (D, E) Luminal diameter and computed angiography-derived index of microcirculatory resistance (angio-IMR) pull back. (F to I) Computed angiography-derived fractional flow reserve and angio-IMR. AccuFFRangio = coronary angiography-derived fractional flow reserve; AccuIMR = coronary angiography-derived index of microcirculatory resistance; MLD = minimal luminal diameter.

calculate the cumulative incidence of both primary and secondary outcomes, and between-group differences were assessed using the log-rank test. Cox proportional hazards regression was applied to identify independent predictors of the POCO among patients. A directed acyclic graph was used to identify the potential covariates. DAGitty software was used to determine the minimal adjustment sets, which included hypertension, diabetes, dyslipidemia, smoking, left ventricular ejection fraction, and high

FIGURE 2 Study Flow



FLAVOUR = Fractional Flow Reserve and Intravascular Ultrasound for Clinical Outcomes in Patients with Intermediate Stenosis; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figure 1.

risk for target vessel failure (Supplemental Figure 2).[31] The Schoenfeld residual test was used to assess the proportional hazards assumption for Cox regression models.

Multivariate models were used to identify the independent predictors of the primary outcome. The variables considered clinical or angiographic relevant were put in the models. The additional value of angio-IMR for risk stratification over clinical risk factors or SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score were evaluated using the net reclassification index (NRI) and integrated discrimination improvement (IDI). Decision curve analysis was used to evaluate the clinical application value of angio-IMR in predicting prognosis with time-to-event data.

All *P* values were 2-sided, and a *P* value <0.05 was considered to indicate statistical significance. All statistical analysis were conducted using R version 4.2.3 (R Foundation for Statistical Computing) and SPSS Statistics version 26 (IBM).

RESULTS

BASELINE CHARACTERISTICS OF PATIENTS AND TARGET VESSELS. Angiographic data from 1,682 patients with or without PCI were screened. Eight patients were excluded because of diagnosis with ST-segment elevation myocardial infarction, and 16 patients were excluded because of severe vascular overlap or significant artifact in angiographic images (**Figure 2**). As a result, a total of 1,658 patients with 1,804 vessels were ultimately included in the study. The median age of the patients was 65.13 ± 9.63 years, 1,170 (70.6%) were men, 488 (27.9%) were diagnosed with acute coronary syndrome, and 1,048 (59.8%) were diagnosed with stable angina. A total of 785 (47.3%) underwent PCI guided by FFR or IVUS, and 10 of them were treated with drug-coated balloons and 775 with drug-eluting stents (**Tables 1 and 2**, Supplemental Table 1).

After measuring the angio-IMR values, patients who did not undergo PCI exhibited higher baseline

TABLE 1 Baseline Patient and Vessel Characteristics of the Non-PCI Group

	Non-PCI Patients/Vessels	Low Angio-IMR	High Angio-IMR	*P* Value
Per patient analysis	873	756 (86.6)	117 (13.4)	
General characteristics				
Age, y	65.46 ± 9.23	65.59 ± 9.09	64.62 ± 10.09	0.332
Male	284 (32.5)	500 (66.1)	89 (76.1)	0.033
BMI, kg/m^2	24.58 ± 3.22	24.52 ± 3.27	24.97 ± 3.27	0.163
FFR/IVUS group	536 (61.4)/337 (38.6)	463 (61.2)/293 (38.8)	73 (62.4)/44 (37.6)	0.812
Diagnosis				
Acute coronary syndrome	179 (20.5)	152 (20.1)	27 (23.1)	0.375
Stable angina	605 (69.3)	523 (69.2)	82 (70.1)	
Other	89 (10.2)	81 (10.7)	8 (6.8)	
Clinical history				
Diabetes mellitus	271 (31)	245 (32.4)	26 (22.2)	0.027
Hypertension	579 (66.3)	499 (66)	80 (68.4)	0.614
Dyslipidemia	667 (76.4)	580 (76.7)	87 (74.4)	0.576
Current smoking	170 (19.5)	145 (19.2)	25 (21.4)	0.578
Chronic kidney disease	136 (15.6)	114 (15.1)	22 (18.8)	0.301
Previous myocardial infarction	47 (5.4)	44 (5.8)	3 (2.6)	0.146
Previous PCI	148 (17)	131 (17.3)	17 (14.5)	0.453
Left ventricular ejection fraction, %	64.18 ± 8.04	64.26 ± 7.83	63.65 ± 9.37	0.482
SYNTAX score at baseline	7 (5-9)	7 (5-9)	7 (5-9)	0.619
SYNTAX score after PCI	6 (3-8)	6 (3-8)	7 (5-9)	0.376
Per vessel analysis				
Vessel	934	814 (87.2)	120 (12.8)	0.404
Left anterior descending branch	584 (62.5)	503 (61.8)	81 (67.5)	
Left circumflex branch	110 (11.8)	96 (11.8)	14 (11.7)	
Right coronary artery	240 (25.7)	215 (26.4)	25 (20.8)	
Pre-PCI angio-FFR	0.89 ± 0.06	0.89 ± 0.05	0.94 ± 0.04	<0.001
Pre-PCI angio-IMR	17.56 ± 5.97	15.88 ± 4.16	28.95 ± 3.34	<0.001

Values are n, mean ± SD, n (%), or median (Q1-Q3), unless otherwise indicated. All patients in this analysis were of Asian descent.

Angio-FFR = angiography-derived fractional flow reserve; Angio-IMR = angiography-derived index of circulatory resistance; BMI = body mass index; FFR = fractional flow reserve; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

angio-IMR than those who underwent PCI (17.76 ± 5.98 vs 14.9 ± 4.84; $P < 0.001$) (Table 3). In patients who underwent PCI, angio-IMR significantly increased after the intervention (18.2 ± 5.16 vs 14.9 ± 4.84; $P < 0.001$) (Table 3). Considering the potential effect of PCI on angio-IMR, the final angio-IMR values were used for the analysis. A total of 194 patients (11.7%) had angio-IMR values >25, with 117 patients (13.4%) in the non-PCI group and 77 patients (9.8%) in the PCI group (Table 3). General and clinical characteristics were similar between low- and high-angio-IMR groups, except for body mass index, the proportion of men, which were higher in patients with elevated angio-IMR (Tables 1 and 2, Supplemental Table 1).

CLINICAL ENDPOINTS. The median follow-up period was 24.8 months (Q1-Q3: 24.4-26.4 months). When analyzing patients with and without PCI, we found that patients with higher angio-IMR exhibited worse outcomes regardless of revascularization status. Among patients who underwent PCI, those with post-PCI angio-IMR > 25 demonstrated significantly higher rates of the POCO at 24 months compared with those with lower post-PCI angio-IMR (35.06% [27 of 77] vs 7.2% [51 of 708]; $P < 0.001$) (Table 4, Figure 3A). This was driven by higher incidence rates of cardiac death (2.6% [2 of 77] vs 0.56% [4 of 708]; $P = 0.049$) and any revascularization (29.87% [23 of 77] vs 4.24% [30 of 708]; $P < 0.001$). Similarly, in the non-PCI group, patients with higher angio-IMR had elevated rates of the POCO (17.95% [21 of 117] vs 4.23% [32 of 756]; $P < 0.001$) (Table 4, Figure 3B), primarily reflected in the rates of revascularization (14.53% [17 of 117] vs 1.98% [15 of 756]; $P < 0.001$).

When using the final angio-IMR value and analyzing the 2 groups together, we found that the high-angio-IMR group still exhibited a significantly

TABLE 2 Baseline of Patient and Vessel Characteristics of the PCI Group

	PCI Patients/Vessels	Low Angio-IMR	High Angio-IMR	*P* Value
Per patient analysis	785	708 (90.2)	77 (9.8)	
General characteristics				
Age, y	64.76 ± 10.05	64.92 ± 9.95	63.36 ± 10.94	0.199
Male	581 (74)	518 (73.2)	63 (81.8)	0.100
BMI, kg/m^2	24.72 ± 3.35	24.62 ± 3.34	25.56 ± 3.30	0.019
FFR/IVUS group	292 (37.2)/493 (62.8)	266 (37.6)/442 (62.4)	26 (33.8)/51 (66.2)	0.512
Diagnosis				
Acute coronary syndrome	309 (39.4)	285 (40.3)	24 (31.2)	0.277
Stable angina	443 (56.4)	393 (55.5)	50 (64.9)	
Other	33 (4.2)	30 (4.2)	3 (3.9)	
Clinical history				
Diabetes mellitus	272 (34.6)	237 (33.5)	35 (45.4)	0.036
Hypertension	548 (69.8)	494 (69.8)	54 (70.1)	0.948
Dyslipidemia	636 (81)	580 (81.9)	56 (72.7)	0.051
Current smoking	144 (18.3)	125 (17.7)	19 (24.7)	0.131
Chronic kidney disease	152 (19.4)	139 (19.6)	13 (16.9)	0.562
Previous myocardial infarction	45 (5.7)	43 (6.1)	2 (2.6)	0.213
Previous PCI	172 (21.9)	155 (21.9)	17 (22.1)	0.970
Left ventricular ejection fraction, %	63.10 ± 8.76	63.07 ± 8.98	63.32 ± 6.60	0.774
SYNTAX score at baseline	9 (7-13.5)	9 (7-13)	9 (6.5-14)	0.936
SYNTAX score after PCI	2 (0-5)	2 (0-5)	3 (0-6)	0.183
Target vessel underwent PCI	785 (47.3)	708 (48.4)	77 (39.7)	0.023
Per vessel analysis	870	787 (90.5)	83 (9.5)	
Vessel				0.087
Left anterior descending branch	533 (61.3)	487 (61.9)	46 (55.4)	
Left circumflex branch	117 (13.4)	109 (13.9)	8 (9.6)	
Right coronary artery	220 (25.3)	191 (24.3)	29 (34.9)	
Pre-PCI angio-FFR	0.75 ± 0.11	0.75 ± 0.11	0.78 ± 0.12	0.020
Pre-PCI angio-IMR	14.97 ± 4.93	14.33 ± 4.31	21.07 ± 6.20	0.000
Post-PCI angio-FFR (817/1,804)	0.90 ± 0.04	0.90 ± 0.04	0.92 ± 0.04	0.000
Post-PCI angio-IMR (817/1,804)	18.06 ± 5.15	17.03 ± 4.09	28.03 ± 3.26	0.000

Values are n, mean ± SD, n (%), or median (Q1-Q3). All patients in this analysis were of Asian descent. Target vessel underwent PCI refers to whether the target vessel with intermediate stenosis had undergone PCI in this trial after evaluation by FFR or IVUS.

Abbreviations as in Table 1.

higher POCO rate than the low-angio-IMR group (24.74% [48 of 194] vs 5.67% [83 of 1464]; $P < 0.001$) (Supplemental Figure 1, Supplemental Table 2). When examining the individual components of the POCO, patients with higher angio-IMR had a higher rate of revascularization (20.62% [40 of 194] vs 3.07% [45 of 1,464]; $P < 0.001$) and cardiac death (2.58% [5 of 194] vs 0.89% [13 of 1,464]; $P < 0.001$) than those with lower angio-IMR, while the incidence rates of myocardial infarction, stent thrombosis, and stroke were similar between the 2 groups (**Table 4**, Supplemental Table 2).

In patients who underwent PCI, angio-IMR was a significant predictor of the POCO (HR: 5.625; 95% CI: 3.525-8.975; $P < 0.001$) (**Table 5**), and after adjustment for related covariates (Supplemental Figure 2), it remained a significant predictor of the POCO (HR: 6.235; 95% CI: 3.811-10.203; $P < 0.001$) (**Table 5**). In patients without PCI, angio-IMR was also a significant predictor of the POCO, both before (HR: 4.450; 95% CI: 2.566-7.711; $P < 0.001$) and after (HR: 5.282; 95% CI: 2.948-9.462; $P < 0.001$) adjustment (**Table 5**).

When angio-IMR presents as a continuous variable instead of a categorical variable, it remained a significant predictor of the POCO in both the PCI and non-PCI groups (Supplemental Table 3).

TABLE 3 Pre-PCI and Post-PCI Angio-IMR

	Pre-PCI Angio-IMR	Post-PCI Angio-IMR	Angio-IMR >25	*P* Value
PCI group (n = 785)	14.9 ± 4.84	18.2 ± 5.16	77 (9.8)	0.000[a]
Non-PCI group (n = 873)	17.76 ± 5.98		117 (13.4)	0.000[b]

Values are mean ± SD or n (%). [a]For pre-PCI angio-IMR vs post-PCI angio-IMR in the PCI group. [b]For pre-PCI angio-IMR between the non PCI group and the PCI group.

Abbreviations as in Table 1.

TABLE 4 Clinical Outcomes of Patients With Intermediate Stenosis Over 2 Years of Follow-Up

	Low Angio-IMR	High Angio-IMR	*P* Value
PCI group (n = 785)	(n = 708)	(n = 77)	
POCO at 24 mo	51 (7.20)	27 (35.06)	0.000
Death	9 (1.27)	3 (3.89)	0.072
Cardiac death	4 (0.56)	2 (2.60)	0.049
Myocardial infarction	18 (2.54)	2 (2.60)	0.970
Revascularization	30 (4.24)	23 (29.87)	0.000
Ischemia-driven revascularization	20 (2.82)	19 (24.68)	0.000
Non-PCI group (n = 873)	(n = 756)	(n = 117)	
POCO at 24 mo	32 (4.23)	21 (17.95)	0.000
Death	14 (1.85)	3 (2.56)	0.609
Cardiac death	9 (1.19)	3 (2.56)	0.239
Myocardial infarction	7 (0.93)	2 (1.71)	0.439
Revascularization	15 (1.98)	17 (14.53)	0.000
Ischemia-driven revascularization	12 (1.59)	16 (13.68)	0.000

Values are n (%). Primary and secondary outcomes were evaluated in the intention-to-treat population at 24 months. The between-group difference was measured between the low-angio-IMR group and the high-angio-IMR group using the Kaplan-Meier method. $P < 0.05$ for significance.

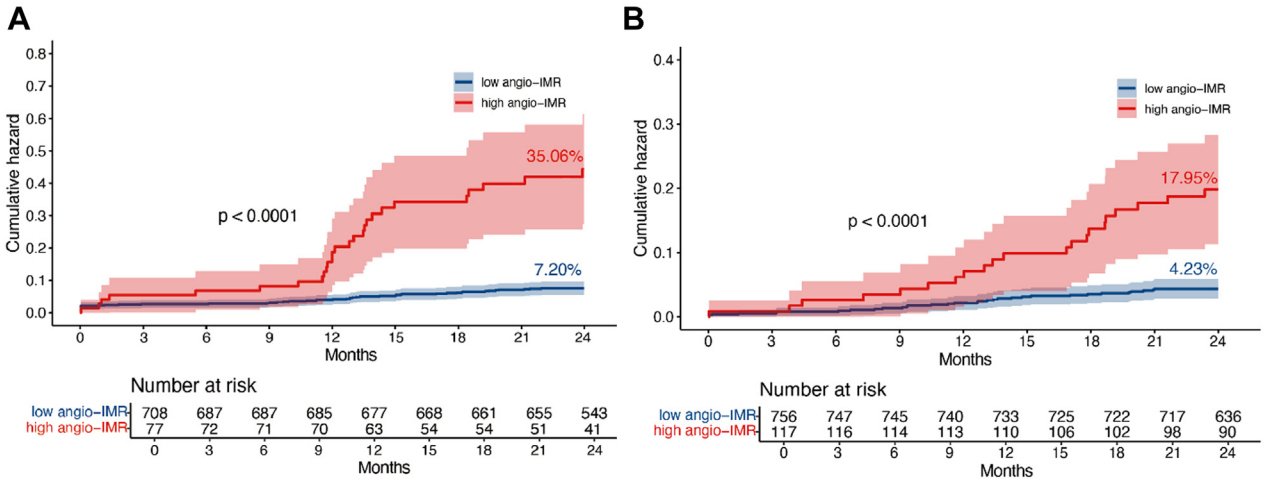
POCO = patient-oriented clinical outcome (death of any cause, myocardial infarction, or revascularization); other abbreviations as in Table 1.

CLINICAL USEFULNESS OF ANGIO-IMR IN PREDICTING THE POCO. The discriminant ability to predict the risk for the POCO significantly increased when angio-IMR group was added to an angiographic risk factor model (C-index 0.710 [95% CI: 0.663-0.756] vs 0.615 [95% CI: 0.563-0.664]; $P < 0.001$) (Figure 4) or a clinical risk factor model (C-index 0.705 [95% CI: 0.658-0.751] vs 0.594 [95% CI: 0.544-0.644]; $P < 0.001$) (Figure 4).The NRI and IDI analyses showed incremental discrimination ability and reclassification indexes by adding angio-IMR group into an angiographic risk factor model (NRI 0.268 [95% CI: 0.191-0.362; $P < 0.001$]; IDI 0.055 [95% CI: 0.030-0.108; $P < 0.001$]) (Figure 5A) and a clinical risk factor model (NRI 0.268 [95% CI: 0.171-0.350; $P < 0.001$]; IDI 0.057 [95% CI: 0.027-0.102; $P < 0.001$] (Figure 5B). Time-dependent decision curve analysis revealed that incorporating angio-IMR offered a greater net benefit when the risk threshold exceeded 0.034 in the angiographic risk factor model and 0.038 in the clinical risk factor model (Figure 5). In summary, the inclusion of angio-IMR improved the model's ability to predict the 2-year risk for the POCO, providing a more accurate estimation of decision outcomes (Figure 5).

DISCUSSION

This post hoc analysis of the FLAVOUR trial demonstrates the prognostic value of angio-IMR in patients with coronary intermediate stenosis for the first time. The major finding was that patients with angio-IMR > 25 possessed a higher risk for death, myocardial infarction, and revascularization at 24 months than those with preserved angio-IMR (Central Illustration). Integration of angio-IMR into the model with clinical risk factors or angiography risk factors also demonstrated significantly better discriminant and reclassification ability. This result suggests that further measurement of angio-IMR in patients with

FIGURE 3 Cumulative Incidence of the Primary Outcome at 24 Months



(A) Patients who underwent PCI. (B) Patients without PCI. Abbreviations as in Figure 1.

TABLE 5 Risk for the POCO in Patients With Intermediate Coronary Stenosis on the Basis of Angio-IMR

	2-Year POCO, n (%)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
PCI group					
Low angio-IMR	51 (7.20)	1.00 (Ref.)	NA	1.00 (Ref.)	NA
High angio-IMR	27 (35.06)	5.625 (3.525-8.975)	<0.001	6.235 (3.811-10.203)	<0.001
Non-PCI group					
Low angio-IMR	32 (4.23)	1.00 (Ref.)	NA	1.00 (Ref.)	NA
High angio-IMR	21 (17.95)	4.450 (2.566-7.711)	<0.001	5.282 (2.948-9.462)	<0.001

The covariates in the adjustment include hypertension, diabetes, smoking, left ventricular ejection fraction, dyslipidemia, and high risk for TVF. High risk for TVF was defined as follows: vessels with FFR >0.92 in the FFR group or minimal luminal area >4.5 mm^2 or plaque burden of 58% or less in the IVUS group were low-TVF risk deferred vessels, and post-PCI vessels with FFR of 0.80 or less in the FFR group or minimal stent area of 6.0 mm^2 or less and plaque burden at stent edge >58% in the IVUS group were high-TVF risk revascularized vessels.[40]

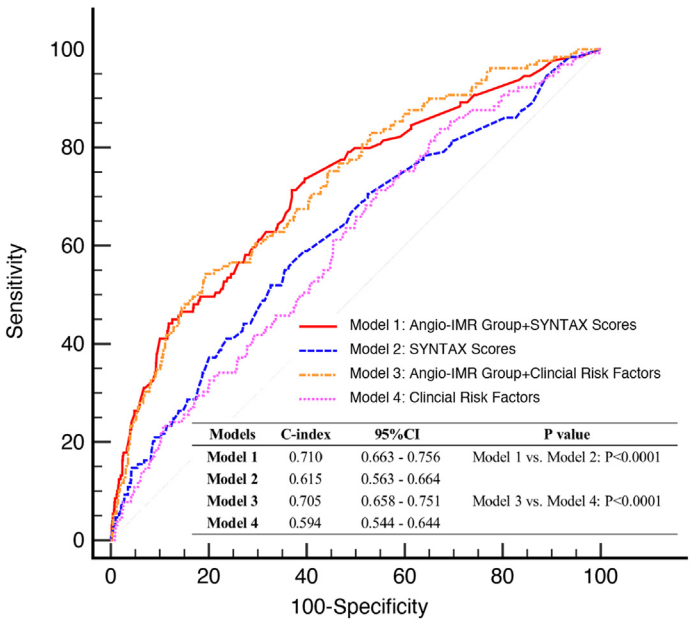
Ref. = reference; TVF = target vessel failure; other abbreviations as in Tables 1 and 2.

FFR-guided PCI or IVUS-guided PCI can enhance the predictive ability for high-risk populations in patients with intermediate coronary stenosis.

The objective in treating coronary intermediate stenosis is to attain sufficient myocardial perfusion, making the evaluation of the lesion of paramount importance. It has been previously pointed out that the angiographic images are limited by the angle and rely on subjective visual estimation. IVUS can evaluate the composition of atherosclerotic plaques and their vulnerability to rupture, while FFR can assess the degree of functional and physiological ischemia, aiding in the identification of high-risk or unstable intermediate lesions.[3] Furthermore, tools such as cardiac magnetic resonance, cardiovascular optical coherence tomography, and CFR can be used. However, the use of these methods remains limited in clinical practice because of cost, technology, and other reasons. Moreover, the ability of these tools to assess coronary microcirculation may be inadequate. Further diagnostic tools are needed to better recognize and evaluate intermediate coronary stenosis, especially to assess the coronary microcirculation in these patients. Angio-IMR provides a convenient and noninvasive way to assess the microcirculatory status and has the potential to guide further medication treatment strategy of coronary intermediate stenosis.

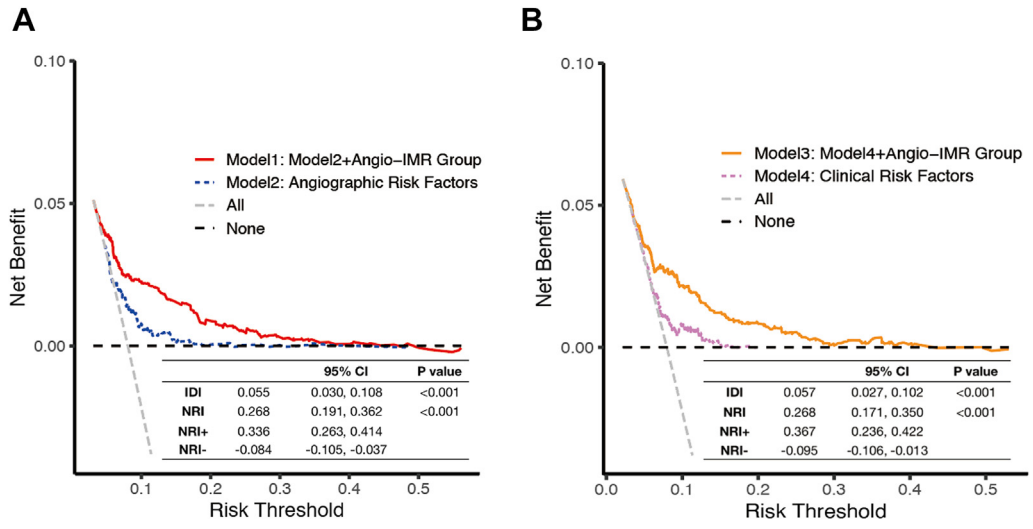
In this post hoc analysis, patients with angio-IMR > 25 exhibited a lower proportion of target vessel PCI at baseline but significantly higher rates of the POCO over 24 months of follow-up. These results further support previous findings indicating an association between coronary microcirculatory resistance and an elevated risk for cardiovascular events, particularly in patients lacking significant ischemia in the epicardial coronary artery.[1,13,14] A previous study highlighted that patients with intermediate coronary stenosis and low CFR along with high IMR exhibited elevated rates of cardiac death and revascularization, suggesting that CFR and IMR improve the risk stratification of patients with high FFR.[14] However, that study included only patients with high FFR and intermediate coronary stenosis who did not undergo PCI. In contrast, we enrolled a broader group of patients with intermediate coronary artery stenosis, regardless of whether they underwent PCI, and focused on the

FIGURE 4 Incremental Prognostic Value of Angio-IMR Over Clinical and Angiographic Factors



Clinical risk factors included age, sex, body mass index, smoking, acute coronary syndrome, diabetes mellitus, left ventricular ejection fraction, and target vessel underwent intervention. Angiographic risk factors included SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score at baseline and after intervention. Angio-IMR = angiography-derived index of microvascular resistance.

FIGURE 5 Decision Curve Analysis of 4 Models



(A) Decision curve of model 1 vs model 2. (B) Decision curve of model 3 vs model 4. Angio-IMR = angiography-derived index of microvascular resistance; IDI = integrated discrimination improvement; NRI = net reclassification index.

assessment of angio-IMR, a more accurate tool for reflecting coronary microcirculation. This renders the results of our research more universal and provides better clinical guidance in this patient population.

Furthermore, our findings indicate that patients with higher angio-IMR are at increased risk for revascularization, specifically during follow-up. This observation may be attributed to the association of coronary microvascular disorders with structural remodeling and functional dysregulation of arterioles, leading to endothelial dysfunction and inadequate myocardial oxygen supply, ultimately contributing to lipid deposition, atherosclerosis, and plaque formation.[32-34] These results support the potential effectiveness of a combined assessment using FFR and angio-IMR in risk stratification for patients with stable coronary syndrome.

Of note, the pathophysiological mechanisms underlying CMD remain poorly understood, primarily because of the lack of appropriate experimental models. One possible explanation is that microvascular dysfunction is associated with endothelial inflammation, thereby contributing to cardiovascular death and revascularization.[32,33,35,36] Additionally, downstream embolization of atherosclerotic material from the epicardial vessel wall into the distal microvasculature is an important cause of CMD following elective PCI.[37] Moreover, the coronary microcirculation may react to the vasoconstrictor, prothrombotic, and proinflammatory soluble substances released by the culprit lesion, which thereby severely impaired the coronary vasodilator reserve.[38,39]

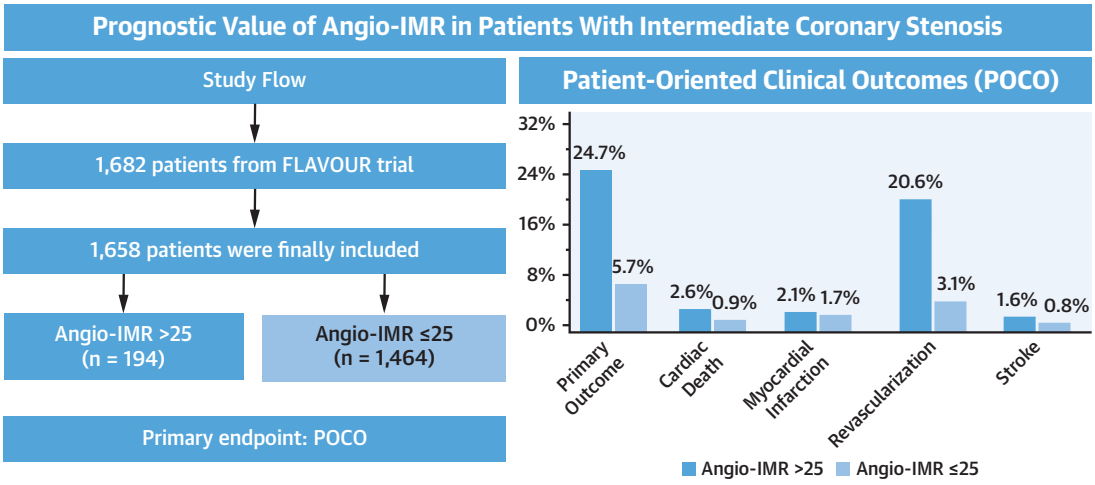
In this study, we used final angio-IMR to represent the microcirculation of patients with deferred and revascularized vessels. Although the pathogenesis of CMD in these 2 conditions may differ, this variation guides cardiologists to more precise therapies. Nevertheless, the role of coronary microcirculation, as assessed by angio-IMR, remains consistent in the risk stratification of patients.

STUDY LIMITATIONS. First, it is important to note that this was a post hoc analysis of the FLAVOUR study, and as such, some findings should be interpreted with caution and regarded as hypothesis generation.

Second, the study population exclusively comprised patients with coronary intermediate stenosis, suggesting a relatively lower cardiovascular risk, and the event rates were correspondingly small. Therefore, the result may not be directly applicable to individuals with severe epicardial coronary stenosis.

Third, patients with intermediate coronary stenosis were further assessed with either FFR or IVUS.

CENTRAL ILLUSTRATION Study Overview and Findings



- In patients with intermediate coronary stenosis, elevated angio-IMR values are linked to an adverse prognosis
- After adjusting for potentially related risk factors, angio-IMR >25 remained an independent predictor of the POCO in the PCI group (HR: 6.235; 95% CI: 3.811-10.203; $P < 0.001$) and the non-PCI group (HR: 5.282; 95% CI: 2.948-9.462; $P < 0.001$)
- Utilizing angio-IMR significantly enhances the capability to reclassify patients and accurately estimate the risk of POCO

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In patients with intermediate coronary stenosis, individuals with angiography-derived index of microcirculatory resistance (angio-IMR) >25 exhibited a significantly higher rate of the patient-oriented composite outcome (POCO; a composite of all-cause death, myocardial infarction, or revascularization) over 2 years of follow-up. FLAVOUR = Fractional Flow Reserve and Intravascular Ultrasound for Clinical Outcomes in Patients with Intermediate Stenosis; PCI = percutaneous coronary intervention.

Throughout the data analysis, we did not separate the 2 cohorts. However, it is important to note that although FFR provides functional assessment and IVUS evaluates plaque burden and luminal diameter, neither method comprehensively evaluates the lesion. The FFR-guided strategy demonstrated non-inferiority to the IVUS-guided strategy in clinical outcomes, however.[3]

Despite these limitations, our study has significant clinical implications. The retrospective computation of angio-IMR can be performed noninvasively and without the need for an extra adenosine injection, making it convenient option for future clinical use. This study highlights the inadequacy of relying solely on an FFR- or IVUS-guided strategy in assessing patient outcomes. It suggests that exclusively using an FFR- or IVUS-guided PCI strategy may be inadequate. The further measurement of angio-IMR is proposed to enhance the predictive ability for high-risk populations in patients with intermediate coronary stenosis. Moreover, further large-scale research is warranted to investigate optimized medication treatments targeting patients with high angio-IMR, comparing their efficacy with standard care to enhance clinical outcomes.

CONCLUSIONS

This post hoc analysis of the FLAVOUR trial showed that in patients with intermediate coronary stenosis, elevated angio-IMR is correlated with an adverse prognosis, regardless of whether PCI was performed or not. The incorporation of angio-IMR markedly enhances the capacity to reclassify patients and estimate the risk for POCO. This improvement can foster optimized subsequent treatment in clinical decision making and justifies the need for future large-scale

research to further determine the optimized medication treatment.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The FLAVOUR trial was funded by Boston Scientific. This post hoc analysis was funded by the National Natural Science Foundation of China (grant 82170332), Zhejiang Provincial Key Research and Development Plan (grant 2024C03095), and Hangzhou Leading Innovation and Entrepreneurship Team Project (grant TD2022007). Dr Hahn has received research grants from Abbott Korea, Biosensors International Group, Biotronik, Boston Scientific, and Medtronic. Dr Koo has received institutional research grants from Abbott Vascular, Boston Scientific, and Philips. Dr Xiang is principal scientist for ArteryFlow Technology. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Coronary microcirculation dysfunction is recognized as a significant factor in patients without significantly severe epicardial stenosis.

WHAT IS NEW? Angio-IMR, a novel index computed retrospectively from angiograms, has emerged as a precise predictor of coronary microcirculation status. Key findings indicate that patients with angio-IMR $>$ 25 face a higher risk for death, myocardial infarction, and revascularization at 24 months compared with those with preserved angio-IMR. Integrating angio-IMR into models with clinical risk factors or angiography risk factors significantly enhances discriminant and reclassification ability.

WHAT IS NEXT? This post hoc analysis of the FLAVOUR trial illuminates the association between angio-IMR and adverse patient prognosis. It prompts future large-scale research to optimize medication treatment strategies and management for patients with coronary intermediate stenosis.

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KEY WORDS coronary angiography, index of microcirculatory resistance, intermediate coronary stenosis, microcirculation, prognosis

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