JACC VOL. 86, NO. 8, 2025

PUBLISHED BY ELSEVIER

# Long-Term Outcomes After Fractional Flow Reserve vs Intravascular Ultrasound to Guide PCI

## The FLAVOUR Trial Extended Follow-Up

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## ABSTRACT

**BACKGROUND** The optimal treatment strategy for patients with intermediate coronary stenosis remains uncertain.

**OBJECTIVES** The aim of this study was to investigate the long-term outcomes of a randomized, open-label, multinational trial comparing fractional flow reserve (FFR)-guided vs intravascular ultrasound (IVUS)-guided treatment strategies.

**METHODS** Patients aged ≥19 years with de novo intermediate coronary stenosis (40%-70%) and target vessel diameters ≥2.5 mm were randomized 1:1 to FFR- or IVUS-guided treatment across 18 sites in Korea and China. The primary endpoint was a composite of all-cause death, myocardial infarction, and any revascularization occurring after the index procedure. Secondary endpoints included individual components of the primary outcome and per vessel outcomes according to treatment type. Extended follow-up continued through September 2024.

**RESULTS** Between July 2016 and August 2019, 1,682 patients were assigned to the FFR-guided (n = 838) and IVUS-guided (n = 844) groups. Over a median follow-up period of 6.3 years (Q1-Q3: 5.6-6.9 years), the primary outcome occurred in 339 patients (22.0%), with no statistically significant difference between groups (179 [23.1%] for FFR vs 160 [20.9%] for IVUS; HR: 1.15; 95% CI: 0.93-1.42; $P = 0.208$). The revascularization rate after the index procedure was higher in the FFR group (113 [14.9%] vs 87 [11.8%]; HR: 1.32; 95% CI: 1.00-1.75; $P = 0.049$), particularly for target vessel revascularization (72 [9.6%] vs 44 [6.2%]; HR: 1.67; 95% CI: 1.15-2.43; $P = 0.007$). Landmark analysis at 2 years and per vessel analyses indicated that the higher revascularization rate after the index procedure was driven primarily by late (2-7 years) revascularizations in vessels in which percutaneous coronary intervention (PCI) was initially deferred. Nevertheless, the overall rate of target vessel PCI, including procedures at index and during follow-up, was significantly lower in the FFR group (38.8% vs 60.5%; $P < 0.001$), with no statistically significant differences in the annual cumulative incidence of death or myocardial infarction between groups.

**CONCLUSIONS** FFR-guided and IVUS-guided treatment strategies resulted in comparable long-term outcomes, with no significant difference in patient-oriented composite outcomes. Although FFR-guided treatment was associated with a higher incidence of late target vessel revascularization, the overall target vessel PCI rate, accounting for both the index procedure and revascularization during follow-up, remained significantly lower in the FFR-guided treatment group, with comparable rates of hard outcomes between the 2 groups. (JACC. 2025;86:593-606) © 2025 by the American College of Cardiology Foundation.


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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2025.06.042

**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome

**CAD** = coronary artery disease

**FFR** = fractional flow reserve

**IVUS** = intravascular ultrasound

**IVI** = intravascular imaging

**MLA** = minimal luminal area

**PCI** = percutaneous coronary intervention

**MI** = myocardial infarction

In the management of coronary artery disease (CAD) in the catheterization laboratory, physiological assessment, including fractional flow reserve (FFR), is recommended for identifying functionally significant lesions that may benefit from percutaneous coronary intervention (PCI).[1,2] Meanwhile, intravascular imaging (IVI), such as intravascular ultrasound (IVUS), is advocated for optimizing PCI outcomes by providing detailed visualization of procedural outcomes related to stent deployment, particularly in complex lesions.[1,3,4] Beyond their established clinical implications, post-PCI FFR has demonstrated prognostic value in predicting long-term clinical outcomes and can aid in achieving optimal physiological results.[5-7] Additionally, IVUS enables pre-PCI lesion characterization by providing plaque morphology and luminal and plaque areas that cannot be captured by conventional angiography, and its emerging role in guiding revascularization decisions has been increasingly recognized.[8,9]

SEE PAGE 607

Likewise, recent evidence suggests that either FFR or IVUS could serve as a stand-alone modality, comprehensively guiding both decision making and procedural optimization without necessarily requiring the other. The FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients With Intermediate Stenosis) trial was designed to compare clinical outcomes between FFR-guided and IVUS-guided treatment, incorporating a comprehensive strategy from initial decision making to PCI optimization, and demonstrated the noninferiority of FFR-guided treatment compared with IVUS-guided treatment, with a lower PCI rate in the FFR-guided group.[10] Given the progressed nature of CAD and the potential for varying prognostic impacts over time for each modality,[11,12] the aim of this extended follow-up was to assess the long-term clinical outcomes of FFR-guided vs IVUS-guided treatment in patients with intermediate stenosis.

## METHODS

**STUDY DESIGN AND PARTICIPANTS.** We conducted the extended follow-up study of the randomized, open-label, multinational FLAVOUR trial to compare FFR-guided vs IVUS-guided treatment in patients with de novo intermediate coronary stenosis (40%-70%). The rationale, trial design, methodology, study conduct, and randomization process of the FLAVOUR trial have been described in previous publications.[10,13] A complete list of participating centers and investigators is provided in the Supplemental Appendix. Patients 19 years or older with CAD and de novo intermediate stenoses (40%-70%), as visually estimated on invasive coronary angiography in a target vessel of ≥2.5 mm, were considered for enrollment. Eligible patients were randomly assigned in a 1:1 ratio to receive either FFR-guided or IVUS-guided treatment. The primary exclusion criteria included noncardiac comorbidities with a life expectancy of <2 years, target lesions in the left main coronary artery or a coronary artery bypass graft, and increased risk for bleeding. A full list of inclusion and exclusion criteria is available in the Supplemental Appendix. The trial protocol was designed by the academic steering committee and received approval from the Institutional Review Board at each participating site. An independent data and safety monitoring board oversaw the trial. This study complied

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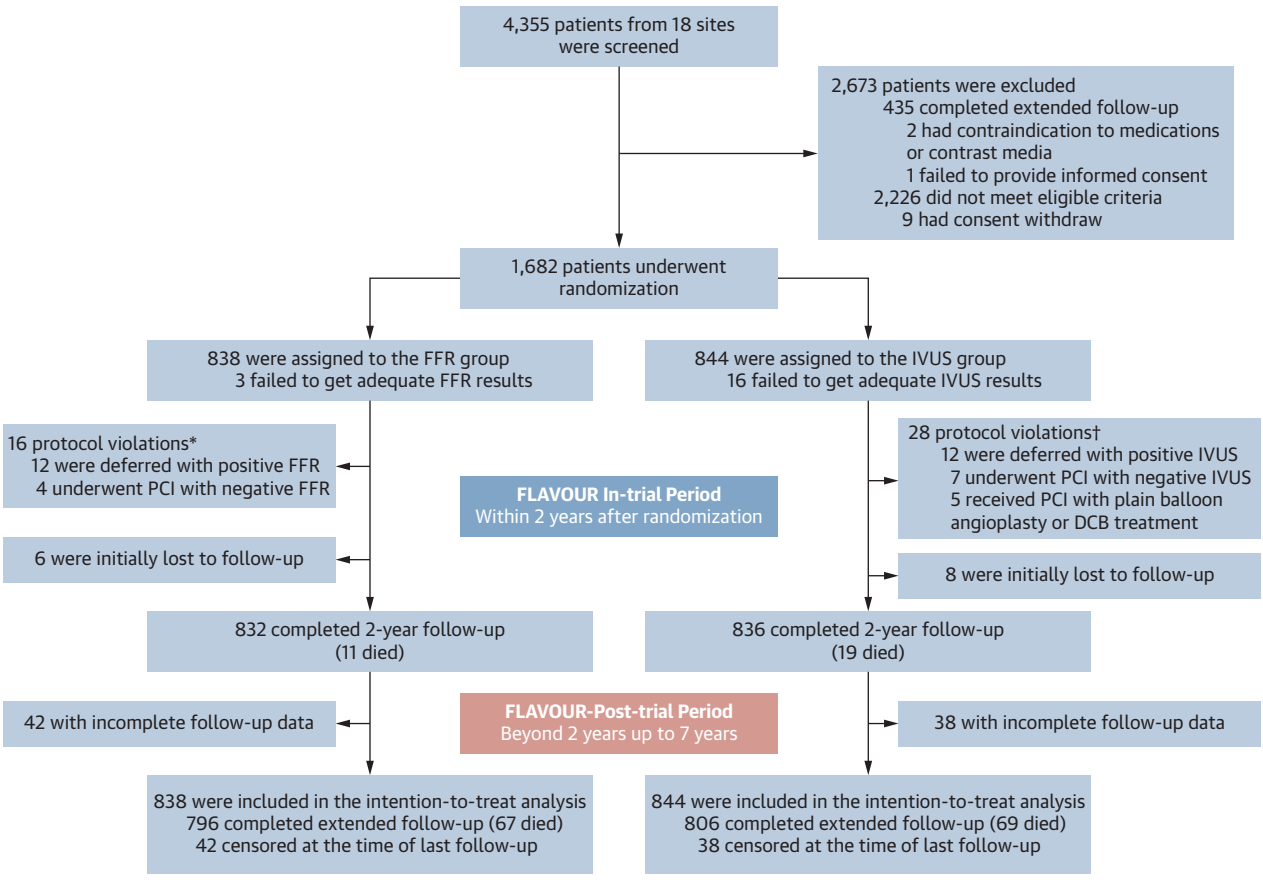
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 4, 2025; revised manuscript received June 12, 2025, accepted June 13, 2025.

**FIGURE 1** Trial Profile




This figure illustrates the study flow for the extended follow-up of the FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients With Intermediate Stenosis) trial, encompassing the in-trial period (within 2 years after randomization) and the post-trial period (beyond 2 years). DCB = drug-coated balloon; FFR = fractional flow reserve; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

with the International Council for Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The executive committee and all authors affirm the accuracy and completeness of the data, as well as the trial's adherence to the protocol.

**OUTCOMES.** The 2-year outcomes of the FLAVOUR trial have been previously reported.[10] The primary endpoint was defined as a composite of all-cause death, myocardial infarction (MI), and any revascularization occurring after the index procedure at 2 years, with findings published in prior reports. Following the publication of the results, all investigators were invited to participate in an extended follow-up analysis, with outcome data collected until September 2024. Clinical outcomes were recorded using a web-based electronic case report form (S-Soft). An independent clinical events committee, blinded to patient characteristics and treatment assignments, adjudicated all clinical outcomes. Key secondary endpoints included the individual components of the primary endpoint, as well as cardiac death, target vessel revascularization, stent thrombosis, and stroke (Supplemental Appendix).

**PROCEDURES.** In the FFR-guided group, revascularization was performed if FFR was ≤0.80.[2] For the IVUS-guided group, revascularization criteria included a minimal luminal area (MLA) of ≤3 $mm^2$ or an MLA between 3 and 4 $mm^2$ with a plaque burden exceeding 70%.[14-17] FFR and IVUS data were analyzed independently by core laboratories at Seoul National University Hospital and Ulsan University Hospital,

**TABLE 1 Baseline Characteristics**

| | Total (N = 1,682) | FFR Group (n = 838) | IVUS Group (n = 844) |
|---|---|---|---|
| Demographics | | | |
| Age, y | 65.1 ± 9.6 | 65.4 ± 9.4 | 64.8 ± 9.9 |
| Male | 1,187 (70.6) | 584 (69.7) | 603 (71.4) |
| Body mass index, kg/m$^2$ | 24.7 ± 3.3 | 24.6 ± 3.3 | 24.7 ± 3.3 |
| Diagnosis | | | |
| Stable angina | 1,063 (63.2) | 519 (61.9) | 544 (64.5) |
| Acute coronary syndrome | 496 (29.5) | 252 (30.1) | 244 (28.9) |
| STEMI | 8 (0.5) | 4 (0.5) | 4 (0.5) |
| NSTEMI | 27 (1.6) | 12 (1.4) | 15 (1.8) |
| Others[a] | 123 (7.3) | 67 (8.0) | 56 (6.6) |
| Diabetes mellitus | 554 (32.9) | 272 (32.5) | 282 (33.4) |
| Hypertension | 1,147 (68.2) | 577 (68.9) | 570 (67.5) |
| Dyslipidemia | 1,322 (78.6) | 667 (79.6) | 655 (77.6) |
| Current smoking | 321 (19.1) | 166 (19.8) | 155 (18.4) |
| Chronic kidney disease | 290 (17.2) | 143 (17.1) | 147 (17.4) |
| Prior MI | 95 (5.6) | 56 (6.7) | 39 (4.6) |
| Prior PCI | 328 (19.5) | 165 (19.7) | 163 (19.3) |
| LV ejection fraction, % | 63.6 ± 8.4 | 63.3 ± 8.5 | 63.9 ± 8.3 |
| Laboratory data | | | |
| Total cholesterol, mg/dL | 154.4 ± 43.0 | 156.7 ± 44.2 | 152.1 ± 41.7 |
| Triglyceride, mg/dL | 140.9 ± 89.2 | 141.9 ± 84.2 | 139.9 ± 93.9 |
| HDL cholesterol, mg/dL | 45.2 ± 11.3 | 45.4 ± 11.0 | 44.9 ± 11.5 |
| LDL cholesterol, mg/dL | 85.6 ± 34.7 | 87.6 ± 35.8 | 83.5 ± 33.5 |

*Continued on the next page*

respectively. In cases of PCI, lesion preparation and stent deployment were guided according to prespecified criteria for optimal PCI as follows. In the FFR-guided group, post-PCI FFR measurement and pull back tracing were recommended to assess residual pressure gradients across both stented and nonstented segments. Optimal PCI was defined as a post-PCI FFR of ≥0.88 or a delta FFR across the stented segment of <0.05. In the IVUS-guided group, post-PCI IVUS evaluation was recommended to evaluate stent malapposition, stent edge dissection, or stent underexpansion. Optimal PCI was achieved when the plaque burden at the stent edge was ≤55% and the minimal stent area was either ≥5.5 mm$^2$ or at least equal to the distal reference luminal area (Supplemental Appendix). If the optimization criteria were not met, further postdilation or lesion modification was recommended at the discretion of the operator to achieve optimal PCI criteria.

**STATISTICAL ANALYSIS.** The sample size calculation for the FLAVOUR trial has been detailed in previous publications.[10,13] Continuous variables are presented as mean ± SD, while categorical variables are reported as absolute numbers and percentages. Time-to-first event estimates were calculated using the Kaplan-Meier method. Follow-up time was censored at the occurrence of an event or at the time of loss to follow-up or last follow-up, whichever came first. As a sensitivity analysis, a hierarchical composite outcome analysis was performed in which events were prioritized by clinical importance, with death given the highest priority, followed by MI and then any revascularization after the index procedure. The primary endpoint comparison between the 2 groups was analyzed using the Cox proportional hazards model, incorporating study sites and the presence of diabetes mellitus as random effects. The proportional hazards assumption was assessed using Schoenfeld residuals and visual assessment of log (−log) plots. All analyses were conducted at the individual patient level, adhering to the intention-to-treat principle. Another sensitivity analysis was performed on the per protocol population, excluding patients who did not have adequate FFR or IVUS data or received treatment that did not meet predefined criteria. Outcomes were further examined in a landmark analysis set at 2 years and evaluated according to treatment strategy (medical treatment vs PCI) on a per vessel basis. All statistical analyses were performed using R version 4.3.3 (R Foundation for Statistical Computing).

**TABLE 1 Continued**

| | Total (N = 1,682) | FFR Group (n = 838) | IVUS Group (n = 844) |
|---|---|---|---|
| Angiographic findings | | | |
| Patients who underwent PCI | 923 (54.9) | 372 (44.4) | 551 (65.3) |
| Total stent number/total number of patients | 0.8 ± 0.9 | 0.6 ± 0.9 | 0.9 ± 1.0 |
| Total stent length/total number of patients, mm | 20.9 ± 26.6 | 16.5 ± 24.1 | 25.2 ± 28.1 |
| Total stent number/number of patients who underwent PCI | 1.4 ± 0.8 | 1.4 ± 0.8 | 1.5 ± 0.8 |
| Total stent length/number of patients who underwent PCI, mm | 38.0 ± 25.2 | 37.2 ± 23.2 | 38.6 ± 26.4 |
| SYNTAX score at baseline | 8.6 ± 6.0 | 8.4 ± 5.8 | 8.9 ± 6.2 |
| Multivessel disease | 875 (52.0) | 445 (53.1) | 430 (50.9) |
| Nonobstructive coronary disease | 31 (1.8) | 15 (1.8) | 16 (1.9) |
| 1-vessel disease | 776 (46.1) | 378 (45.1) | 398 (47.2) |
| 2-vessel disease | 568 (33.8) | 295 (35.2) | 273 (32.3) |
| 3-vessel disease | 307 (18.3) | 150 (17.9) | 157 (18.6) |
| Target vessel | (n = 1,820) | (n = 919) | (n = 901) |
| Location | | | |
| LAD | 1,127 (61.9) | 573 (62.4) | 554 (61.5) |
| LCx | 229 (12.6) | 119 (12.9) | 110 (12.2) |
| RCA | 464 (25.5) | 227 (24.7) | 237 (26.3) |
| Diameter stenosis, % | 56.8 ± 10.1 | 56.7 ± 10.1 | 56.9 ± 10.1 |
| Lesion length, mm | 20.3 ± 10.6 | 20.1 ± 10.3 | 20.5 ± 11.0 |
| Reference vessel diameter, mm | 3.0 ± 0.5 | 3.0 ± 0.5 | 3.0 ± 0.5 |
| Minimum luminal diameter, mm | 1.3 ± 0.4 | 1.3 ± 0.4 | 1.3 ± 0.4 |
| Target vessel PCI | 831 (45.7) | 305 (33.2) | 526 (58.4) |
| Total stent number/number of stented vessel | 1.2 ± 0.4 | 1.2 ± 0.5 | 1.2 ± 0.4 |
| Total stent length per stented vessel, mm | 31.3 ± 14.5 | 32.7 ± 15.5 | 30.4 ± 13.8 |
| Stent diameter per stented vessel, mm | 3.16 ± 0.43 | 3.11 ± 0.43 | 3.19 ± 0.43 |
| IVUS findings | | | |
| Minimal luminal area, $mm^2$ | | | 3.4 ± 1.3 |
| Plaque burden, % | | | 70.1 ± 10.2 |
| Post PCI minimal stent area, $mm^2$ | | | 7.0 ± 2.2 |
| FFR findings | | | |
| FFR in the entire vessel | | 0.83 ± 0.09 | |
| FFR in the medical treatment group | | 0.88 ± 0.05 | |
| FFR in the PCI group | | | |
| Pre-PCI FFR | | 0.73 ± 0.06 | |
| Post-PCI FFR | | 0.88 ± 0.06 | |

Values are mean ± SD or n (%). [a]Among the 123 patients, 112 patients presented with atypical chest discomfort, 7 patients with dyspnea on exertion, and 4 patients with variant angina.

FFR = fractional flow reserve; HDL = high-density lipoprotein; IVUS = intravascular ultrasound; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LDL = low-density lipoprotein; LV = left ventricular; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

## RESULTS

Participants were recruited between July 2016 and August 2019. Of the 4,355 patients who were screened, 1,682 patients with intermediate coronary stenosis were randomly allocated to receive either FFR-guided treatment (n = 838) or IVUS-guided treatment (n = 844) (**Figure 1**). Baseline characteristics were well balanced between the 2 groups (**Table 1**). The mean age of participants was 65.1 ± 9.6 years; 1,187 (70.6%) were men and 495 (29.4%) women, and 554 (32.9%) patients had diabetes mellitus (**Table 1**). Medication history during the extended follow-up did not differ significantly between the groups (Supplemental Table 1), except for a consistent trend toward higher use of dual antiplatelet therapy in the IVUS group.

During the extended follow-up period, with a median duration of 6.3 years (Q1-Q3: 5.6-6.9 years), 1,602 patients (95.2%) had complete follow-up data.

The primary outcome of death, MI, and any revascularization after the index procedure occurred in 339 patients (22.0%), with no statistically significant differences between the FFR-guided and IVUS-guided groups (179 [23.1%] vs 160 [20.9%], respectively; HR: 1.15; 95% CI: 0.93-1.42; $P = 0.208$) (**Figure 2**, **Table 2**). For consistency with the original trial design, noninferiority was assessed using a 6.2% margin, derived by proportionally adjusting the prespecified 2.5% margin for 2-year outcomes on the basis of the observed 2- and 7-year event rates in the IVUS group, with the FFR-guided strategy meeting the noninferiority criterion ($P = 0.037$). Findings were consistent in a hierarchical composite outcome analysis in the order of death, MI, and any revascularization event after the index procedure (Supplemental Figure 1) and stratified by clinical presentation (HR: 1.24 [95% CI: 0.87-1.76; $P = 0.239$] in patients with acute coronary syndrome [ACS]; HR: 1.12 [95% CI: 0.86-1.46; $P = 0.410$] in patients with stable angina). There were no statistically significant differences between the 2 groups in terms of all-cause death, cardiac death, MI, or stroke, though interpretation should consider the limited number of events for some endpoints. However, the rates of any and target vessel revascularization after the index procedure was higher in the FFR-guided group. The results for the primary and key secondary endpoints were consistent in the per protocol analysis (Supplemental Figure 1).

In a landmark analyses set at 2 years, there were no statistically significant differences in the primary outcome between the 2 groups during the first 2 years (0-2 years: 67 [8.0%] vs 71 [8.4%] [HR: 0.96; 95% CI: 0.69-1.34; $P = 0.824$]; during extended follow-up from 2 to 7 years: 112 [16.4%] vs 89 [13.6%] [HR: 1.29; 95% CI: 0.98-1.71; $P = 0.069$]) (**Figure 3**). This trend was similar for death and MI (**Figure 3**). However, for revascularization events after the index procedure, although no statistical difference was observed between the 2 groups during the first 2 years (47 [5.7%] vs 44 [5.3%]; HR: 1.08; 95% CI: 0.72-1.64; $P = 0.698$), the rate of revascularization after the index procedure became higher in the FFR-guided group between 2 and 7 years (66 [9.8%] vs 43 [6.9%]; HR: 1.57; 95% CI: 1.07-2.30; $P = 0.022$). This difference was driven primarily by target vessel revascularization (45 [6.6%] vs 24 [3.9%]; HR: 1.93; 95% CI: 1.17-3.16; $P = 0.010$). Other secondary outcomes assessed in the 2-year landmark analysis are presented in **Table 3**. The per protocol analysis yielded consistent findings (Supplemental Table 2).

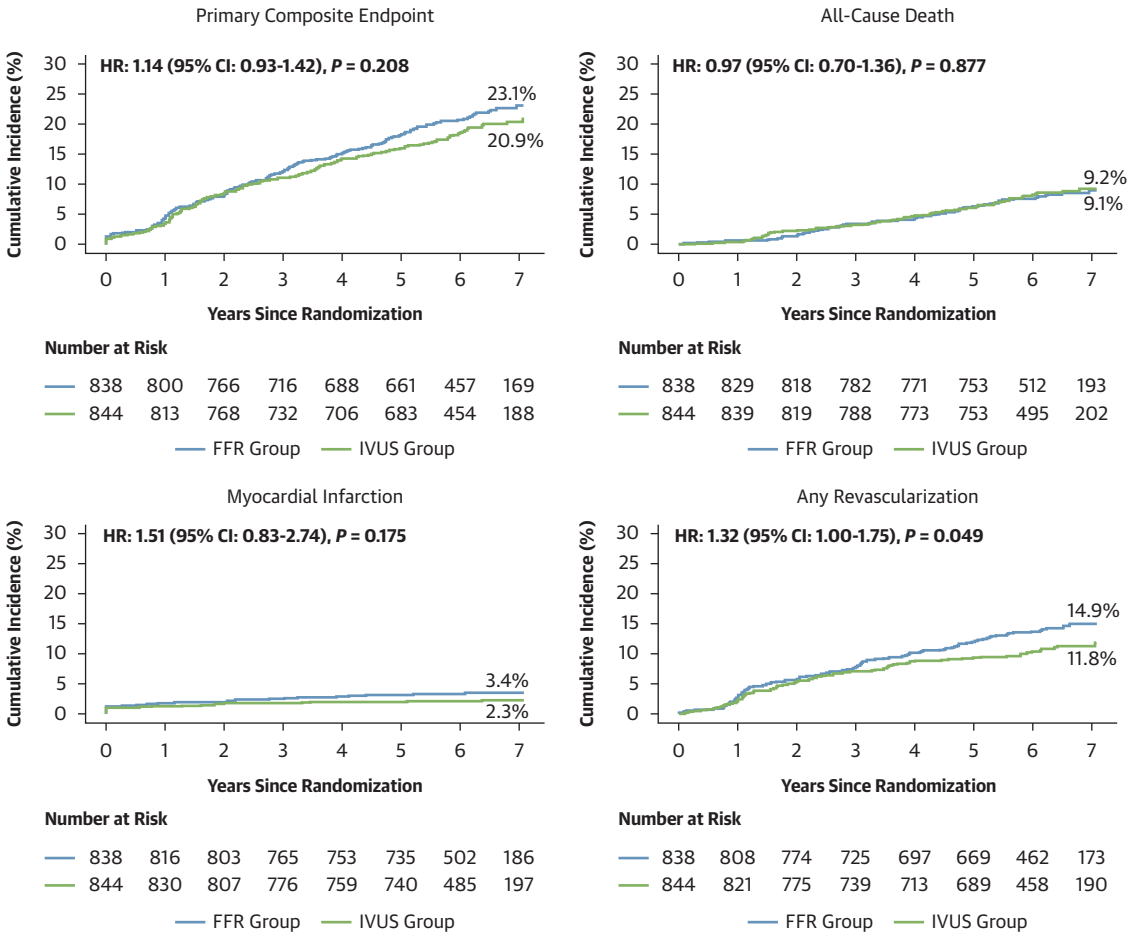
In the per vessel analysis based on treatment type, the risk for target vessel failure did not statistically differ between the groups within the vessels that received medical treatment (76 [13.8%] vs 35 [10.1%]; HR: 1.37; 95% CI: 0.91-2.06; $P = 0.135$) or those who underwent PCI (32 [11.3%] vs 47 [10.4%]; HR: 1.17; 95% CI: 0.74-1.85; $P = 0.489$) (**Table 4**). However, the rate of target vessel revascularization after the index procedure was higher in the FFR-guided group among the medically treated vessels (52 [9.5%] vs 19 [5.6%]; HR: 1.72; 95% CI: 1.01-2.92; $P = 0.045$) (**Table 4**). This result was similar in the per protocol population (Supplemental Table 3), and clinical outcomes by achievement of PCI optimization criteria are shown in Supplemental Figure 2. With the higher incidence of late target vessel revascularization after the index procedure in the FFR-guided group, the difference in cumulative target vessel PCI rates, comprising both index and follow-up revascularization, narrowed over time (**Figure 4**). However, by 7 years, the overall rate of target vessel PCI remained significantly lower in the FFR-guided group compared with the IVUS-guided group (38.8% vs 60.5%), and the cumulative incidence of death or MI remained comparable between the 2 groups throughout the extended follow-up despite this late catch-up in target vessel revascularization.

## DISCUSSION

The main findings of the extended follow-up of the FLAVOUR trial were as follows. First, FFR-guided and IVUS-guided treatment strategies demonstrated comparable long-term primary outcomes, which included a composite of death, MI, and any revascularization after the index procedure. Second, FFR-guided treatment was associated with a higher revascularization rate after the index procedure, particularly driven by late events occurring beyond 2 years. Third, the increased revascularization rate after the index procedure in the FFR group was attributed primarily to target vessel revascularization after the index procedure in medically treated vessels. However, the overall target vessel PCI rate, including PCI at both the index procedure and during follow-up, remained significantly lower in the FFR-guided group, with comparable rates of hard outcomes between the 2 groups (**Central Illustration**).

Understanding the long-term prognostic implications of initial treatment decisions and stent optimization remains crucial in patients with CAD, given the variable time sequences of de novo lesion progression and the residual risk for stented lesions for target lesion failure over the long-term follow-up.[18,19] Moreover, in the contemporary era of highly effective medical therapy for primary and secondary

**FIGURE 2** **Time-to-Event Curves for the Primary Endpoint and Individual Components of the Primary Endpoint**




Kaplan-Meier curves depict the cumulative incidence of the primary composite endpoint and its individual components during the extended follow-up in the FFR- and IVUS-guided treatment groups. The primary endpoint was a composite of death due to any cause, myocardial infarction, and any revascularization after the index procedure. Abbreviations as in Figure 1.

prevention, a substantial proportion of lesions may stabilize over time, potentially altering the prognostic impact of different revascularization strategies.[20] Consequently, with an increasing number of patients with CAD requiring long-term follow-up in daily practice,[11,12] it is important to determine whether the prognostic benefits of coronary physiology-guided or IVI-guided treatment, which has been proved superior to angiography alone in the catheterization laboratory,[21] are sustained over long-term follow-up to better guide management of CAD following initial treatment strategies. Several studies have reported on long-term outcomes, comparing angiography-guided PCI with physiology- or IVI-guided PCI. In the 5-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial, the reduction in clinical events with FFR-guided PCI, compared with angiography-guided PCI, was evident up to 2 years but did not extend beyond that timeframe.[22] In the meantime, IVUS-guided PCI has demonstrated sustained benefits in reducing target vessel failure up to 3 years in all-comers populations,[23] and the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on the Outcomes of Xience Prime Stents in Long Lesions) trial consistently showed the benefit of IVUS-guided PCI for up to 5 years in patients with long lesions.[24] Nonetheless, evidence on the long-term effects of physiology- vs IVI-guided treatments remains limited, particularly from head-to-head

**TABLE 2 Primary and Secondary Outcomes in the Intention-to-Treat Population**

| | FFR Group (n = 838) | IVUS Group (n = 844) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Primary outcome | | | | |
| All-cause death, myocardial infarction, or revascularization | 179 (23.1) | 160 (20.9) | 1.15 (0.93-1.42) | 0.208 |
| Secondary outcome | | | | |
| All-cause death | 67 (9.1) | 69 (9.2) | 0.97 (0.70-1.36) | 0.877 |
| Cardiac death | 33 (4.5) | 34 (4.7) | 0.97 (0.60-1.57) | 0.913 |
| Myocardial infarction | | | | |
| Any | 27 (3.4) | 18 (2.3) | 1.51 (0.83-2.74) | 0.175 |
| Spontaneous | 17 (2.2) | 10 (1.4) | 1.71 (0.78-3.73) | 0.180 |
| Target vessel | 7 (1.0) | 5 (0.8) | 1.39 (0.44-4.39) | 0.571 |
| Death or myocardial infarction | 89 (11.8) | 85 (11.2) | 1.06 (0.78-1.42) | 0.716 |
| Stent thrombosis | 3 (0.4) | 1 (0.1) | 3.01 (0.31-28.9) | 0.340 |
| Revascularization | | | | |
| Any | 113 (14.9) | 87 (11.8) | 1.32 (1.00-1.75) | 0.049 |
| Ischemia driven | 95 (12.7) | 71 (9.8) | 1.36 (1.00-1.86) | 0.048 |
| Target vessel | 72 (9.6) | 44 (6.2) | 1.67 (1.15-2.43) | 0.007 |
| Stroke | 17 (2.2) | 24 (4.0) | 0.71 (0.38-1.33) | 0.289 |

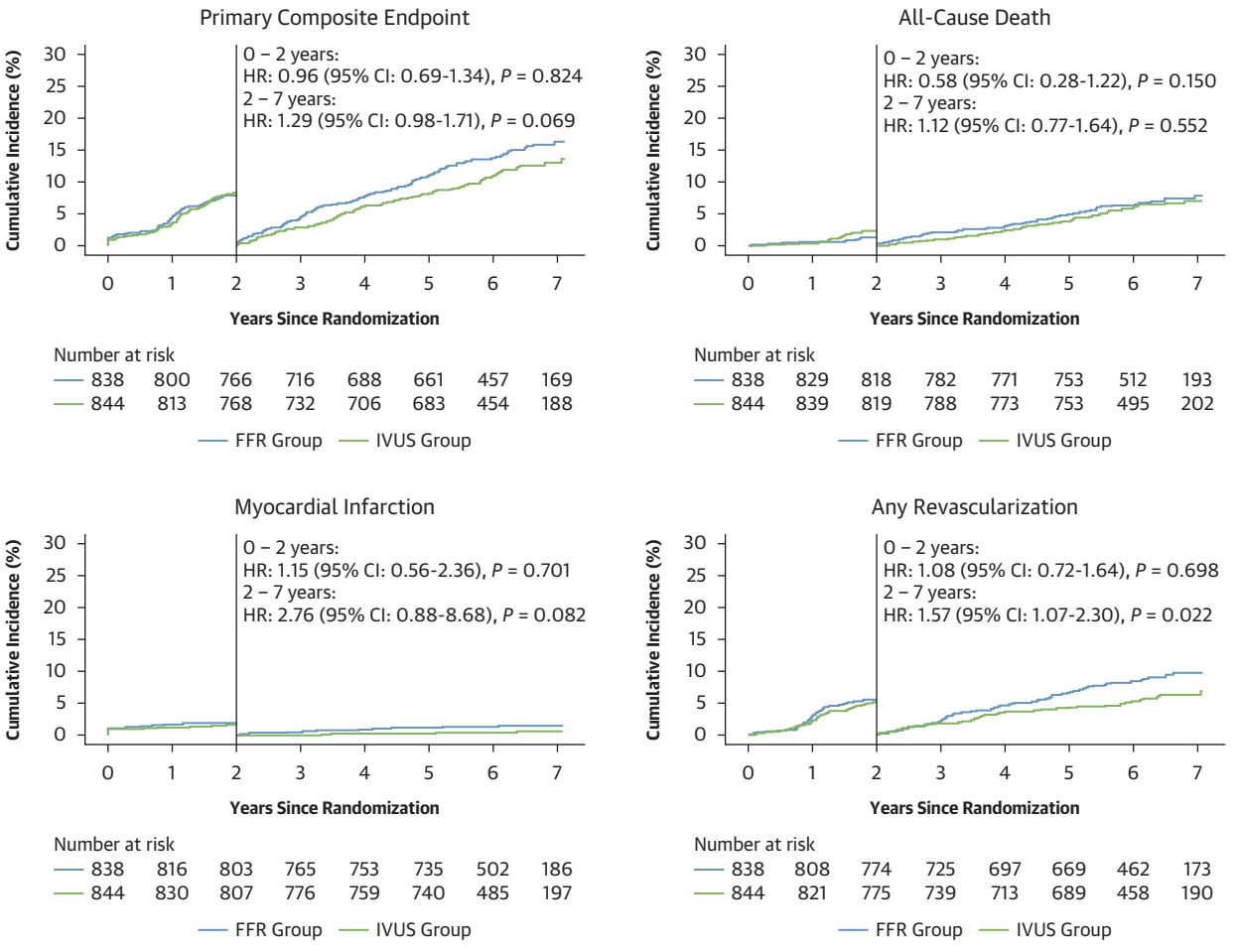
Values are n (%).
Abbreviations as in Table 1.

comparison. Given that plaque progression, vulnerable transformation, and subsequent coronary events are driven by the dynamic interplay among lumen, plaque, and physiological characteristics over time,[25,26] identifying the distinct long-term prognostic implications of physiology- and IVI-guided treatment by direct comparison is essential to better define the durability of treatment effects for each modality. Therefore, we aimed to further explore the similarities and differences between FFR- and IVUS-guided treatment with long-term follow-up data from the FLAVOUR trial.

In the present study, with a median follow-up duration of 6.3 years after randomization to FFR- vs IVUS-guided treatment, the primary composite outcome of death, MI, and any revascularization showed no difference in rates between the 2 groups (23.1% vs 20.9%), consistent with the previously reported 2-year outcomes.[10] Our findings align with the 5-year results of the FORZA (FFR or OCT Guidance to Revascularize Intermediate Coronary Stenosis Using Angioplasty) trial, a single-center trial that randomized 350 patients with intermediate stenoses to FFR- or OCT-guided PCI, reporting comparable rates of death, MI, and target vessel revascularization (17.2% vs 18.8%). Given that the prespecified FLAVOUR protocol mandated the use of FFR and IVUS for both treatment decision making and PCI optimization within each group, the comparable long-term outcomes may reflect the shared ability of both modalities to provide comprehensive preprocedural lesion characterization and stent optimization. This is in line with the association of IVUS-derived MLA and plaque burden for low FFR,[16] as well as the prognostic value of post-PCI pressure gradients in detecting IVUS-detected suboptimal PCI results.[27] These overlapping characteristics between FFR and IVUS for pre- and postprocedural assessment may contribute to their comparable long-term prognostic implications, highlighting similarities between the 2 strategies.

Despite comparable composite outcomes, the FFR-guided group exhibited a higher rate of any revascularization after the index procedure, driven primarily by an increasing trend beyond 2 years, as observed in the landmark analysis. When evaluating outcomes by treatment type, the overall 5-year rate of patient-level death or MI in medically treated patients was 8.2%, approximately one-half of the 19.4% reported in the individual patient-level meta-analysis of 5-year outcomes following FFR-guided medical therapy.[28] This favorable outcome was similarly observed at the vessel level: the 5-year rate of target vessel failure in deferred vessels was 9.6%, numerically lower than the 11.6% rate reported for FFR-guided deferred vessels in the 5-year outcomes of the J-CONFIRM (Long-Term Outcomes of Japanese Patients With Deferral of Coronary Intervention Based on Fractional Flow Reserve in Multicenter Registry) registry.[29] These findings likely reflect the relatively noncomplex nature of lesions in the FLAVOUR study population and highlight the

**FIGURE 3** Time-to-Event Curves for the Primary Endpoint and Individual Components of the Primary Endpoint With a Landmark Set at 2 Years




A landmark analysis was performed at 2 years to evaluate event rates during the early (0-2 years) and late (2-7 years) phases for the primary composite endpoint and its individual components. Abbreviations as in Figure 1.

importance of guideline-directed medical therapy, even in patients for whom PCI was deferred. Although overall outcomes were favorable in medical treatment group, a subsequent per vessel analysis based on treatment type revealed that the higher revascularization rate after the index procedure was attributed largely to target vessel revascularization after the index procedure in medically treated vessels within the FFR-guided group compared with the IVUS-guided group (9.5% vs 5.6%). This observation may be explained partially by previous studies showing an increased risk for repeat revascularization, even after deferral of PCI on the basis of high FFR, in specific lesion and patient subsets.[30] Although deferral of PCI with high FFR has been generally considered safe, the 5-year follow-up of the FAME II study reported a 17.5% rate of any revascularization among medically treated patients with FFR $> 0.80$.[2] In later studies, the risk for 5-year adverse cardiac events was associated with adverse plaque characteristics, including IVUS-detected positive remodeling or plaque burden $\geq$ 70%, as well as adverse patient characteristics such as diabetes and reduced ejection fraction.[31] Notably, the presence of high-risk plaque was associated with a 2- to 3-fold higher risk for future coronary events over 5 years in vessels with high FFR regardless of imaging modality, with prevalence ranging from 20% to 30%.[31-33] In contrast, given that the observed prevalence of plaque burden >70% in the group with IVUS-guided deferral of PCI in our study was substantially lower (16.1%), it is plausible that the increased rate of late

**TABLE 3 Landmark Analysis at 2 Years for the Primary and Secondary Outcomes in the Intention-to-Treat Population**

| | FFR Group (n = 838) | IVUS Group (n = 844) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Baseline to 2 y | | | | |
| Primary outcome | | | | |
| All-cause death, myocardial infarction, or revascularization | 67 (8.0) | 71 (8.4) | 0.96 (0.69-1.34) | 0.824 |
| Secondary outcome | | | | |
| All-cause death | 11 (1.3) | 19 (2.3) | 0.58 (0.28-1.22) | 0.150 |
| Cardiac death | 7 (0.8) | 11 (1.3) | 0.64 (0.25-1.64) | 0.349 |
| Myocardial infarction | | | | |
| Any | 16 (1.9) | 14 (1.7) | 1.15 (0.56-2.36) | 0.701 |
| Spontaneous | 6 (0.7) | 6 (0.7) | 1.01 (0.33-3.13) | 0.987 |
| Target vessel | 3 (0.4) | 2 (0.2) | 1.50 (0.25-9.00) | 0.655 |
| Death or myocardial infarction | 27 (3.2) | 32 (3.8) | 0.85 (0.51-1.42) | 0.542 |
| Stent thrombosis | 1 (0.1) | 1 (0.1) | 1.09 (0.07-17.5) | 0.951 |
| Revascularization | | | | |
| Any | 47 (5.7) | 44 (5.3) | 1.08 (0.72-1.64) | 0.698 |
| Ischemia driven | 38 (4.6) | 33 (4.0) | 1.17 (0.73-1.86) | 0.521 |
| Target vessel | 27 (3.3) | 20 (2.4) | 1.37 (0.77-2.43) | 0.291 |
| Stroke | 6 (0.7) | 10 (1.2) | 0.61 (0.22-1.67) | 0.333 |
| 2-7 y | | | | |
| Primary outcome | | | | |
| All-cause death, myocardial infarction, or revascularization | 112 (16.4) | 89 (13.6) | 1.29 (0.98-1.71) | 0.069 |
| Secondary outcome | | | | |
| All-cause death | 56 (7.9) | 50 (7.1) | 1.12 (0.77-1.64) | 0.552 |
| Cardiac death | 26 (3.7) | 23 (3.4) | 1.13 (0.65-1.99) | 0.658 |
| Myocardial infarction | | | | |
| Any | 11 (1.5) | 4 (0.7) | 2.76 (0.88-8.68) | 0.082 |
| Spontaneous | 11 (1.5) | 4 (0.7) | 2.75 (0.88-8.65) | 0.083 |
| Target vessel | 4 (0.6) | 3 (0.5) | 1.33 (0.30-5.92) | 0.712 |
| Death or myocardial infarction | 62 (8.8) | 53 (7.7) | 1.18 (0.82-1.70) | 0.379 |
| Stent thrombosis | 2 (0.3) | 0 (0.0) | NA | NA |
| Revascularization | | | | |
| Any | 66 (9.8) | 43 (6.9) | 1.57 (1.07-2.30) | 0.022 |
| Ischemia driven | 57 (8.5) | 38 (6.1) | 1.53 (1.02-2.31) | 0.041 |
| Target vessel | 45 (6.6) | 24 (3.9) | 1.93 (1.17-3.16) | 0.010 |
| Stroke | 11 (1.5) | 14 (2.8) | 0.79 (0.36-1.74) | 0.560 |

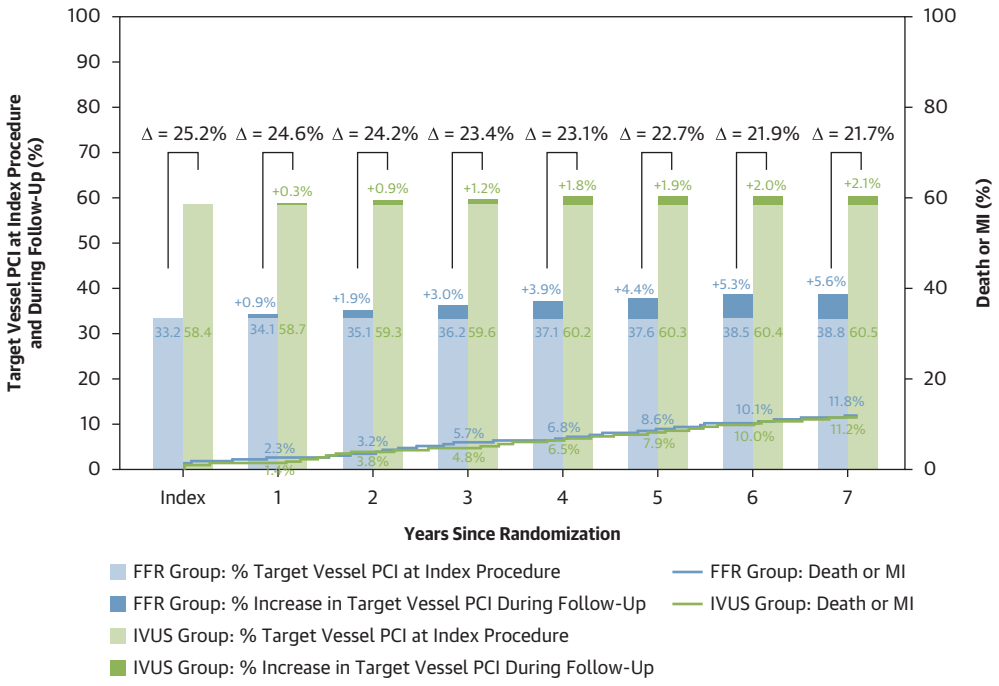
Values are n (%).
NA = not applicable; other abbreviations as in Table 1.

**TABLE 4 Per Vessel Clinical Outcomes According to Treatment Types in the Intention-to-Treat Population**

| | Medical Treatment Group (n = 989) | | | | PCI Group (n = 831) | | | |
|---|---|---|---|---|---|---|---|---|
| | FFR-Guided Group (n = 614) | IVUS-Guided Group (n = 375) | HR (95% CI) | *P* Value | FFR-Guided Group (n = 305) | IVUS-Guided Group (n = 526) | HR (95% CI) | *P* Value |
| Target vessel failure | 76 (13.8) | 35 (10.1) | 1.37 (0.91-2.06) | 0.135 | 32 (11.3) | 47 (10.4) | 1.17 (0.74-1.85) | 0.489 |
| Cardiac death | 27 (5.0) | 15 (4.2) | 1.12 (0.58-2.15) | 0.743 | 11 (3.8) | 20 (4.7) | 0.93 (0.44-1.96) | 0.844 |
| Target vessel myocardial infarction | 4 (0.8) | 2 (0.8) | 1.26 (0.23-6.81) | 0.789 | 3 (1.0) | 3 (0.6) | 1.70 (0.34-8.43) | 0.514 |
| Target vessel revascularization | 52 (9.5) | 19 (5.6) | 1.72 (1.01-2.92) | 0.045 | 22 (7.9) | 26 (5.6) | 1.46 (0.82-2.60) | 0.197 |

Values are n (%).
Abbreviations as in Table 1.

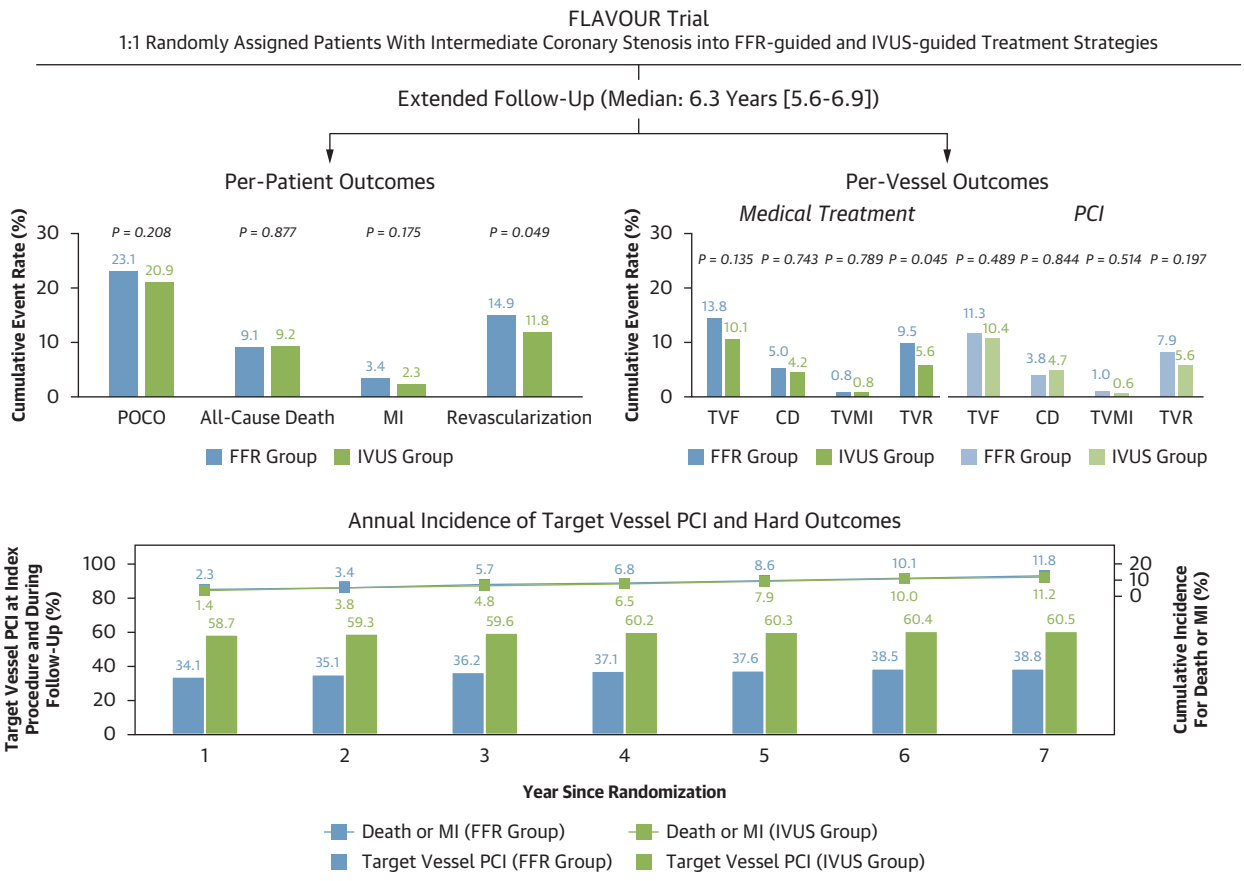
**FIGURE 4** Cumulative Incidence for Target Vessel PCI and Death or MI




Stacked bar graphs depict the cumulative rate of target vessel PCI on a per vessel basis, incorporating both index PCI and target vessel revascularization during follow-up, in the FFR-guided and IVUS-guided treatment groups. Overlaid line plots represent the cumulative incidence of death or myocardial infarction (MI) over time on a per patient basis for each group. Although the FFR-guided treatment group showed a lower rate of initial target vessel PCI, a greater proportion of target vessel revascularization occurred during extended follow-up, reflecting a late catch-up in revascularization. Nevertheless, the overall cumulative rate of target vessel PCI remained lower in the FFR-guided group compared with the IVUS-guided group at 7 years (38.8% vs 60.5%), and the cumulative incidence of death or MI did not differ significantly between the 2 groups over time ($P > 0.05$ for all). Abbreviations as in Figure 1.

revascularization in FFR-guided deferred vessels in the present study may reflect the prognostic impact of underlying high-risk plaque within the high FFR group. This interpretation is further supported by the PREVENT (Preventive PCI or Medical Therapy Alone for Vulnerable Atherosclerotic Coronary Plaque) trial, which randomized patients with vulnerable plaque and high FFR to PCI vs medical treatment, showing ischemia-driven target vessel revascularization rates of 8.0% vs 4.9% at 7 years.[9] Notably, more than 90% of the PREVENT study population had small MLA and high plaque burden, which overlapped with the revascularization criteria in the FLAVOUR trial. This suggests that the IVUS-guided group in FLAVOUR paralleled the PCI arm of PREVENT, while a subset of the FFR-guided group, given the absence of routine intracoronary imaging, may have partially resembled the medical therapy arm of PREVENT. Collectively, both PREVENT and the extended follow-up of the FLAVOUR trials support the concept that upfront preventive PCI, guided by IVI-based anatomical evaluation, may help reduce future revascularization events. Nonetheless, it is noteworthy that hard clinical outcomes occurred at similar rates between the 2 groups. In addition, when accounting for both the initial PCI and subsequent target vessel PCI over the follow-up period, the cumulative incidence of target vessel PCI remained consistently lower in the FFR group. This finding implies that the differential prognostic significance of coronary physiology's high specificity and coronary anatomy's high sensitivity remains consistent for long-term clinical events, as demonstrated by a head-to-head comparison. Therefore, our findings indicate that when selecting a single adjunctive modality between physiology and IVI, FFR may be the preferred option in cases in which the purpose is to avoid unnecessary PCI without compromising long-term hard outcomes.

**CENTRAL ILLUSTRATION** **Long-Term Outcomes After FFR- vs IVUS-Guided Treatment**




**Yang S, et al. JACC. 2025;86(8):593-606.**

In this extended follow-up of the FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients With Intermediate Stenosis) trial, event rates for per patient outcomes (primary composite outcome, including all-cause death, myocardial infarction, and any revascularization after the index procedure) and per vessel outcomes (target vessel failure [TVF], including cardiac death, target vessel myocardial infarction [TVMI], and target vessel revascularization [TVR] after the index procedure) were compared between fractional flow reserve (FFR)-guided and intravascular ultrasound (IVUS)-guided groups over a median follow-up period of 6.3 years. Both FFR- and IVUS-guided strategies for intermediate coronary lesions resulted in comparable long-term patient-oriented outcomes. Although FFR-guided treatment was associated with a higher rate of late TVR after the index procedure, the overall procedural burden was lower, with similar long-term rates of death and myocardial infarction (MI) between the 2 strategies, highlighting a trade-off between initial deferral and subsequent revascularization. CD = cardiac death; PCI = percutaneous coronary intervention; POCO = patient-oriented composite outcome.

Conversely, if a more proactive revascularization strategy is desired to potentially reduce future coronary events, IVUS can serve as an effective upfront tool for guiding treatment decisions and optimizing procedural results. On the basis of this result, future studies are warranted to define optimal candidates, at both the lesion and patient levels, for PCI or intensive medical therapy, as well as to identify the role and timing of regular follow-up strategies using noninvasive physiological or morphologic assessment in clinical practice. Moreover, as two-thirds of the present study population had stable angina, and given that the natural history and lesion characteristics of untreated nonculprit lesions in ACS may differ from those presented with stable angina,[34] which was also reflected in the present study population (ACS vs non-ACS: HR: 1.43; 95% CI: 1.13-0.81; $P = 0.003$), further investigation is required to

explore the comparative effectiveness of IVUS- vs FFR-guided treatment strategies according to clinical presentation.

**STUDY LIMITATIONS.** First, the extended follow-up was conducted retrospectively following a 2-year investigation. However, the majority of patients attended regular clinical visits after randomization, and outcomes were assessed in 95.2% of the cohort with independent adjudication and validation.

Second, the initial treatment decisions, including FFR and IVUS results, were not blinded to study participants and physicians, which may have influenced the rate of late revascularization.

Third, medical treatment was left to the physician's discretion, which might have introduced potential bias.

Last, as the trial enrolled patients with intermediate coronary stenosis and excluded those with left main disease, the present findings may not be directly applicable to high-risk or complex PCI cases.

## CONCLUSIONS

Both FFR-guided and IVUS-guided treatment strategies in patients with intermediate coronary stenosis resulted in similar long-term clinical outcomes in terms of the patient-oriented composite outcomes. Although FFR-guided treatment was associated with a higher rate of late target vessel revascularization after the index procedure, the cumulative target vessel PCI rate, including both the initial procedure and subsequent revascularizations during follow-up, remained significantly lower in the FFR-guided group, without compromising long-term hard outcomes.

**DATA SHARING STATEMENT.** Individual patient data will not be available to others. Data are available to the collaborators. The data will be shared on reasonable request to the corresponding author.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by Yuhan Pharmaceutical. The funder had no role in trial design, data collection, analysis, interpretation, or manuscript preparation. Drs Wang and Hu have received an institutional research grant from Boston Scientific. Dr Nam has received an institutional research grant from Abbott. Dr Koo has received institutional research grants from Abbott Vascular, Boston Scientific, Philips, and Yuhan Pharmaceutical. Dr Hahn has received funding from the South Korean National Evidence-Based Healthcare Collaborating Agency, the South Korean Ministry of Health and Welfare, Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Daiichi-Sankyo, Dong-A ST, Hanmi Pharmaceutical, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** coronary artery disease, fractional flow reserve, intravascular ultrasound, long-term outcomes, percutaneous coronary intervention

**APPENDIX** For a list of investigators and collaborators, the data sharing statement, a description of trial design, a list of inclusion and exclusion criteria, a list of revascularization and optimization criteria, definitions of clinical outcomes, and supplemental figures, tables, and references, please see the online version of this paper.