JAMA Network Open

Original Investigation | Cardiology

Physiology- or Imaging-Guided Strategies for Intermediate Coronary Stenosis

Seokhun Yang, MD; Jeehoon Kang, MD; Doyeon Hwang, MD; Jinlong Zhang, MD, PhD; Jun Jiang, MD; Xinyang Hu, MD, PhD; Joo-Yong Hahn, MD, PhD; Chang-Wook Nam, MD, PhD; Joon-Hyung Doh, MD, PhD; Bong-Ki Lee, MD; Weon Kim, MD; Jinyu Huang, MD; Fan Jiang, MD; Hao Zhou, MD; Peng Chen, MD; Lijiang Tang, MD; Wenbing Jiang, MD; Xiaomin Chen, MD; Wenming He, MD; Sung Gyun Ahn, MD; Myeong-Ho Yoon, MD; Ung Kim, MD; Joo Myung Lee, MD, PhD; You-Jeong Ki, MD, PhD; Eun-Seok Shin, MD, PhD; Hyo-Soo Kim, MD, PhD; Seung-Jea Tahk, MD, PhD; Jian'an Wang, MD, PhD; Bon-Kwon Koo, MD, PhD

Abstract

IMPORTANCE Treatment strategies for intermediate coronary lesions guided by fractional flow reserve (FFR) and intravascular ultrasonography (IVUS) have shown comparable outcomes. Identifying low-risk deferred vessels to ensure the safe deferral of percutaneous coronary intervention (PCI) and high-risk revascularized vessels that necessitate thorough follow-up can help determine optimal treatment strategies.

OBJECTIVES To investigate outcomes according to treatment types and FFR and IVUS parameters after FFR- or IVUS-guided treatment.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included patients with intermediate coronary stenosis from the Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients With Intermediate Stenosis (FLAVOUR) trial, an investigator-initiated, prospective, open-label, multicenter randomized clinical trial that assigned patients into an IVUS-guided strategy (which recommended PCI for minimum lumen area [MLA] ≤3 mm^2 or 3 mm^2 to 4 mm^2 with plaque burden [PB] ≥70%) or an FFR-guided strategy (which recommended PCI for FFR ≤0.80). Data were analyzed from November to December 2022.

EXPOSURES FFR or IVUS parameters within the deferred and revascularized vessels.

MAIN OUTCOMES AND MEASURES The primary outcome was target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction, and revascularization at 2 years.

RESULTS A total of 1619 patients (mean [SD] age, 65.1 [9.6] years; 1137 [70.2%] male) with 1753 vessels were included in analysis. In 950 vessels for which revascularization was deferred, incidence of TVF was comparable between IVUS and FFR groups (3.8% vs 4.1%; *P* = .72). Vessels with FFR greater than 0.92 in the FFR group and MLA greater than 4.5 mm^2 or PB of 58% or less in the IVUS group were identified as low-risk deferred vessels, with a decreased risk of TVF (hazard ratio [HR], 0.25 [95% CI, 0.09-0.71]; *P* = .009). In 803 revascularized vessels, the incidence of TVF was comparable between IVUS and FFR groups (3.6% vs 3.7%; *P* = .95), which was similar in the revascularized vessels undergoing PCI optimization (4.2% vs 2.5%; *P* = .31). Vessels with post-PCI FFR of 0.80 or less in the FFR group or minimum stent area of 6.0 mm^2 or less or with PB at stent edge greater than 58% in the IVUS group had an increased risk for TVF (HR, 7.20 [95% CI, 3.20-16.21]; *P* < .001).

CONCLUSIONS AND RELEVANCE In this cohort study of patients with intermediate coronary stenosis, FFR- and IVUS-guided strategies showed comparable outcomes in both deferred and

(continued)

Key Points

Question Are fractional flow reserve (FFR) and intravascular ultrasonography (IVUS) parameters associated with target vessel failure (TVF) according to treatment type after FFR- or IVUS-guided treatment?

Findings In this cohort study of 1619 patients and 1753 vessels with intermediate coronary stenosis from a randomized clinical trial, clinical outcomes were similar between FFR- and IVUS-guided treatment groups within deferred and revascularized vessels. Vessels with FFR greater than 0.92 in the FFR group or minimum lumen area greater than 4.5 mm^2 or plaque burden 58% or less in the IVUS group were low-TVF risk deferred vessels, and post–percutaneous coronary intervention vessels with FFR 0.80 or less in the FFR group or minimum stent area 6.0 mm^2 or less and plaque burden at stent edge greater than 58% in the IVUS group were high-TVF risk revascularized vessels.

Meaning These findings suggest that binary FFR and IVUS parameters could enhance risk stratification for future clinical events, such as TVF, in deferred and revascularized vessels.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

revascularized vessels. Binary FFR and IVUS parameters could further define low-risk deferred vessels and high-risk revascularized vessels.

JAMA Network Open. 2024;7(1):e2350036. doi:10.1001/jamanetworkopen.2023.50036

Introduction

Coronary physiological and intravascular imaging assessments are verified tools with additive diagnostic and prognostic implications in addition to coronary angiography.[1,2] According to clinical practice guidelines,[3,4] the use of physiological indices, such as fractional flow reserve (FFR), is recommended to identify ischemia-causing lesions that can benefit from revascularization, while intravascular imaging, such as intravascular ultrasonography (IVUS), is recommended for the planning and optimization of percutaneous coronary intervention (PCI). Although these 2 modalities have been considered distinct in guidance of PCI, several studies have proposed a similar prognostic impact of physiology- and imaging-guided treatment.[5,6] In particular, a 2022 randomized clinical trial, the Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients With Intermediate Stenosis (FLAVOUR) trial, demonstrated comparable outcomes of FFR-guided and IVUS-guided decision-making, with a lower revascularization rate in the FFR group in patients with intermediate coronary stenosis.[6] Therefore, FFR- and IVUS-guided therapies are currently considered the optimal treatment strategies for intermediate coronary stenosis. Nonetheless, direct comparisons of clinical outcomes based on treatment types (deferral of PCI vs PCI) between these strategies have rarely been reported, and clinical events still occur after physiology- or imaging-guided treatment. In this context, it is important to identify low-risk vessels in which PCI has been deferred to warrant the safe continued deferral of PCI and high-risk revascularized vessels that should be considered for additional procedures or meticulous follow-up to optimize treatment strategies following physiology- or imaging-guided PCI.[7,8] Considering prior studies have proposed cutoff values to determine low-risk deferred vessels and high-risk revascularized vessels based on FFR or IVUS parameters,[9-11] we hypothesized that it might be possible to identify high-risk lesion subsets based on treatment types using binary FFR or IVUS parameters even after physiology- or imaging-guided treatment for intermediate stenosis. In this post hoc analysis of the FLAVOUR trial, we aimed to investigate the clinical outcomes of FFR- and IVUS-guided strategies in deferred and revascularized vessels and to define high-risk groups using FFR and IVUS parameters via a binary approach in each group.

Methods

This cohort study used data from the FLAVOUR trial, and the trial protocol was approved by the institutional review board at each participating site. This study was conducted following the principles of the International Council for Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki, and all patients provided written informed consent. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Flow and Population

The FLAVOUR trial was an investigator-initiated, prospective, open-label, multinational randomized clinical trial performed at 18 sites in Korea and China (ClinicalTrials.gov identifier: NCT02673424). The detailed study protocol has been published elsewhere.[6,12] Briefly, the FLAVOUR trial was designed to compare the clinical outcomes of FFR- and IVUS-guided treatment. Patients with an angiographically intermediate stenosis (ie, 40% to 70% diameter stenosis) in a target vessel sized at

least 2.5 mm were included. The main exclusion criteria were patients who had noncardiac comorbid conditions with a life expectancy of 2 years or less, target lesion located in the left main coronary artery or in a coronary artery bypass graft, and patients with high bleeding risk. Patients who met all inclusion criteria without any exclusion criteria were 1:1 randomized into the FFR or IVUS groups after enrollment. In this study, clinical outcomes were compared between IVUS and FFR groups and by whether PCI was deferred vessels or vessels were revascularized. Then, the deferred and revascularized vessels were classified according to binary FFR and IVUS parameters, and their clinical outcomes were further investigated (**Figure 1**).

Invasive Coronary Angiography

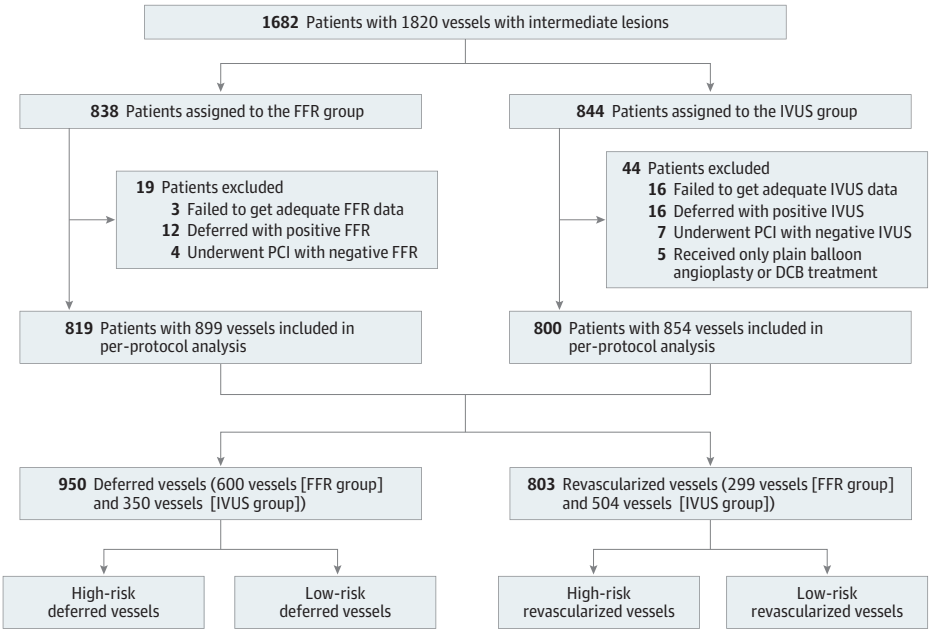
Invasive coronary angiography was conducted using standard techniques. After the procedure, quantitative coronary angiography was performed at the core laboratory (Seoul National University Hospital, Seoul, South Korea) to assess reference diameter, minimal lumen diameter, percentage of diameter stenosis, and lesion length using a validated software program (CAAS II; Pie Medical System).

FFR-Guided and IVUS-Guided Revascularization and Criteria for Optimal PCI

In the IVUS group, PCI was performed if lesions had IVUS-derived minimum lumen area (MLA) less than 3 mm^2 or MLA of 3 mm^2 to 4 mm^2 with plaque burden of 70% or greater.[13,14] IVUS images were acquired after intracoronary administration of nitroglycerin using commercially available systems. Then, MLA, external elastic membrane (EEM) area, and plaque burden (calculated by the percentage value of 1 − MLA / EEM area) were obtained. Minimal stent area (MSA) was defined as the smallest area observed along the entire length of the stent.

In the FFR group, PCI was performed if lesions had FFR no greater than 0.80.[8] For FFR measurement, a pressure sensor guide wire was located at the distal segment of the target vessel after calibration and equalization to aortic pressure after engagement of a guide catheter. Intravenous adenosine and adenosine triphosphate (140 µg/kg/min) or intracoronary nicorandil (2 mg) was used to induce maximal hyperemia. The FFR value was calculated as the mean distal coronary arterial pressure divided by the aortic pressure during maximum hyperemia.

Figure 1. Study Recruitment Flowchart



DCB indicates drug-coated balloon; FFR, fractional flow reserve; IVUS, intravascular ultrasonography; and PCI, percutaneous coronary intervention.

The FFR and IVUS raw data were collected and analyzed in independent core laboratories blinded to clinical and procedural characteristics (Seoul National University Hospital for FFR data; Ulsan University Hospital for IVUS data). In cases of 2 or more separate lesions in the same vessel, the vessels were assigned as revascularized vessels if there were any lesions undergoing revascularization according to the prespecified IVUS or FFR criteria in that vessel. The prespecified criteria for optimal PCI were plaque burden at the stent edge 55% or less and MSA of at least 5.5 mm^2 or MSA equal to or greater than the distal reference lumen area in the IVUS group and a post-PCI FFR of at least 0.88 or change in FFR across the stent less than 0.05 in the FFR group.[12,15,16]

Primary Outcomes and Definitions

The primary outcome was target vessel failure (TVF), a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularization (TVR) at 24 months after randomization. All outcome definitions were in accordance with the Academic Research Consortium consensus.[17] TVR was defined as any revascularization event of the target vessel with 1 of the following: (1) a positive history of recurrent angina pectoris, (2) objective signs of ischemia at rest or during exercise test (or equivalent), (3) positive results on any invasive functional diagnostic test, or (4) a diameter stenosis of 70% or greater at angiography, even in the absence of ischemic signs or symptoms. Ischemia-driven TVR was defined as a revascularization event meeting criteria 1, 2, or 3. An independent committee adjudicated all clinical events and was blinded to treatment assignment.

Statistical Analysis

Detailed statistical methods are described in the eMethods in Supplement 1. Outcome analysis was performed on a per-vessel basis. The marginal Cox proportional hazard regression was applied to account for the clustering of the interrogated vessels within the same patient. The optimal cutoff values of FFR and IVUS parameters were obtained using the maximal log-rank statistics to define low-risk deferred vessels and high-risk revascularized vessels. *P* values were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed using R statistical software version 4.2.0 (R Project for Statistical Computing). Data were analyzed from November to December 2022.

Results

Baseline Characteristics

Among 1682 patients in the FLAVOUR trial, this cohort study included 1619 patients (mean [SD] age, 65.1 [9.6] years; 1137 [70.2%] male) with 1753 vessels who met the inclusion criteria (Figure 1). During the 2-year follow-up, 14 patients were lost to follow-up. Among 729 patients with deferred vessels, patients in the FFR group were older and had a higher prevalence of hypertension than patients in the IVUS group (**Table 1**). In 890 patients who underwent PCI, patients in the FFR group had a higher proportion of acute coronary syndrome and prevalence of hypercholesterolemia (Table 1). Regarding vessel characteristics, the distributions of FFR and IVUS parameters are shown in eFigure 1 in Supplement 1. In deferred vessels, mean (SD) FFR was 0.88 (0.050), MLA was 4.5 (1.3) mm^2, and plaque burden was 62.6% (8.5%). In revascularized vessels, mean (SD) FFR was 0.73 (0.08), MLA was 2.7 (0.6) mm^2, and plaque burden was 75.4% (7.6%); after PCI, mean (SD) FFR was 0.88 (0.06), MSA was 7.0 (2.1) mm^2, and plaque burden at stent edge was 41.6% (11.9%). The mean percentage diameter stenosis was higher and minimum lumen diameter was lower in the FFR group than the IVUS group in both deferred and revascularized vessels (Table 1).

Clinical Outcomes in Deferral of PCI Group and Defining Low-Risk Deferred Vessels

In 950 deferred vessels, the incidence rate of TVF was 4.2% in the FFR group and 3.8% in the IVUS group (hazard ratio [HR], 0.88 [95% CI, 0.44-1.76]; $P = .72$) (eFigure 2 in Supplement 1). The per-vessel optimal cutoff values for estimating risk of TVF were 0.92 for FFR, 4.5 mm^2 for MLA, and 58% plaque burden (eFigure 3 in Supplement 1). According to these features, the low-risk deferred

vessels were defined as those with FFR greater than 0.92 in the FFR group and MLA greater than 4.5 mm^2 or plaque burden no greater than 58% in the IVUS group (**Figure 2**A). These low-risk deferred vessels had a decreased risk of TVF compared with high-risk deferred vessels (HR, 0.25 [95% CI, 0.09-0.71]; *P* = .009), which was mainly associated with ischemia-driven TVR (eTable 1 in Supplement 1). When the outcomes of deferred vessels were compared with the revascularized vessels, the event rate of TVF was the lowest in the low-risk deferred vessels (1.4%), followed by the IVUS-guided revascularized vessels (3.6%), the FFR-guided revascularized vessels (3.7%), and the high-risk deferred vessels (5.3%) (*P* = .03) (Figure 2B). This association was similar after adjustment

Table 1. Baseline Characteristics of Included Patients and Vessels

Characteristic	Deferral of PCI			PCI[a]		
	No, (%)			No, (%)		
	FFR group	IVUS group	*P* value	FFR group	IVUS group	*P* value
Patient-level						
Included patients	455 (28.1)	274 (16.9)	NA	364 (22.5)	526 (32.5)	NA
Age, mean (SD), y	66.2 (9.2)	64.1 (9.4)	.004	64.5 (9.5)	65.0 (10.1)	.46
Sex						
Female	167 (36.7)	87 (31.8)	.20	85 (23.4)	143 (27.2)	.23
Male	288 (63.3)	187 (68.2)		279 (76.6)	383 (72.8)	
BMI, mean (SD), kg/m^2	24.5 (3.3)	24.6 (3.1)	.79	24.8 (3.2)	24.7 (3.4)	.45
Diagnosis						
Stable ischemic heart disease	370 (81.3)	215 (78.5)	.40	202 (55.5)	350 (66.5)	.001
Acute coronary syndrome	85 (18.7)	59 (21.5)		162 (44.5)	176 (33.5)	
Diabetes	135 (29.7)	83 (30.3)	.93	130 (35.7)	187 (35.6)	>.99
Hypertension	315 (69.2)	164 (59.9)	.01	249 (68.4)	371 (70.5)	.55
Hypercholesterolemia	342 (75.2)	201 (73.4)	.65	311 (85.4)	420 (79.8)	.04
Current smoking	91 (20.0)	49 (17.9)	.55	68 (18.7)	98 (18.6)	>.99
Chronic kidney disease	69 (15.2)	36 (13.1)	.52	68 (18.7)	104 (19.8)	.75
Prior myocardial infarction	28 (6.2)	12 (4.4)	.40	27 (7.4)	27 (5.1)	.21
Prior PCI	86 (18.9)	42 (15.3)	.26	78 (21.4)	110 (20.9)	.92
LV ejection fraction, mean (SD), %	64.0 (8.0)	64.8 (8.5)	.28	62.2 (9.1)	63.5 (8.2)	.05
Discharge medication						
Aspirin	260 (57.1)	140 (51.1)	.13	353 (97.0)	517 (98.3)	.29
$P2Y_{12}$ inhibitor	279 (61.3)	170 (62.0)	.91	359 (98.6)	523 (99.4)	.38
ACEI/ARB	230 (50.5)	121 (44.2)	.11	182 (50.0)	271 (51.5)	.71
β-blocker	191 (42.0)	121 (44.2)	.62	154 (42.3)	241 (45.8)	.33
Calcium channel blocker	167 (36.7)	100 (36.5)	>.99	111 (30.5)	169 (32.1)	.66
Statin	428 (94.1)	266 (97.1)	.10	353 (97.0)	505 (96.0)	.56
Target vessel-level						
No.						
Included vessels	600 (34.2)	350 (20.0)	NA	299 (17.1)	504 (28.8)	NA
Target vessel location						
Left anterior descending artery	344 (57.3)	233 (66.6)	.002	217 (72.6)	299 (59.3)	.001
Left circumflex artery	93 (15.5)	29 (8.3)		24 (8.0)	69 (13.7)	
Right coronary artery	163 (27.2)	88 (25.1)		58 (19.4)	136 (27.0)	
Diameter stenosis, mean (SD), %	53.5 (9.1)	51.1 (9.0)	<.001	62.9 (0.9)	60.9 (8.9)	.002
MLD, mean (SD), mm	1.4 (0.4)	1.5 (0.4)	<.001	1.1 (0.3)	1.1 (0.3)	.001
Lesion length, mean (SD), mm	17.9 (8.4)	17.5 (8.1)	.54	24.6 (12.1)	22.8 (12.3)	.04
Reference diameter, mean (SD), mm	3.0 (0.5)	3.1 (0.5)	.08	2.9 (0.4)	2.9 (0.4)	.28

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FFR, fractional flow reserve; IVUS, intravascular ultrasonography; LV, left ventricle; MLD, minimum lumen diameter; NA, not applicable; PCI, percutaneous coronary intervention.

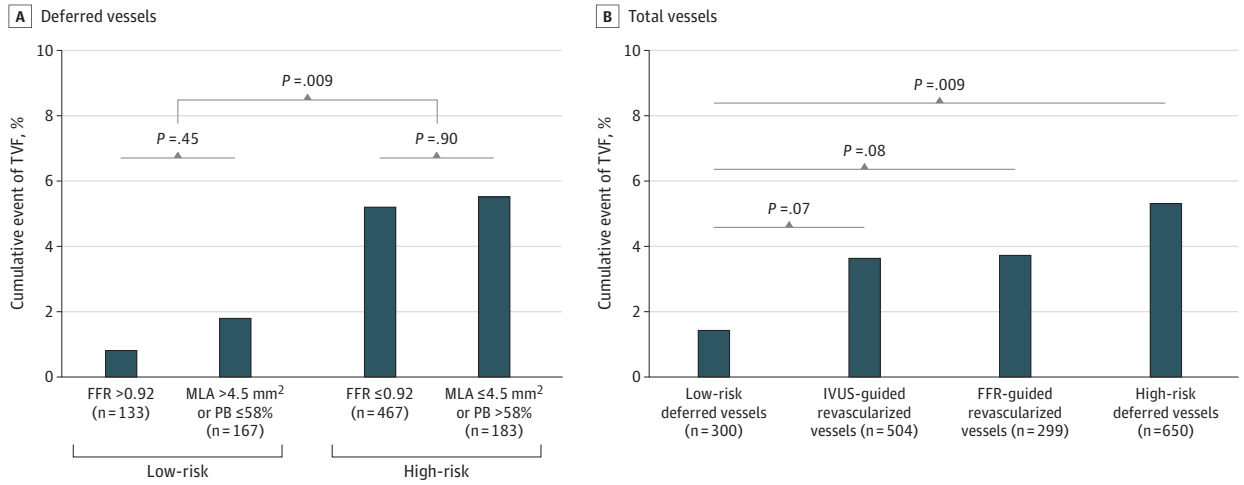
[a] Patients undergoing PCI for any vessels were included in the PCI group.

for clinical characteristics (**Table 2**) or accounting for multiple comparisons (eTable 2 in Supplement 1).

Outcome Comparison Between IVUS and FFR Groups in the PCI Group and Prespecified Optimal PCI Group

In 803 revascularized vessels, the event rates of TVF were comparable between FFR and IVUS groups (3.7% vs 3.6%; HR, 0.97 [95% CI, 0.46-2.06]; *P* = .95) (eFigure 4 in Supplement 1). Among revascularized vessels, procedural optimization data were available in 711 vessels (88.5%). According to the prespecified PCI optimization criteria, optimal PCI was performed in 191 vessels (70.0%) in the FFR group and 283 vessels (64.6%) in the IVUS group (eFigure 5 in Supplement 1). There were no

Figure 2. Risk of Target Vessel Failure (TVF) in Deferred Vessels by Binary Fractional Flow Reserve (FFR) and Intravascular Ultrasonography (IVUS) Parameters



A, Two-year rate of TVF in low-risk and high-risk deferred vessels defined by optimal cutoff values for estimating risk of TVF. Low-risk deferred vessels were defined as those with FFR greater than 0.92 or minimum lumen area (MLA) greater than 4.5 mm^2 or plaque burden (PB) of 58% or less. B, Two-year rate of TVF of low-risk deferred vessels, high-risk deferred vessels, FFR-guided revascularized vessels, and IVUS-guided revascularized vessels.

Table 2. Risk of TVF According to High- and Low-Risk Features

Group	Vessels, No. (%)	2-Y cumulative TVF, No. (%)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)[a]	*P* value
Deferred vessels						
Low-risk[b]	300 (17.1)	4 (1.4)	1 [Reference]	NA	1 [Reference]	NA
High-risk[b]	650 (37.1)	34 (5.3)	4.01 (1.41-11.4)	.009	3.99 (1.40-11.4)	.01
FFR-guided revascularized vessels	299 (17.1)	11 (3.7)	2.78 (0.88-8.74)	.08	2.68 (0.84-8.54)	.10
IVUS-guided revascularized vessels	504 (28.8)	18 (3.6)	2.71 (0.92-8.00)	.07	2.69 (0.91-7.99)	.07
Revascularized vessels[c]						
High-risk[d]	47 (2.8)	8 (17.1)	1 [Reference]	NA	1 [Reference]	NA
Low-risk[d]	697 (41.1)	17 (2.5)	0.14 (0.06-0.31)	<.001	0.14 (0.06-0.33)	<.001
FFR-guided deferred vessels	600 (35.4)	25 (4.2)	0.24 (0.11-0.52)	<.001	0.25 (0.11-0.56)	<.001
IVUS-guided deferred vessels	350 (20.7)	13 (3.8)	0.21 (0.09-0.49)	<.001	0.21 (0.09-0.51)	<.001

Abbreviations: FFR, fractional flow reserve; HR, hazard ratio; IVUS, intravascular ultrasonography; MLA, minimum lumen area; MSA, minimum stent area; NA, not applicable; PCI, percutaneous coronary intervention; TVF, target vessel failure.

[a] Adjusted for age, sex, body mass index, acute coronary syndrome, diabetes, hypertension, and dyslipidemia.

[b] High-risk deferred vessels were defined as medically treated vessels with FFR 0.92 or less in the FFR group and with MLA 4.5 mm^2 or less and plaque burden greater than 58% in the IVUS group; low-risk deferred vessels, medically treated vessels with FFR greater than 0.92 in the FFR group and with MLA greater than 4.5 mm^2 or plaque burden no more than 58% in the IVUS group.

[c] Among revascularized vessels, 59 vessels with missing data of high-risk features were excluded.

[d] High-risk revascularized vessels were defined as revascularized vessels with post-PCI FFR 0.80 or less in the FFR group and with MSA 6.0 mm^2 or less and plaque burden at stent edge greater than 58% in the IVUS group; low-risk revascularized vessels, revascularized vessels with post-PCI FFR greater than 0.80 in the FFR group and with MSA greater than 6.0 mm^2 or plaque burden at stent edge 58% or less in the IVUS group.

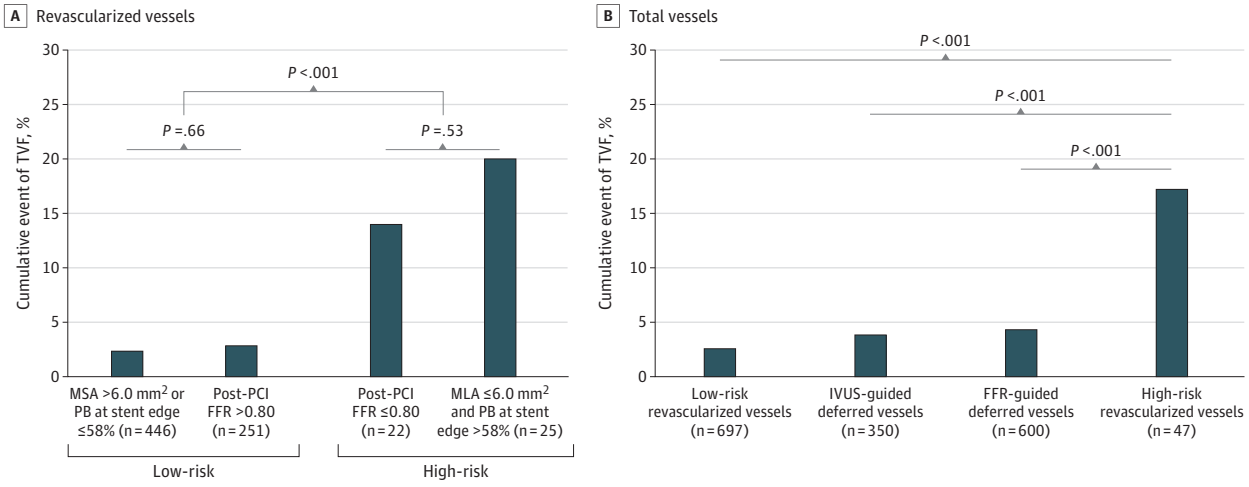
differences in the rate of optimal PCI between the FFR and IVUS groups. In the PCI subgroup that underwent optimal PCI, the rate of 2-year TVF was 4.2% in the FFR group and 2.5% in the IVUS group (HR, 0.59 [95% CI, 0.21-1.63]; *P* = .31) (eFigure 5 in Supplement 1). This result was consistent after adjustment for clinical characteristics (eTable 3 in Supplement 1).

Identification of High-Risk Revascularized Vessels by Post-PCI FFR and IVUS Parameters

The per-vessel optimal cutoff values for estimating risk of TVF after PCI were 0.81 for FFR, 6.01 mm^2 for MSA, and 58.1% for plaque burden at stent edge (eFigure 6 in Supplement 1). Among revascularized vessels, 744 vessels were stratified after exclusion of 59 vessels with missing data of these features, and the high-risk revascularized vessels were defined as those with post-PCI FFR 0.80 or less in the FFR group and MSA 6.0 mm^2 or less and plaque burden at stent edge greater than 58% in the IVUS group (**Figure 3**A). These vessels showed an increased risk for TVF (HR, 7.20 [95% CI, 3.2X-16.2X]; *P* < .001), primarily associated with ischemia-driven TVR (eTable 4 in Supplement 1). When the outcomes of post-PCI vessels were compared with the deferred vessels, the event rate of TVF was the highest in the high-risk revascularized vessels (17.1%), followed by the FFR-guided deferred vessels (4.2%), the IVUS-guided deferred vessels (3.8%), and low-risk revascularized vessels (2.5%) (*P* < .001) (Figure 3B). This finding was similar after adjustment for clinical characteristics (Table 2) and accounting for multiple comparisons (eTable 5 in Supplement 1).

In the sensitivity analysis, overall findings remained consistent for 1665 vessels that excluded 88 vessels from 40 patients who had a mix of both deferred vessels and revascularized vessels that belonged to either the FFR or IVUS group (eTable 6 in Supplement 1). When the optimal cutoff values were calculated using receiver operating characteristic curve analysis, all cutoff values were exactly the same as those derived from maximal log-rank statistics, except for plaque burden at stent edge (eTable 7 in Supplement 1). Overall results were consistent when the cutoff values from the receiver operating characteristic curve analysis (eFigure 7 in Supplement 1) or other cutoff values based on prior literature (eFigure 8 in Supplement 1) were used.

Figure 3. Risk of Target Vessel Failure (TVF) in Revascularized Vessels by Binary Fractional Flow Reserve (FFR) and Intravascular Ultrasonography (IVUS) Parameters After Percutaneous Coronary Intervention (PCI)



A, Two-year rate of TVF in low-risk and high-risk revascularized vessels, defined by optimal cutoff values for estimating risk of TVF. High-risk revascularized vessels were defined as those with post-PCI FFR 0.80 or less or minimum stent area (MSA) 6.0 mm^2 or less and plaque burden (PB) at stent edge greater than 58%. B, Two-year rate of TVF of low-risk revascularized vessels, high-risk revascularized vessels, FFR-guided deferred vessels, and IVUS-guided deferred vessels.

Discussion

This cohort study investigated the clinical outcomes of FFR- and IVUS-guided treatment strategies according to treatment type and defined low-risk deferred vessels and high-risk revascularized vessels based on binary FFR and IVUS parameters. We found that FFR- and IVUS-guided strategies showed comparable outcomes in the deferred vessels and that low-risk deferred vessels were those with FFR greater than 0.92 in the FFR group or MLA greater than 4.5 mm^2 or plaque burden 58% or less in the IVUS group. Clinical outcomes were not different between FFR- and IVUS-guided strategies in the group that underwent PCI or in the optimal PCI subgroup. High-risk revascularized vessels were those with post-PCI FFR of 0.80 or less in the FFR group or minimum stent area of 6.0 mm^2 or less and plaque burden at stent edge greater than 58% in the IVUS group.

Outcomes After FFR- and IVUS-Guided Treatment Decisions

Recent studies have suggested the similarity of FFR and IVUS modalities for treatment decision-making in terms of clinical outcomes.[5,6] Nonetheless, there is a paucity of data on the relative prognostic value between physiology- and imaging-based approaches according to treatment type. It is well known that the presence of high-risk plaque features, even in vessels with high FFR, is associated with poor prognosis under medical treatment.[18,19] In addition, deferred low FFR lesions, which can happen in patients with IVUS-guided decisions, are also associated with poor prognosis.[8] In this study, incidences of the composite outcome of cardiac death, target vessel myocardial infarction, and TVR at 24 months were similar between FFR and IVUS groups in the deferred vessels (4.2% vs 3.8%) as well as in the revascularized vessels (3.7% vs 3.7%). This result can be explained by the high specificity of imaging criteria for detection of myocardial ischemia[20,21] and a low prevalence of high-risk plaque in lesions with high FFR[22] and is supported by the correlation of both IVUS and FFR revascularization criteria with plaque or patient risk.[23-25] Moreover, when coronary lesions were classified by FFR and IVUS parameters, the prevalence was similar between mismatch and reverse mismatch of anatomical and physiological severity,[21] which indicates similar diagnostic performance for high-risk patients between the modalities. Therefore, the use of FFR or IVUS can be equally appropriate for decision-making for each treatment type.

Low-Risk Deferred Vessels Identified by Binary FFR and IVUS Parameters

Although FFR-guided treatment is the standard approach in patients with intermediate coronary stenosis,[3,4] clinical events still occur in medically treated patients whose PCI was deferred because of FFR findings,[8] and this observation is similar when imaging criteria are applied for deferral of PCI.[6,7] Considering prior studies have indicated that certain thresholds may exist for defining low-risk deferred vessels,[9,10] we investigated whether FFR and IVUS parameters could discriminate vessels that were at low risk of future clinical events after FFR- or IVUS-guided deferral of PCI via a binary approach. We found that low-risk deferred vessels (defined by the binary cutoff values) showed a lower risk of TVF than high-risk deferred vessels (1.4% vs 5.3%). This finding is in line with those of the PROSPECT II study,[9] which reported the lowest plaque burden of 56.2% among culprit lesions causing an adverse event or the 2023 coronary computed tomography angiography-based study[10] that the prognostic value of plaque features was diminished in the range of FFR greater than 0.90. Although the definite cutoff value needs to be further defined, our findings support the existence of physiological or imaging criteria to warrant safe deferral of PCI and the necessity for future studies to find an optimized diagnostic process and treatment strategy for patients with high-risk deferred vessels.

Outcomes After Physiology- or Imaging-Based PCI Optimization

While intravascular imaging is recommended for planning and optimization of PCI,[11] poststent physiological assessment can also independently estimate risk of adverse clinical events after stent

implantation.[26,27] Nonetheless, head-to-head comparison of clinical outcomes between physiology- and imaging-based PCI optimization has rarely been conducted. In the FLAVOUR trial, FFR- and IVUS-guided PCI optimization were assessed by prespecified criteria, and the rate of optimal PCI was 70.0% in the FFR group and 64.6% in the IVUS group (P = .16), similar to prior reports.[28-30] When their outcomes were directly compared, the 2-year rates of TVF were not statistically different between FFR-guided optimal PCI and IVUS-guided optimal PCI groups (4.2% vs 2.5%; P = .31), which might suggest the similarity between strategies. Nonetheless, given that an IVUS-defined optimal procedure is known to be associated with a lower risk of adverse events in patients overall[29] and in patients with complex lesions,[31] while PCI optimization based on post-PCI FFR values failed to reduce 1-year TVF in the FFR-REACT study,[32] whether physiology- or imaging-based PCI optimization can warrant similar outcomes or not should be demonstrated in the long-term follow-up data or in a larger study population that can provide adequate statistical power.

Prognostic Implications of Binary Post-PCI FFR or IVUS Parameters

Although clinical outcomes between IVUS and FFR groups were not significantly different according to the prespecified optimization criteria in this study, high-risk revascularized vessels can be defined using the optimal cutoff of post-PCI FFR, MSA, and plaque burden at stent edge, which were associated with a higher risk of TVF than low-risk revascularized vessels. This finding aligns with prior publications that reported the prognostic value of residual ischemia,[27,33] or IVUS-defined post-PCI plaque burden or stent underexpansion.[34,35] It should be noted that there was no statistically significant association of continuous FFR and IVUS parameters with TVF did in this study. This result should be interpreted in consideration of the unique characteristics of the study population. Since the FLAVOUR trial mandates FFR- or IVUS-guided treatment decision-making and stent optimization for PCI, leading treatment strategies for intermediate stenosis, both deferred and revascularized vessels inherently had a lower clinical event risk compared with other studies showing the prognostic significance of FFR and IVUS parameters,[27,34,36,37] which may diminish the statistical power to show the prognostic value of each parameter. Although the prognostic significance of each parameter after FFR- or IVUS-guided treatment should be tested in a larger study population with long-term outcomes data and adequate statistical power, our findings were consistent across various different cutoff values in sensitivity analyses and spotlight the potential of using binary FFR and IVUS parameters to discern low-risk deferred and high-risk revascularized vessels after FFR- or IVUS-guided treatment. This finding broadens the current evidence of the clinical value of FFR and IVUS parameters to distinct study populations undergoing physiological- or imaging-guided optimal treatment and could help physicians to determine lesion subsets necessitating thorough follow-up, even after the current optimal treatment strategies in clinical practice. Optimal physiological- and imaging-based procedural end points to improve clinical outcomes incorporating new indices, such as imaged-based PCI planning or longitudinal vessel analysis with pressure pullback curve,[38,39] should be defined in future studies.

Limitations

This study has several limitations. First, since this is a post hoc analysis of a randomized clinical trial, the statistical analysis results may be underpowered to support some of the findings. Thus, these findings should be limited to hypothesis generation. Second, several clinical characteristics were different between FFR and IVUS groups when patients were stratified by treatment type; however, all results were consistent after adjustment for clinical characteristics. Third, FFR and IVUS were used as representative tools for invasive physiologic and imaging studies in our study. Further studies are needed to assess the comparative roles of other physiologic and imaging tools. Fourth, the medication history during follow-up was not included in the analysis, which might have caused a potential bias in the results. Fifth, this study could not determine the association of continuous FFR and IVUS parameters with outcomes due to an underpowered analysis. This association should be explored in future studies with adequate statistical power. Sixth, this analysis was mainly based on a

binary approach, and the cutoff values of each parameter should be extrapolated in the external cohort. Seventh, the event rate was relatively low, and a small number of events in each group could impact the results, which necessitates adequately powered future studies to generalize the current results. Eighth, the clinical value of FFR and IVUS parameters has already been suggested in prior studies; however, this study population was distinct from the prior literature in that this study comprised deferred vessels with negative FFR or negative IVUS criteria or revascularized vessels that met stent optimization criteria in approximately two-third of vessels, which could be regarded as already received optimal treatment strategies for intermediate stenosis under the guidance of physiological- and imaging-based assessment. Our analysis showed the prognostic value of binary FFR and IVUS parameters in this unique population.

Conclusions

The findings of this cohort study suggest that clinical outcomes were comparable between FFR- and IVUS-guided treatment in both deferred and revascularized vessels, and low-risk deferred vessels and high-risk revascularized vessels could be defined by using binary FFR and IVUS parameters after FFR- and IVUS-guided decision-making and stent optimization. This approach can further help determine the optimal management for patients with intermediate coronary stenosis.

ARTICLE INFORMATION

Accepted for Publication: November 15, 2023.

Published: January 3, 2024. doi:10.1001/jamanetworkopen.2023.50036

Corresponding Author: Bon-Kwon Koo, MD, PhD, Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehang-ro, Chongno-gu, Seoul 110-744, Korea (bkkoo@snu.ac.kr).

Author Affiliations: Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea (Yang, Kang, Hwang, H.-S. Kim, Koo); The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China (Zhang, J. Jiang, Hu, Wang); Samsung Medical Center, Seoul, Republic of Korea (Hahn, J. M. Lee); Keimyung University Dongsan Medical Center, Daegu, Republic of Korea (Nam); Inje University Ilsan Paik Hospital, Goyang, Republic of Korea (Doh); Kangwon National University Hospital, Chuncheon, Gangwon-Do, Republic of Korea (B.-K. Lee); Kyung Hee University Hospital, Seoul, Republic of Korea (W. Kim); Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China (Huang); Hangzhou Normal University Affiliated Hospital, Hangzhou, China (F. Jiang); The 1st Affiliated Hospital of Wenzhou Medical University, Wenzhou, China (Zhou); The 2nd Affiliated Hospital of Wenzhou Medical University, Wenzhou, China (P. Chen); Zhejiang Hospital, Hangzhou, China (Tang); The Third Clinical Institute Affiliated To Wenzhou Medical University, Wenzhou, China (W. Jiang); Ningbo First Hospital, Ningbo, China (X. Chen); The Affiliated Hospital of Medical School of Ningbo University, Ningbo, China (He); Wonju Severance Christian Hospital, Wonju, Gangwon-Do, Republic of Korea (Ahn); Ajou University Hospital, Suwon, Republic of Korea (Yoon, Tahk); Yeungnam University Medical Center, Daegu, Republic of Korea (U. Kim); Uijeongbu Eulji Medical Center, Uijeongbu, Gyeonggi-Do, Republic of Korea (Ki); Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea (Shin).

Author Contributions: Drs Koo and Yang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Yang and Kang contributed equally to this work as co–first authors.

Concept and design: Yang, Hwang, Zhang, Hu, Huang, F. Jiang, Zhou, P. Chen, Tang, W. Jiang, X. Chen, Yoon, J.M. Lee, H.-S. Kim, Tahk, Wang, Koo.

Acquisition, analysis, or interpretation of data: Yang, Kang, Hwang, J. Jiang, Hahn, Nam, Doh, B.-K. Lee, W. Kim, Huang, Tang, He, Ahn, U. Kim, J.M. Lee, Ki, Shin, Tahk, Koo.

Drafting of the manuscript: Yang, Huang, Tang, Tahk, Koo.

Critical review of the manuscript for important intellectual content: Yang, Kang, Hwang, Zhang, J. Jiang, Hu, Hahn, Nam, Doh, B.-K. Lee, W. Kim, Huang, F. Jiang, Zhou, P. Chen, Tang, W. Jiang, X. Chen, He, Ahn, Yoon, U. Kim, J.M. Lee, Ki, Shin, H.-S. Kim, Tahk, Wang, Koo.

Statistical analysis: Yang, Tang, Koo.

Obtained funding: Tang, Koo.

Administrative, technical, or material support: Kang, J. Jiang, Doh, B.-K. Lee, W. Kim, Huang, Tang, Yoon, Koo.

Supervision: Hwang, Zhang, Hu, Doh, B.-K. Lee, F. Jiang, Zhou, P. Chen, Tang, W. Jiang, X. Chen, Yoon, J.M. Lee, Ki, H.-S. Kim, Tahk, Wang, Koo.

Conflict of Interest Disclosures: Dr Han reported receiving grants from Abbott Korea, Biosensors International Group, Biotronik, Boston Scientific, and Medtronic. Dr Koo reported receiving grants from Abbott Vascular, Boston Scientific, and Philips. Dr J. M. Lee reported receiving grants from Abbott and Philips. No other disclosures were reported.

Funding/Support: This study was funded by grants from Boston Scientific and the Patient-Centered Clinical Research Coordinating Center (grant No. HI19C0481, HC19C0305).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. *JACC Cardiovasc Interv*. 2020;13(14):1617-1638. doi:10.1016/j.jcin.2020.04.040

2. Mintz GS, Guagliumi G. Intravascular imaging in coronary artery disease. *Lancet*. 2017;390(10096):793-809. doi:10.1016/S0140-6736(17)31957-8

3. Lawton JS, Tamis-Holland JE, Bangalore S, et al; Writing Committee Members. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):e21-e129. doi:10.1016/j.jacc.2021.09.006

4. Knuuti J, Wijns W, Saraste A, et al; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477. doi:10.1093/eurheartj/ehz425

5. Iannaccone M, Abdirashid M, Annone U, et al. Comparison between functional and intravascular imaging approaches guiding percutaneous coronary intervention: A network meta-analysis of randomized and propensity matching studies. *Catheter Cardiovasc Interv*. 2020;95(7):1259-1266. doi:10.1002/ccd.28410

6. Koo BK, Hu X, Kang J, et al; FLAVOUR Investigators. Fractional flow reserve or intravascular ultrasonography to guide PCI. *N Engl J Med*. 2022;387(9):779-789. doi:10.1056/NEJMoa2201546

7. Burzotta F, Leone AM, Aurigemma C, et al. Fractional flow reserve or optical coherence tomography to guide management of angiographically intermediate coronary stenosis: a single-center trial. *JACC Cardiovasc Interv*. 2020;13(1):49-58. doi:10.1016/j.jcin.2019.09.034

8. Xaplanteris P, Fournier S, Pijls NHJ, et al; FAME 2 Investigators. Five-year outcomes with PCI guided by fractional flow reserve. *N Engl J Med*. 2018;379(3):250-259. doi:10.1056/NEJMoa1803538

9. Erlinge D, Maehara A, Ben-Yehuda O, et al; PROSPECT II Investigators. Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. *Lancet*. 2021;397(10278):985-995. doi:10.1016/S0140-6736(21)00249-X

10. Yang S, Hoshino M, Yonetsu T, et al. Outcomes of non-ischaemic coronary lesions with high-risk plaque characteristics on coronary CT angiography. *EuroIntervention*. 2023;18(12):1011-1021. doi:10.4244/EIJ-D-22-00562

11. Räber L, Mintz GS, Koskinas KC, et al; ESC Scientific Document Group. Clinical use of intracoronary imaging: part 1: guidance and optimization of coronary interventions—an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. 2018;39(35):3281-3300. doi:10.1093/eurheartj/ehy285

12. Kang J, Koo BK, Hu X, et al. Comparison of Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients With Intermediate Stenosis (FLAVOUR): rationale and design of a randomized clinical trial. *Am Heart J*. 2018;199:7-12. doi:10.1016/j.ahj.2017.11.001

13. Koo BK, Yang HM, Doh JH, et al. Optimal intravascular ultrasound criteria and their accuracy for defining the functional significance of intermediate coronary stenoses of different locations. *JACC Cardiovasc Interv*. 2011;4(7):803-811. doi:10.1016/j.jcin.2011.03.013

14. Waksman R, Legutko J, Singh J, et al. FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. *J Am Coll Cardiol*. 2013;61(9):917-923. doi:10.1016/j.jacc.2012.12.012

15. Song HG, Kang SJ, Ahn JM, et al. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv*. 2014;83(6):873-878. doi:10.1002/ccd.24560

16. Li SJ, Ge Z, Kan J, et al. Cutoff value and long-term prediction of clinical events by FFR measured immediately after implantation of a drug-eluting stent in patients with coronary artery disease: 1- to 3-year results from the DKCRUSH VII registry study. *JACC Cardiovasc Interv*. 2017;10(10):986-995. doi:10.1016/j.jcin.2017.02.012

17. Garcia-Garcia HM, McFadden EP, Farb A, et al; Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation*. 2018;137(24):2635-2650. doi:10.1161/CIRCULATIONAHA.117.029289

18. Yang S, Koo BK, Hwang D, et al. High-risk morphological and physiological coronary disease attributes as outcome markers after medical treatment and revascularization. *JACC Cardiovasc Imaging*. 2021;14(10):1977-1989. doi:10.1016/j.jcmg.2021.04.004

19. Cho YK, Hwang J, Lee CH, et al. Influence of anatomical and clinical characteristics on long-term prognosis of FFR-guided deferred coronary lesions. *JACC Cardiovasc Interv*. 2020;13(16):1907-1916. doi:10.1016/j.jcin.2020.05.040

20. Han JK, Koo BK, Park KW, et al. Optimal intravascular ultrasound criteria for defining the functional significance of intermediate coronary stenosis: an international multicenter study. *Cardiology*. 2014;127(4):256-262. doi:10.1159/000356480

21. Cho YK, Nam CW, Han JK, et al. Usefulness of combined intravascular ultrasound parameters to predict functional significance of coronary artery stenosis and determinants of mismatch. *EuroIntervention*. 2015;11(2):163-170. doi:10.4244/EIJV11I2A30

22. Ahmadi A, Stone GW, Leipsic J, et al. Association of coronary stenosis and plaque morphology with fractional flow reserve and outcomes. *JAMA Cardiol*. 2016;1(3):350-357. doi:10.1001/jamacardio.2016.0263

23. Tian J, Dauerman H, Toma C, et al. Prevalence and characteristics of TCFA and degree of coronary artery stenosis: an OCT, IVUS, and angiographic study. *J Am Coll Cardiol*. 2014;64(7):672-680. doi:10.1016/j.jacc.2014.05.052

24. Ahmadi A, Leipsic J, Øvrehus KA, et al. Lesion-specific and vessel-related determinants of fractional flow reserve beyond coronary artery stenosis. *JACC Cardiovasc Imaging*. 2018;11(4):521-530. doi:10.1016/j.jcmg.2017.11.020

25. Usui E, Yonetsu T, Kanaji Y, et al. Optical coherence tomography-defined plaque vulnerability in relation to functional stenosis severity and microvascular dysfunction. *JACC Cardiovasc Interv*. 2018;11(20):2058-2068. doi:10.1016/j.jcin.2018.07.012

26. Hwang D, Yang S, Zhang J, Koo BK. Physiologic assessment after coronary stent implantation. *Korean Circ J*. 2021;51(3):189-201. doi:10.4070/kcj.2020.0548

27. Hwang D, Koo BK, Zhang J, et al. Prognostic implications of fractional flow reserve after coronary stenting: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(9):e2232842. doi:10.1001/jamanetworkopen.2022.32842

28. Hong SJ, Kim BK, Shin DH, et al; IVUS-XPL Investigators. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314(20):2155-2163. doi:10.1001/jama.2015.15454

29. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72(24):3126-3137. doi:10.1016/j.jacc.2018.09.013

30. Collison D, Didagelos M, Aetesam-Ur-Rahman M, et al. Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR). *Eur Heart J*. 2021;42(45):4656-4668. doi:10.1093/eurheartj/ehab449

31. Choi KH, Song YB, Lee JM, et al. Impact of intravascular ultrasound-guided percutaneous coronary intervention on long-term clinical outcomes in patients undergoing complex procedures. *JACC Cardiovasc Interv*. 2019;12(7):607-620. doi:10.1016/j.jcin.2019.01.227

32. Neleman T, van Zandvoort LJC, Tovar Forero MN, et al. FFR-guided PCI optimization directed by high-definition IVUS versus standard of care: the FFR REACT trial. *JACC Cardiovasc Interv*. 2022;15(16):1595-1607. doi:10.1016/j.jcin.2022.06.018

33. Yang S, Zhang J, Hwang D, et al. Effect of coronary disease characteristics on prognostic relevance of residual ischemia after stent implantation. *Front Cardiovasc Med*. 2021;8:696756. doi:10.3389/fcvm.2021.696756

34. Lee YJ, Zhang JJ, Mintz GS, et al. Impact of intravascular ultrasound-guided optimal stent expansion on 3-year hard clinical outcomes. *Circ Cardiovasc Interv*. 2021;14(10):e011124. doi:10.1161/CIRCINTERVENTIONS.121.011124

35. Kang SJ, Cho YR, Park GM, et al. Intravascular ultrasound predictors for edge restenosis after newer generation drug-eluting stent implantation. *Am J Cardiol*. 2013;111(10):1408-1414. doi:10.1016/j.amjcard.2013.01.288

36. Barbato E, Toth GG, Johnson NP, et al. A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *J Am Coll Cardiol*. 2016;68(21):2247-2255. doi:10.1016/j.jacc.2016.08.055

37. Schuurman AS, Vroegindewey MM, Kardys I, et al. Prognostic value of intravascular ultrasound in patients with coronary artery disease. *J Am Coll Cardiol*. 2018;72(17):2003-2011. doi:10.1016/j.jacc.2018.08.2140

38. Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74(14):1772-1784. doi:10.1016/j.jacc.2019.07.072

39. Sonck J, Nagumo S, Norgaard BL, et al. Clinical validation of a virtual planner for coronary interventions based on coronary CT angiography. *JACC Cardiovasc Imaging*. 2022;15(7):1242-1255. doi:10.1016/j.jcmg.2022.02.003

SUPPLEMENT 1.

eMethods.

SUPPLEMENT 2.

Data Sharing Statement