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Fractional Flow Reserve or Intravascular Ultrasonography to Guide PCI

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ABSTRACT

BACKGROUND

In patients with coronary artery disease who are being evaluated for percutaneous coronary intervention (PCI), procedures can be guided by fractional flow reserve (FFR) or intravascular ultrasonography (IVUS) for decision making regarding revascularization and stent implantation. However, the differences in clinical outcomes when only one method is used for both purposes are unclear.

METHODS

We randomly assigned 1682 patients who were being evaluated for PCI for the treatment of intermediate stenosis (40 to 70% occlusion by visual estimation on coronary angiography) in a 1:1 ratio to undergo either an FFR-guided or IVUS-guided procedure. FFR or IVUS was to be used to determine whether to perform PCI and to assess PCI success. In the FFR group, PCI was to be performed if the FFR was 0.80 or less. In the IVUS group, the criteria for PCI were a minimal lumen area measuring either 3 mm^2 or less or measuring 3 to 4 mm^2 with a plaque burden of more than 70%. The primary outcome was a composite of death, myocardial infarction, or revascularization at 24 months after randomization. We tested the noninferiority of the FFR group as compared with the IVUS group (noninferiority margin, 2.5 percentage points).

RESULTS

The frequency of PCI was 44.4% among patients in the FFR group and 65.3% among those in the IVUS group. At 24 months, a primary-outcome event had occurred in 8.1% of the patients in the FFR group and in 8.5% of those in the IVUS group (absolute difference, −0.4 percentage points; upper boundary of the one-sided 97.5% confidence interval, 2.2 percentage points; P=0.01 for noninferiority). Patient-reported outcomes as reported on the Seattle Angina Questionnaire were similar in the two groups.

CONCLUSIONS

In patients with intermediate stenosis who were being evaluated for PCI, FFR guidance was noninferior to IVUS guidance with respect to the composite primary outcome of death, myocardial infarction, or revascularization at 24 months. (Funded by Boston Scientific; FLAVOUR ClinicalTrials.gov number, NCT02673424.)

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*A list of the FLAVOUR trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

In patients with coronary artery disease (CAD), the degree of luminal narrowing, plaque burden and characteristics, and physiologic significance are prognostic indicators.[1,2] Although coronary angiography is the standard method for evaluating CAD and guiding percutaneous coronary intervention (PCI), various measurements are used for incremental information. Intravascular ultrasonography (IVUS) is a commonly used adjunctive technique that can provide detailed anatomical information regarding the lumen, vessel, and plaque. Moreover, IVUS can guide the PCI procedure to improve stent placement and minimize stent-related problems,[3] and IVUS-guided PCI has been reported to improve clinical outcomes in comparison with angiography-guided PCI.[4,5] Fractional flow reserve (FFR) is an invasive physiologic index that is used to determine whether a stenosis is causing ischemia, and previous trials have shown that FFR-guided PCI is associated with fewer clinical events than angiography-guided PCI and medical treatment.[6,7]

Although the basic concepts underlying the use of FFR and IVUS during PCI are distinct, both are the most commonly used adjunctive tools in the diagnosis and treatment of CAD during cardiac catheterization. However, data are lacking regarding the difference between the two strategies with respect to clinical outcomes. In the FLAVOUR (Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis) trial, we wanted to perform a head-to-head comparison of FFR- and IVUS-guided procedures regarding clinical and patient-reported outcomes in those with intermediate coronary stenosis.

Methods

Trial Design and Oversight

The trial was an investigator-initiated, prospective, randomized, open-label, multinational trial conducted at 18 sites in Korea and China. Details regarding the trial design have been described previously,[8] and a schematic diagram is provided in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. All participating centers and trial personnel are also listed in the Supplementary Appendix.

The trial was conducted in accordance with the standards specified in the International Council for Harmonisation of Technical Requirements for Good Clinical Practice and the principles of the Declaration of Helsinki. The trial protocol (also available at NEJM.org) was approved by the institutional review board at each participating site. All the patients provided oral consent before randomization and provided written informed consent after the completion of the procedure. An independent data and safety monitoring board monitored the trial, and an independent clinical-events committee adjudicated all clinical outcomes in a blinded manner. The trial sponsor, Boston Scientific, had no role in the trial design, in the collection, analysis, or interpretation of the data, or in the writing of the manuscript. The executive committee and all the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Major Protocol Revision

The initial aim of the trial was to prove the superiority of the FFR-guided strategy over the IVUS-guided strategy. However, after the initiation of the trial in July 2016, the published results of several studies showed that IVUS-guided stenting could further improve clinical outcomes, especially with the use of drug-eluting stents.[9] Therefore, in June 2017, we modified the trial to assess the noninferiority of FFR-guided procedures in comparison with IVUS-guided procedures. The noninferiority design of our trial can be justified because establishing that FFR is noninferior with regard to clinical events would be relevant, given that FFR is expected to result in placement of fewer stents and consumption of fewer medical resources. The database lock for the trial occurred on January 28, 2022, and the investigators did not look at or share the data before that time. These changes are summarized in the Major Protocol Revision section in the Supplementary Appendix.

Population and Randomization

Patients who were 19 years of age or older were screened for enrollment if they were suspected of having ischemic heart disease and were found to have a de novo intermediate stenosis (40 to 70%) in a target vessel measuring at least 2.5 mm by visual estimation on coronary angiography. Patients were excluded if they had a noncardiac coexisting illness and a life expectancy of less

than 2 years, a target lesion that was located in the left main coronary artery or in a coronary-artery bypass graft, or an increased bleeding risk. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

Eligible patients were randomly assigned in a 1:1 ratio to undergo FFR- or IVUS-guided procedures (Figs. S1 and S2). Concealed randomization was performed with the use of a Web-based program (Apache 2, PHP 5.3, and MySOL5) developed by an independent organization (S-Soft). Randomization was stratified according to the trial center and the presence or absence of diabetes mellitus. A Web-based electronic case report form (S-Soft) was used to capture clinical and procedural data.

INDICATIONS FOR REVASCULARIZATION AND PCI SUCCESS

In the FFR group, the criterion for revascularization was an FFR of 0.80 or less (i.e., the stenosis was found to cause a reduction in coronary blood flow of ≥20%). Hyperemia was induced by intravenous infusion of adenosine or adenosine triphosphate (at a dose of 140 μg per kilogram of body weight per minute) or intracoronary nicorandil (2 mg).[10] In the IVUS group, two alternative criteria for PCI were a minimal lumen area measuring either 3 mm^2 or less or measuring 3 mm^2 to 4 mm^2 with a plaque burden of more than 70%.[11-14] Analysis of the raw data was performed in independent core laboratories at the Seoul National University Hospital (for FFR) and at Ulsan University Hospital (for IVUS). In the two groups, data collection for core laboratory analysis was performed after completion of the whole procedure, including PCI. In the FFR group, successful PCI was defined as a postprocedural FFR value of at least 0.88 or a difference in the FFR across the stent (i.e., the FFR at the proximal edge of the stent minus the FFR at the distal edge) of less than 0.05. In the IVUS group, successful PCI was defined as a plaque burden at the stent edge of 55% or less and a minimal stent area of 5.5 mm^2 or more or a minimal stent area that was equal to or larger than the distal reference lumen area. Detailed criteria for successful PCI are provided in the Supplementary Appendix.

OUTCOMES AND DEFINITIONS

The primary outcome was a composite of death from any cause, myocardial infarction, or any revascularization at 24 months after randomization, according to the Academic Research Consortium consensus.[15] Key secondary outcomes were the individual components of the primary outcome, the number of stents that were placed per patient and per vessel, stroke, and patient-reported outcomes as measured on the Seattle Angina Questionnaire (SAQ). Table S1 presents a complete list of secondary outcomes. Quantitative coronary angiography and calculation of the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score,[16] an angiography-based scoring system that estimates the burden and complexity of CAD, were performed at the Seoul National University Hospital angiographic core laboratory. Detailed definitions of each clinical event and assessment on the SAQ (as measured in five domains, with scores ranging from 0 to 100, with lower scores indicating more frequent angina or more functional limitations) are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample-size calculation was based on the assumption that the event rate for the primary outcome at 24 months would be 10% in the FFR group and 12% in the IVUS group.[17-19] We determined that the enrollment of 1700 patients would provide 90% power to test the hypothesis that the event rate in the FFR group would be noninferior to that in the IVUS group according to a noninferiority margin of 2.5 percentage points, with the use of a one-sided 95% confidence interval and with a type I error rate of 5%. Although a one-sided type I error rate of 2.5% is considered to be robust for a noninferiority assessment, we used a one-sided error rate of 5% that is sometimes used for evaluating medical devices.[20,21] We report results for the assessment of noninferiority on the basis of both a one-sided 95% confidence interval and a one-sided 97.5% confidence interval. Details regarding this power calculation are provided in the Supplementary Appendix.

Continuous variables were reported as means and standard deviations, and categorical variables were reported as total numbers and percentages. We used a Cox proportional-hazards model to analyze the primary outcome, with trial sites and the presence or absence of diabetes mellitus as a random effect. The Kaplan–Meier method was used to characterize the time until

the first event. The assumptions of the proportional-hazards model were evaluated with a two-sided test of the scaled Schoenfeld residuals over time at a level of 0.05. Event-free survival with incomplete follow-up was counted as censored data for all time-to-event analyses. All outcomes were analyzed in both the intention-to-treat and per-protocol populations and on a per-patient basis or per-vessel basis, as appropriate. The per-protocol analysis excluded patients with missing or inadequate data regarding the assigned device and those who had received the assigned treatment without meeting prespecified criteria (Fig. S2).

Because the statistical analysis plan did not include a provision for correcting for multiple comparisons in the evaluation of secondary outcomes, results are reported as point estimates and two-sided 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. Statistical tests were performed with the use of SPSS software, version 24 (SPSS), and R programming language, version 3.6.2 (R Foundation for Statistical Computing).

RESULTS

PATIENTS AND FOLLOW-UP

From July 2016 through August 2019, a total of 4355 patients were screened, and 1682 patients with intermediate coronary stenosis were randomly assigned to undergo either an FFR-guided procedure (838 patients) or an IVUS-guided procedure (844 patients) (Fig. S2). The mean age of the patients was 65 years, and 554 patients (32.9%) had diabetes mellitus (Table 1). The discharge medications are shown in Table S2.

The target vessel was the left anterior descending coronary artery in 61.9% of the patients, and the two groups had similar values in the lesion length, diameter of the reference vessel, and diameter of stenosis in the target lesion (Table 2). The number of patients who underwent PCI was higher in the IVUS group (65.3%) than in the FFR group (44.4%). The total number of stents and total length of stents were similar among patients who had undergone PCI in the FFR group and in those who had undergone PCI in the IVUS group. In the per-vessel analysis, the frequency of PCI was higher in the IVUS group than in the FFR group (Table S3).

During the index procedure, 19 patients did not undergo the procedure according to the assigned strategy because of failure of adequate measurement or of passage of the FFR wire or the IVUS catheter across the target lesion. In addition, protocol violations occurred in 44 patients, which included 11 cases in which PCI was performed on lesions that did not meet the revascularization criteria, 28 cases in which PCI was deferred despite satisfaction of the revascularization criteria, and 5 cases in which PCI was not performed with a drug-eluting stent.

PRIMARY OUTCOME

Follow-up evaluations were completed in 99.2% of the patients, with 14 patients lost to follow-up. During the 24-month evaluation period in the time-to-event analysis, a primary-outcome event occurred in 67 patients in the FFR group and in 71 patients in the IVUS group (8.1% vs. 8.5%) (absolute difference, −0.4 percentage points; upper boundary of the one-sided 95% confidence interval, 1.8 percentage points; upper boundary of the one-sided 97.5% confidence interval, 2.2 percentage points; P=0.01 for noninferiority) (Table 3 and Fig. 1). The global test statistic for the Schoenfeld residuals over time was not significant (P=0.99), indicating that the assumptions of the proportional-hazards model had not been violated. The hazard ratio for a primary-outcome event was 0.96 (upper boundary of the one-sided 95% confidence interval, 1.27; upper boundary of the one-sided 97.5% confidence interval, 1.35).

SECONDARY AND OTHER OUTCOMES

The incidence of secondary outcomes was similar in the two groups (Table 3). Results were similar in analyses stratified according to the presence or absence of diabetes (Fig. S3). The per-protocol analysis showed similar results to those in the intention-to-treat analysis for the primary outcome in the FFR group as compared with the IVUS group (8.2% vs. 8.7%; absolute risk difference, −0.5 percentage points; upper boundary of the one-sided 95% confidence interval, 1.8 percentage points; upper boundary of the one-sided 97.5% confidence interval, 2.3 per-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	FFR Group (N=838)	IVUS Group (N=844)	All Patients (N=1682)
Age — yr	65.4±9.4	64.8±9.9	65.1±9.6
Male sex — no. (%)	584 (69.7)	603 (71.4)	1187 (70.6)
Body-mass index†	24.6±3.3	24.7±3.3	24.7±3.3
Diagnosis — no. (%)			
Stable angina	519 (61.9)	544 (64.5)	1063 (63.2)
Acute coronary syndrome‡	252 (30.1)	244 (28.9)	496 (29.5)
STEMI	4 (0.5)	4 (0.5)	8 (0.5)
NSTEMI	12 (1.4)	15 (1.8)	27 (1.6)
Other§	67 (8.0)	56 (6.6)	123 (7.3)
Medical history — no. (%)			
Diabetes mellitus	272 (32.5)	282 (33.4)	554 (32.9)
Hypertension	577 (68.9)	570 (67.5)	1147 (68.2)
Dyslipidemia	667 (79.6)	655 (77.6)	1322 (78.6)
Current smoking	166 (19.8)	155 (18.4)	321 (19.1)
Chronic kidney disease¶	143 (17.1)	147 (17.4)	290 (17.2)
Previous myocardial infarction	56 (6.7)	39 (4.6)	95 (5.6)
Previous PCI	165 (19.7)	163 (19.3)	328 (19.5)
Left ventricular ejection fraction — %	63.3±8.5	63.9±8.3	63.6±8.4
Laboratory data			
White-cell count — per mm^3	6500±1800	6500±1900	6500±1900
Hemoglobin — g/dl	13.6±1.7	13.7±1.7	13.6±1.7
Creatinine — mg/dl	0.9±0.8	0.9±0.9	0.9±0.9
Total cholesterol — mg/dl	156.7±44.2	152.1±41.7	154.4±43.0
High-density lipoprotein	45.4±11.0	44.9±11.5	45.2±11.3
Low-density lipoprotein	87.6±35.8	83.5±33.5	85.6±34.7
Triglycerides — mg/dl	141.9±84.2	139.9±93.9	140.9±89.2

* Plus–minus values are means ±SD. All the patients in this trial were of Asian descent. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. FFR denotes fractional flow reserve, IVUS intravascular ultrasonography, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The lesion regarded as the target by the operator was included as a trial lesion in 299 of 496 patients with acute coronary syndrome.

§ Among the 123 patients in this category, 112 presented with atypical chest discomfort, 7 with dyspnea on exertion, and 4 with variant angina.

¶ Chronic kidney disease was defined as a history of chronic kidney disease or an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.

centage points; P=0.02 for noninferiority), as well for the secondary outcomes (Table S4 and Fig. S4). The protocol specified the use of adenosine, but 288 patients underwent FFR that was performed with the use of nicorandil as the hyperemic agent. In a post hoc analysis with the removal of data from these patients, the results were similar to those in the intention-to-treat analysis (Table S5 and Fig. S5).

Successful PCI as defined according to prespecified criteria occurred in 52.9% of the patients in PCI population, with similar rates in

Table 2. Procedural Characteristics at Baseline.*

Characteristic	FFR Group	IVUS Group	Difference (95% CI)†
Angiographic findings			
No. of patients	838	844	
Multivessel disease — no. (%)	445 (53.1)	430 (50.9)	2.2 (–2.7 to 7.0)‡
Diseased vessels — no. (%)§			
Nonobstructive	15 (1.8)	16 (1.9)	
1 vessel	378 (45.1)	398 (47.2)	
2 vessels	295 (35.2)	273 (32.3)	
3 vessels	150 (17.9)	157 (18.6)	
Trial target vessels — no. (%)			
1 vessel	763 (91.1)	791 (93.7)	
2 vessels	69 (8.2)	49 (5.8)	
3 vessels	6 (0.7)	4 (0.5)	
Patients who underwent PCI — no. (%)			
Any procedure	372 (44.4)	551 (65.3)	–20.9 (–25.7 to –16.1)‡
Multivessel	66 (7.9)	125 (14.8)	–6.9 (–10.1 to –3.8)‡
Stent data			
Total no. per patient	0.6±0.9	0.9±1.0	–0.3 (–0.4 to –0.3)
Total length per patient — mm	16.5±24.1	25.2±28.1	–8.7 (–11.2 to –6.2)
Total no. per patient who underwent PCI	1.4±0.8	1.5±0.8	–0.1 (–0.2 to 0.0)
Total length per patient who underwent PCI — mm	37.2±23.2	38.6±26.4	–1.4 (–4.7 to 1.9)
SYNTAX score¶			
At baseline	8.4±5.8	8.9±6.2	–0.5 (–1.1 to 0.1)
After PCI	5.4±4.6	4.6±4.7	0.8 (0.3 to 1.2)
Target-vessel findings‖			
No. of vessels	919	901	
Diameter of stenosis — %	56.7±10.1	56.9±10.1	–0.2 (–1.2 to 0.7)‡
Target-vessel PCI — no./total no. (%)	305/919 (33.2)	526/901 (58.4)	–25.2 (–29.6 to –20.8)‡
Stent data			
Total no. per stented vessels	1.2±0.5	1.2±0.4	0.04 (–0.02 to 0.10)
Total length per stented vessels — mm	32.7±15.5	30.4±13.8	2.3 (0.2 to 4.3)
Diameter per stented vessels — mm	3.11±0.43	3.19±0.43	–0.08 (–0.15 to –0.02)
Procedural outcome**			
Device success	305/305 (100)	525/526 (99.8)	0.2 (–0.4 to 0.8)‡
Lesion success	305/305 (100)	525/526 (99.8)	0.2 (–0.4 to 0.8)‡
Procedural success	305/305 (100)	525/526 (99.8)	0.2 (–0.4 to 0.8)‡
Quantitative flow ratio††	0.84±0.10	0.84±0.10	0.00 (–0.01 to 0.02)
IVUS findings			
Minimal luminal area — mm^2	—	3.4±1.3	—
Plaque burden — %	—	70.1±10.2	—
Minimal stent area after PCI — mm^2	—	7.0±2.2	—

Table 2. (Continued.)

Characteristic	FFR Group	IVUS Group	Difference (95% CI)†
FFR findings			
At baseline	0.83±0.09	—	—
After PCI	0.88±0.06	—	—

* Plus–minus values are means ±SD.
† The between-group difference was measured in the FFR group as compared with the IVUS group. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.
‡ This difference is reported in percentage points.
§ A diseased vessel was defined as the presence of at least 50% stenosis. Nonobstructive coronary disease was defined as the presence of 1 vessel with less than 50% stenosis.
¶ The SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score reflects a comprehensive angiographic assessment of the coronary vasculature. A higher score denotes higher anatomical complexity, and a score of 32 or less typically indicates low or intermediate anatomical complexity of coronary artery disease.
‖ The lesion that was regarded as the target by the operator was included as a trial lesion in 299 of 496 patients with acute coronary syndrome.
** The listed procedural outcomes in the target vessels include device success (residual diameter stenosis of <30% at the in-stent segment without device failure or malfunction), lesion success (in-stent segment diameter stenosis of <30% with normal coronary flow and no more than a type C dissection), and procedural success (lesion success without cardiac death, target-vessel myocardial infarction, or repeat revascularization of the target lesion during the hospital stay).
†† The quantitative flow ratio is a measure of the functional significance of coronary stenosis. The ratio is assessed by calculation of the pressure in the vessel based on two angiographic projections. Data for this measure were available for 860 vessels (446 in the FFR group and 414 in the IVUS group).

the FFR and the IVUS group (50.1% vs. 54.8%). The two groups had similar results regarding the baseline and final SAQ scores in all five domains (Table S6).

DISCUSSION

In this trial, we found that in patients with intermediate coronary stenosis, FFR-guided procedures were noninferior to IVUS-guided procedures with respect to a composite of death from any cause, nonfatal myocardial infarction, or any revascularization at 24 months. The noninferiority of FFR guidance occurred with a lower incidence of target-vessel PCI in the FFR group than in the IVUS group, which led to the implantation of fewer stents and less frequent administration of dual antiplatelet agents. The patient-reported outcomes were similar in the two groups.

As compared with coronary angiography, intravascular imaging and physiological assessment have distinct strengths in guiding PCI. Physiological assessment is more effective in ischemia-directed PCI,[6,7] whereas intracoronary imaging is more effective in the assessment of anatomical characteristics and in the planning of the PCI procedure.[3,19] Because these two methods were originally developed with different objectives,[1-3] clinicians generally use FFR in revascularization decision making and IVUS in the planning of PCI and stent implantation. However, many clinicians substitute one method for the other to a certain extent. It is well known that in addition to the presence of ischemia, the quantity and quality of plaque and the appropriateness of PCI are important prognostic indicators.[6,7,22-26] Therefore, the comparative efficacy of intracoronary imaging- and physiology-guided decision making for revascularization and PCI success needs to be defined.

Our trial was conducted to compare the clinical outcomes of the most commonly used intravascular imaging and physiology tools in PCI guidance. Because of the different criteria for stent implantation, we found that the IVUS-guided strategy was associated with a higher frequency of PCI along with the use of more stents and more frequent administration of dual antiplatelet agents than the FFR-guided strategy, as has been shown in previous studies.[22,27,28] For clinical outcomes, several recent studies have not shown the superiority of ischemia- or FFR-

Table 3. Primary and Secondary Outcomes.*

Outcome	FFR Group (N=838)	IVUS Group (N=844)	Difference (95% CI)†
	no. of patients (%)		*percentage points*
Primary outcome			
Death from any cause, myocardial infarction, or revascularization	67 (8.1)	71 (8.5)	–0.4‡
Secondary outcomes			
Death from any cause, myocardial infarction, or revascularization at 12 mo	38 (4.6)	29 (3.4)	1.1 (–0.8 to 3.0)
Death from cardiac cause, target-vessel myocardial infarction, or target-lesion revascularization	27 (3.3)	25 (3.0)	0.3 (–1.4 to 1.9)
Death			
From any cause	11 (1.3)	19 (2.3)	–0.9 (–2.2 to 0.3)
From cardiac cause	7 (0.8)	11 (1.3)	–0.5 (–1.5 to 0.5)
From noncardiac cause	4 (0.5)	8 (1.0)	–0.5 (–1.3 to 0.3)
Myocardial infarction			
Any	16 (1.9)	14 (1.7)	0.2 (–1.1 to 1.5)
Periprocedural§	10 (1.2)	8 (0.9)	0.2 (–0.7 to 1.2)
Spontaneous	6 (0.7)	6 (0.7)	0.0 (–0.8 to 0.8)
Target vessel	3 (0.4)	2 (0.2)	0.1 (–0.4 to 0.6)
Stent thrombosis	1 (0.1)	1 (0.1)	0.0 (–0.3 to 0.3)
Revascularization			
Any	47 (5.7)	44 (5.3)	0.4 (–1.8 to 2.6)
Ischemia driven	38 (4.6)	33 (4.0)	0.6 (–1.3 to 2.6)
Target vessel	27 (3.3)	20 (2.4)	0.9 (–0.7 to 2.5)
Target lesion	21 (2.5)	15 (1.8)	0.7 (–0.7 to 2.1)
Nontarget vessel	23 (2.8)	28 (3.4)	–0.6 (–2.3 to 1.1)
Nontarget lesion	31 (3.8)	33 (4.0)	–0.2 (–2.1 to 1.6)
Stroke	6 (0.7)	10 (1.2)	–0.5 (–1.4 to 0.5)

* Primary and secondary outcomes were evaluated in the intention-to-treat population at 24 months after randomization, unless otherwise indicated. The listed percentages were estimated with the use of the Kaplan–Meier method, so values may not calculate mathematically. Detailed definitions of the outcomes are provided in the Supplementary Appendix.

† The between-group difference was measured in the FFR group as compared with the IVUS group. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.

‡ For the between-group difference in the primary outcome, the upper boundary of the one-sided 95% confidence interval was 1.8 percentage points; the upper boundary of the one-sided 97.5% confidence interval was 2.2 percentage points (P=0.01 for noninferiority).

§ Periprocedural myocardial infarction was defined as follows: among patients with stable angina, an increase in the creatine kinase MB isoform (CK-MB) of more than 3 times the upper limit of the normal range or an increase in the troponin level of more than 5 times the 99th percentile of diagnostic value for the specific institution and the presence of new pathological Q waves or new persistent nonrate-related left bundle-branch block, symptoms of ischemia with electrocardiographic (ECG) changes indicative of new ischemia, or angiographic documentation of new coronary-artery occlusion or dissection; and among patients with acute coronary syndrome, the occurrence of a peak CK-MB or troponin level or a new increase in the CK-MB level of more than 3 times the upper limit of the normal range or an increase in the troponin level of more than 5 times the 99th percentile and the presence of new pathological Q waves or new persistent nonrate-related left bundle-branch block, symptoms of ischemia with ECG changes indicative of new ischemia, or angiographic documentation of new coronary-artery occlusion or dissection.

guided strategies over an angiography-guided strategy or medical treatment,[28-31] and the presence of high-risk plaque has been associated with a poor prognosis in patients receiving medical treatment, even in those with an FFR of more than 0.80.[24-26] In addition, IVUS guidance has

been shown to reduce hard end points (e.g., death or myocardial infarction) in comparison with angiographic guidance in patients undergoing PCI.[5,19,23] In a previous single-center, randomized study that compared optical coherence tomography (OCT) and FFR for the treatment of intermediate lesions, investigators found that OCT guidance resulted in fewer clinical events, whereas FFR guidance resulted in the use of fewer medical resources.[22] In a recent network meta-analysis, IVUS performed better than angiography with respect to a composite outcome of death, myocardial infarction, or target-vessel revascularization, whereas FFR showed only a trend for a reduction in major adverse clinical events.[32] In our multicenter and randomized trial, the FFR-guided strategy was noninferior to the IVUS-guided strategy with respect to clinical outcomes. Regarding the angina symptoms (SAQ scores), the two groups had similar results at baseline and during follow-up. These findings may be explained by the fact that the severity of coronary stenosis does not always correlate with clinical symptoms and the influence of guideline-based medical therapy.

Successful PCI was achieved in 52.9% of the patients with stent implantation in our trial. Previous trials have also shown corresponding frequencies of approximately 50% with either FFR guidance or IVUS guidance, according to differing definitions of successful PCI.[4,33,34] These results show that the prespecified goals of PCI may not always be achievable with the use of either FFR or IVUS guidance. Additional studies are needed to define the specific imaging and physiologic criteria for PCI success, the relative importance of disease burden in nonstented segments, and profiles for both patients and lesions that are associated with greater clinical benefit with adjunctive procedures.

The results of our trial should be interpreted in light of certain limitations. First, our trial population included low-risk patients with a mean SYNTAX score of less than 10, indicating low anatomical complexity of the coronary lesions. Therefore, the results may not be applicable to higher-risk patients. Second, the operating physicians were necessarily aware of the trial-group assignments. This factor may have influenced the frequency of revascularization during follow-up, because the operators knew the strengths and weaknesses of FFR and IVUS. Third, the frequency of revascularization can differ according to the criteria for PCI and baseline characteristics. Fourth, FFR and IVUS were representative tools for guidance regarding the evaluation of physiology and intracoronary imaging in our trial. Several other techniques can be used in the cardiac catheterization laboratory, including the measurement of nonhyperemic pressure ratios, angiography-derived FFR, OCT, and near-infrared spectroscopy–IVUS. Additional studies are needed to determine the comparative roles of these methods in PCI guidance. Fifth, the criteria for PCI in our trial did not incorporate lesion-level hemodynamic significance[35,36] and features of plaque vulnerability. Sixth, patients of non-Asian races were not included in our trial (Table S7).

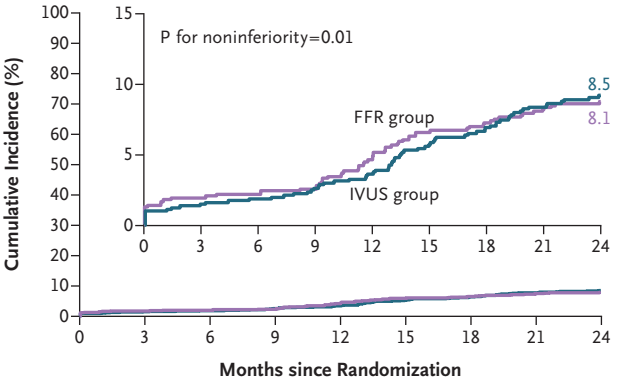

Figure 1. Cumulative Incidence of the Primary Outcome at 24 Months.

The primary outcome was a composite of death from any cause, myocardial infarction, or any revascularization at 24 months after randomization among patients who were undergoing a procedure guided by fractional flow reserve (FFR) or intravascular ultrasonography (IVUS). The inset shows the same data on an enlarged y axis.

Among patients with intermediate coronary stenosis, FFR guidance was noninferior to IVUS guidance with respect to a composite of death, myocardial infarction, or any revascularization at 24 months after the index procedure. FFR guidance was associated with a lower frequency of stent implantation, and patient-reported outcomes were similar with the two strategies.

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APPENDIX

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