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Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

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ABSTRACT

BACKGROUND

The preferred initial treatment for patients with stable coronary artery disease is the best available medical therapy. We hypothesized that in patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), percutaneous coronary intervention (PCI) plus the best available medical therapy would be superior to the best available medical therapy alone.

METHODS

In patients with stable coronary artery disease for whom PCI was being considered, we assessed all stenoses by measuring FFR. Patients in whom at least one stenosis was functionally significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Patients in whom all stenoses had an FFR of more than 0.80 were entered into a registry and received the best available medical therapy. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

RESULTS

Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical-therapy group (hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% vs. 11.1%; hazard ratio, 0.13; 95% CI, 0.06 to 0.30; P<0.001); in particular, in the PCI group, fewer urgent revascularizations were triggered by a myocardial infarction or evidence of ischemia on electrocardiography (hazard ratio, 0.13; 95% CI, 0.04 to 0.43; P<0.001). Among patients in the registry, 3.0% had a primary end-point event.

CONCLUSIONS

In patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization. In patients without ischemia, the outcome appeared to be favorable with the best available medical therapy alone. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT01132495.)

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*The investigators in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Percutaneous coronary intervention (PCI) improves the outcome in patients with acute coronary syndromes.[1] In contrast, for the treatment of patients with stable coronary artery disease, controversy persists regarding the extent of the benefit from PCI, as compared with the best available medical therapy, as an initial management strategy.[2-5] The potential benefit of revascularization depends on the presence and extent of myocardial ischemia.[6-8] Performing PCI on nonischemic stenoses is not beneficial[9] and is probably harmful.[10] Thus, careful selection of ischemia-inducing stenoses is essential for deriving the greatest benefit from revascularization in patients with stable coronary artery disease.

Fractional flow reserve (FFR) is a pressure-wire–based index that is used during coronary angiography to assess the potential of a coronary stenosis to induce myocardial ischemia.[11-14] The usefulness of FFR-guided PCI as compared with PCI guided by angiography alone is supported by robust clinical outcome data.[9,10,14-17]

The aim of this trial was to determine whether FFR-guided PCI with drug-eluting stents plus the best available medical therapy is superior to the best available medical therapy alone in reducing the rate of death, myocardial infarction, or unplanned hospitalization leading to urgent revascularization among patients with stable coronary artery disease.

Methods

Study Design and Oversight

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) study is a randomized "all comers" trial (i.e., involving the consecutive enrollment of all eligible patients with stable coronary artery disease). The trial was conducted at 28 sites in Europe and North America and was approved by the institutional review board at each participating center. The members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study without involvement of the sponsor, St. Jude Medical. The sponsor was involved in the collection and source verification of the data but not in the conduct of the trial or in the decision to terminate it. An independent data and safety monitoring board (see the Supplementary Appendix) oversaw the trial and met twice a year or more frequently, as necessary for the oversight of the trial. No formal stopping rules were specified. The academic members of the steering committee had full access to all the data in the study, vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol, wrote the manuscript, and had final responsibility for the decision to submit it for publication. The research protocol is available at NEJM.org.

Patients

Patients in stable condition who were appropriate candidates for PCI and who had angiographically assessed one-, two-, or three-vessel coronary artery disease suitable for PCI were included in the trial. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. The investigator first indicated which stenoses were thought to require stenting on the basis of the clinical and angiographic data. FFR was then measured with a coronary guidewire (PressureWire Certus or PressureWire Aeris, St. Jude Medical) during adenosine-induced hyperemia to assess the hemodynamic severity of each indicated stenosis. Patients who had at least one stenosis in a major coronary artery with an FFR of 0.80 or less were randomly assigned, by means of an interactive voice-response system, to FFR-guided PCI plus the best available medical therapy (hereinafter called the PCI group) or to the best available medical therapy alone (hereinafter called the medical-therapy group). The randomization schedule was computer-generated; randomization was stratified according to site and performed in blocks, with block sizes varied randomly. Patients with an FFR of more than 0.80 in all vessels with indicated stenoses were enrolled in a registry and received the best available medical therapy. A random sample of 50% of the registry patients underwent the same follow-up as the patients in the randomized trial. The treatment assignments were known to the patients. All patients provided written informed consent.

Treatment

All patients were prescribed aspirin at a dose of 80 to 325 mg daily, metoprolol at a dose of 50 to 200 mg daily (or any other beta-1–selective blocker, alone or in combination with a calcium-channel blocker or a long-acting nitrate), lisinopril (≥5 mg daily, or another angiotensin-converting–enzyme [ACE] inhibitor or an angiotensin II–receptor

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blocker if the patient had unacceptable side effects with the ACE inhibitor), and atorvastatin (20 to 80 mg daily, or another statin of similar potency alone or in combination with ezetimibe, to reduce the low-density-lipoprotein [LDL] level to less than 70 mg per deciliter [1.8 mmol per liter]).

Patients who were randomly assigned to PCI received a loading dose of clopidogrel (600 mg) and aspirin immediately before the procedure if they were not already taking these medications. All stenoses with an FFR of 0.80 or less were treated with second-generation drug-eluting stents.[18-20] After PCI, all patients received clopidogrel at a dose of 75 mg per day for at least 12 months in addition to the best available medical therapy. All patients were given a medication tracking form for recording weekly medication use and doses. Patients who smoked were counseled regarding smoking cessation. Patients with diabetes were referred to a diabetes specialist to receive the best available treatment for that disease.

FOLLOW-UP

Electrocardiography (ECG) was performed with the patient at rest, and the creatine kinase level and the MB fraction of creatine kinase were measured in all patients before angiography was performed and between 12 and 24 hours after enrollment. Follow-up visits were scheduled at 1 and 6 months and at 1, 2, 3, 4, and 5 years. At baseline and all follow-up visits, we obtained information regarding the presence or absence (and, if present, the severity) of angina, the patient's work status, and the number and doses of cardiac medications and assessed the patient's quality of life with the use of the European Quality of Life–5 Dimensions [EQ-5D] instrument.[21] In addition, we performed resting ECG, measured the levels of total cholesterol and cholesterol fractions, and assessed the patient's utilization of medical resources.

END POINTS

The prespecified primary end point was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization during the first 2 years. Secondary end points included individual components of the primary end point, cardiac death, nonurgent revascularization, and angina class. All outcomes were adjudicated by an independent clinical events committee (see the Supplementary Appendix) whose members were unaware of the treatment assignments. For each revascularization procedure, a detailed description was included. Revascularization was considered to be urgent when a patient was admitted to the hospital with persistent or increasing chest pain (with or without ST-segment or T-wave changes or elevated biomarker levels) and the revascularization procedure was performed during the same hospitalization.

STATISTICAL ANALYSIS

The trial was powered to determine whether PCI with the best available medical therapy was superior to the best available medical therapy alone with respect to the primary end point at 24 months. On the basis of findings from previous studies and using binomial proportions, we estimated that the cumulative incidence of the primary end point at 24 months would be 12.6% in the PCI group[18-20] and 18.0% in the medical-therapy group,[3] corresponding to a relative risk reduction with PCI of 30%, and that with 816 patients in each group, the study would have more than 84% power to detect that relative risk reduction, at a two-sided type I error rate of 0.05. Continuous variables are presented as means and standard deviations, and categorical data are presented as numbers and percentages. All patients were included in the analysis according to the groups to which they were originally assigned (intention-to-treat analysis). We used the Mantel–Cox method to calculate hazard ratios and 95% confidence intervals for the between-group comparisons of clinical outcomes and the log-rank test to calculate corresponding P values. We constructed Kaplan–Meier curves for the primary end point and its components.

In an exploratory analysis, we also calculated the hazard ratio for urgent revascularization triggered by a myocardial infarction or by unstable angina with evidence of ischemia on ECG. We used a chi-square test to assess the interaction between treatment effect and these characteristics. Landmark analyses were performed according to a landmark point at 7 days, with the hazard ratio calculated separately for events that occurred up to 7 days after randomization and events that occurred between 8 days and the end of the follow-up period. We then performed a test for the interaction between treatment and time (first 7 days vs. subsequent period). In all time-to-event analyses (i.e., overall and landmark), for each type of event, data for a patient

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Table 1. Baseline Clinical, Angiographic, and Fractional Flow Reserve (FFR) Characteristics.*

Variable	Randomly Assigned Groups		Registry Cohort	P Value†
	PCI plus Medical Therapy	Medical Therapy Alone		
Patient characteristics				
Total no. of patients	447	441	166	
Age — yr	63.52±9.35	63.86±9.62	63.58±9.75	0.90
Male sex — no. (%)	356 (79.6)	338 (76.6)	113 (68.1)	0.005
Body-mass index‡	28.29±4.27	28.44±4.55	27.83±3.94	0.14
Family history of coronary artery disease — no. (%)	216 (48.3)	207 (46.9)	76 (45.8)	0.65
Current smoking — no. (%)	89 (19.9)	90 (20.4)	35 (21.1)	0.79
Hypertension — no. (%)	347 (77.6)	343 (77.8)	136 (81.9)	0.23
Hypercholesterolemia — no. (%)	330 (73.8)	348 (78.9)	118 (71.1)	0.15
Diabetes mellitus — no. (%)				
Any	123 (27.5)	117 (26.5)	42 (25.3)	0.65
Insulin-dependent	39 (8.7)	39 (8.8)	10 (6.0)	0.24
Renal insufficiency — no. (%)§	8 (1.8)	12 (2.7)	7 (4.2)	0.14
Peripheral vascular disease — no. (%)	43 (9.6)	47 (10.7)	8 (4.8)	0.03
History of stroke or transient ischemic attack — no. (%)	33 (7.4)	28 (6.3)	10 (6.0)	0.69
History of myocardial infarction — no./total no. (%)	164/442 (37.1)	165/436 (37.8)	60/164 (36.6)	0.83
History of PCI in target vessel — no. (%)	80 (17.9)	76 (17.2)	34 (20.5)	0.37
Angina — no./total no (%)¶				0.64
Asymptomatic	53/447 (11.9)	46/440 (10.5)	17/166 (10.2)	
CCS class I	82/447 (18.3)	98/440 (22.3)	42/166 (25.3)	
CCS class II	204/447 (45.6)	197/440 (44.8)	74/166 (44.6)	
CCS class III	80/447 (17.9)	65/440 (14.8)	23/166 (13.9)	
CCS class IV, stabilized	28/447 (6.3)	34/440 (7.7)	10/166 (6.0)	
Silent ischemia — no. (%)	73 (16.3)	73 (16.6)	27 (16.3)	0.96
Left ventricular ejection fraction <50% — no./total no. (%)	83/423 (19.6)	56/410 (13.7)	27/150 (18.0)	0.69
Angiographic findings				
Angiographically significant lesions — no. per patient	1.87±1.05	1.73±0.94	1.32±0.59	<0.001
Vessels with at least one significant lesion — no. of patients (%)				<0.001
1	251 (56.2)	261 (59.2)	136 (81.9)	
2	156 (34.9)	146 (33.1)	26 (15.7)	
3	40 (8.9)	34 (7.7)	4 (2.4)	
At least one significant lesion in proximal or middle left anterior descending artery — no. (%)	291 (65.1)	276 (62.6)	74 (44.6)	<0.001
FFR findings				
Functionally significant lesions — no. per patient	1.52±0.78	1.42±0.73	0.03±0.17	<0.001
Vessels with at least one significant lesion — no. of patients (%)				<0.001
1	331 (74.0)	343 (77.8)	5 (3.0)‖	
2	102 (22.8)	85 (19.3)	0	
3	14 (3.1)	13 (2.9)	0	
At least one significant lesion in proximal or middle left anterior descending artery — no. (%)	279 (62.4)	263 (59.6)	1 (0.6)	<0.001

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Table 1. (Continued.)

Variable	Randomly Assigned Groups		Registry Cohort	P Value†
	PCI plus Medical Therapy	Medical Therapy Alone		
Lesion characteristics				
Total no. of lesions	890	815	241	
Angiographic findings				
Lesions with stenosis of >50% of diameter — no. (%)	837 (94.0)	764 (93.7)	219 (90.9)	0.13
Stenosis — no. (%)				<0.001
<50% of diameter	53 (6.0)	51 (6.3)	22 (9.1)	
50–69% of diameter	317 (35.6)	331 (40.6)	176 (73.0)	
70–90% of diameter	383 (43.0)	331 (40.6)	38 (15.8)	
>90% of diameter	101 (11.3)	80 (9.8)	0	
Total occlusion	36 (4.0)	22 (2.7)	5 (2.1)	
FFR findings				
Lesions with FFR ≤0.80 — no. (%)	679 (76.3)	625 (76.7)	5 (2.1)‖	<0.001
Mean FFR in lesions with FFR ≤0.80	0.68±0.10	0.68±0.15	0.50±0.00	0.01

* Plus–minus values are means ±SD. There were no significant differences between the two randomly assigned groups in any of the baseline characteristics, with the exception of left ventricular ejection fraction of less than 50% (P=0.04). PCI denotes percutaneous coronary intervention.
† The P values are for the combined groups that underwent randomization (the group assigned to PCI plus the best available medical therapy and the group assigned to the best available medical therapy alone) as compared with the group of patients who did not undergo randomization (patients in whom all stenoses had an FFR of more than 0.80) and were enrolled in a registry. In patient-level analyses, the P values were calculated with the use of a chi-square test except when cell numbers were small (<15 patients), in which case Fisher's exact test was used. In lesion-level analyses, mixed maximum-likelihood logistic-regression models were used for between-group comparisons of dichotomous variables, and mixed maximum-likelihood linear-regression models were used for comparisons of continuous variables, to account for the correlation of multiple lesions within patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Renal insufficiency was defined as a creatinine level of more than 2.0 mg per deciliter (176.8 μmol per liter).
¶ Angina was classified according to the Canadian Cardiovascular Society (CCS) functional classification, in which classes range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.
‖ Five totally occluded arteries supplied infarcted areas and were therefore not considered for revascularization by means of PCI.

were censored at the time of the first event that occurred in that patient. All analyses were performed by an independent statistician from an academic clinical trials unit (CTU Bern, University of Bern, Switzerland) with the use of Stata software, version 11.2.

RESULTS

STUDY TERMINATION AND PATIENT FOLLOW-UP

At the recommendation of the independent data and safety monitoring board, patient recruitment was stopped on January 15, 2012, owing to a highly significant difference in the incidence rates of the primary end point between the PCI and medical-therapy groups. Between May 15, 2010, and January 15, 2012, a total of 1220 patients were enrolled (Fig. S1 in the Supplementary Appendix). A total of 888 patients had at least one stenosis with an FFR of 0.80 or less in a large epicardial artery: 447 patients were randomly assigned to FFR-guided PCI plus the best available medical therapy, and 441 patients to the best available medical therapy alone. In 332 patients with angiographically significant stenoses, none of the stenoses had an FFR of 0.80 or less; these patients were enrolled in the registry and received the best available medical therapy alone. The mean (±SD) duration of follow-up was 213±128 days among patients assigned to PCI plus the best medical available therapy, 214±127 days among patients assigned to the best available medical therapy alone, and 206±119 days among patients enrolled in the registry.

BASELINE CHARACTERISTICS

Table 1 shows the baseline clinical, angiographic, and FFR characteristics of the patients who under-

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went randomization, as compared with the patients who were enrolled in the registry. There were higher percentages of men, patients with peripheral vascular disease, and patients with multivessel disease in the groups that underwent randomization than in the registry cohort. More than 25% of the patients had diabetes, and 68% of the patients had angina of class II to IV on the Canadian Cardiovascular Society (CCS) scale (which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina). There were more lesions per patient and more lesions with stenosis of more than 70% of the diameter of the artery among patients who underwent randomization than among patients in the registry. A total of 1601 stenoses in the patients who underwent randomization were considered for PCI on the basis of angiographic findings, whereas 1304 were considered for PCI on the basis of an FFR of 0.80 or less. Among the latter, the FFR ranged from 0.19 to 0.80. Table S1 in the Supplementary Appendix shows the medications the patients were taking at baseline and during the follow-up period.

PRIMARY END POINT

By January 15, 2012, a total of 75 patients in the randomized groups had had at least one primary end-point event. The percentage of patients who had a primary end-point event was lower in the PCI group than in the medical-therapy group (4.3% vs. 12.7%; hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001) (Fig. 1A and Table 2). In the registry cohort, 5 patients had at least one primary end-point event (3.0%). There was little difference in the incidence of a primary end-point event between patients in the PCI group and patients in the registry (hazard ratio for the PCI group, 1.29; 95% CI, 0.49 to 3.39; P=0.61), but there was a large difference between patients in the medical-therapy group and patients in the registry (hazard ratio for the medical-therapy group, 4.32; 95% CI, 1.75 to 10.66; P=0.001) (Table S2 in the Supplementary Appendix).

SECONDARY END POINTS

The Kaplan–Meier curves for the individual components of the primary end point are shown in Figures 1B, 1C, and 1D. Neither the rate of death from any cause nor the rate of myocardial infarction differed significantly between the PCI group and the medical-therapy group, but the rate of urgent revascularization did differ significantly between the groups (hazard ratio with PCI, 0.13; 95% CI, 0.06 to 0.30; P<0.001). Among the 56 patients who underwent urgent revascularization, the procedure was triggered by a myocardial infarction in 12 patients (21.4%), by unstable angina accompanied by evidence of ischemia on ECG in 15 patients (26.8%), and by unstable angina diagnosed on the basis of clinical features in 29 patients (51.8%). In an exploratory analysis, 4 patients in the PCI group (0.9%) and 23 patients in the medical-therapy group (5.2%) underwent an urgent revascularization that was triggered by a myocardial infarction or by unstable angina with evidence of ischemia on ECG (hazard ratio with PCI, 0.13; 95% CI, 0.04 to 0.43; P<0.001). As compared with patients in the medical-therapy group, patients in the PCI group were significantly less likely to undergo any revascularization (hazard ratio with PCI, 0.14; 95% CI, 0.08 to 0.26) or nonurgent revascularization (hazard ratio, 0.17; 95% CI, 0.08 to 0.39) (Table 2, and Fig. S2 in the Supplementary Appendix). Among patients in the registry, the rates of death from any cause, myocardial infarction, urgent revascularization, and nonurgent revascularization were all low (Fig. 1, and Table S2 in the Supplementary Appendix).

Figure 2 shows the results from landmark analyses of the primary end point and its components. PCI plus the best available medical therapy was shown to be consistently more beneficial after the landmark point of 7 days after randomization than before; there were significant interactions between time and treatment with respect to the primary end point, the individual components of death and myocardial infarction, and the composite of death or myocardial infarction, as well as a trend toward an interaction with respect to urgent revascularization. Corresponding Kaplan–Meier curves are presented in Figure S3 in the Supplementary Appendix. Stratified analyses according to patient characteristics are shown in Figure S4 in the Supplementary Appendix. Effects were similar across most subgroups; however, the benefit of PCI appeared to be more pronounced among patients who had lesions with an FFR of less than 0.65 than among patients who had only lesions with larger FFR values (P=0.01 for the interaction). The reduction from baseline in the percentage of patients with angina of CCS grade II to IV was greater in the PCI group than in the medical-therapy group and the registry cohort (Fig. 3).

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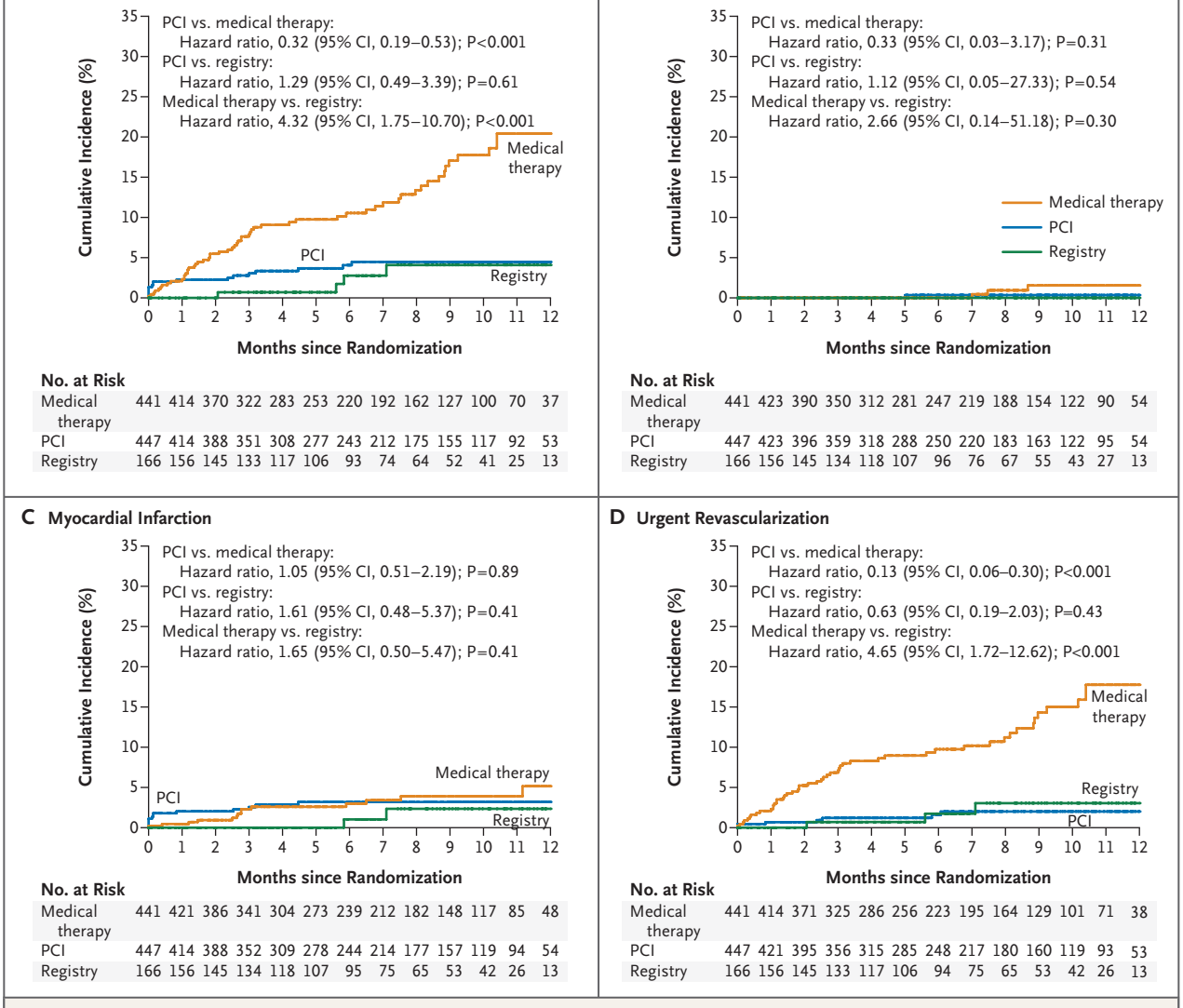

Figure 1. Cumulative Incidence of the Primary End Point and Its Components.

Kaplan–Meier curves are shown for the cumulative incidence of the primary end point of death, myocardial infarction, or urgent revascularization (Panel A) and the individual components of the primary end point (Panels B, C, and D) in the group that was randomly assigned to PCI and the best available medical therapy (PCI), the group that was randomly assigned to the best available medical therapy alone (medical therapy), and the group that did not undergo randomization and was enrolled in a registry (registry). After 12 months, a total of two primary end-point events occurred in the PCI group, none in the medical-therapy group, and one in the registry cohort. No deaths occurred after 12 months in any of the groups. Two patients in the PCI group, none in the medical-therapy group, and one in the registry cohort had a myocardial infarction after 12 months. One patient in the registry cohort, and none in the other two groups, had an urgent revascularization performed after 12 months.

DISCUSSION

In the FAME 2 trial, we compared the treatment strategy of PCI, performed according to current quality standards, plus the best available medical therapy with the best available medical therapy alone in patients with stable coronary artery disease and hemodynamically significant stenoses. FFR-guided PCI with drug-eluting stents plus the best available medical therapy, as compared with the best available medical therapy alone, resulted in significantly improved clinical outcomes. The difference between the two strategies was driven by an increase by a factor of 8 in the need for

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Table 2. Clinical Events.

Event	Randomly Assigned Groups				Registry Cohort (N=166)
	PCI plus Medical Therapy (N=447)	Medical Therapy Alone (N=441)	Hazard Ratio with PCI (95% CI)	P Value	
	no. (%)				*no. (%)*
Primary end point	19 (4.3)	56 (12.7)	0.32 (0.19–0.53)	<0.001	5 (3.0)
Components of primary end point					
Death from any cause	1 (0.2)	3 (0.7)	0.33 (0.03–3.17)	0.31	0
Myocardial infarction	15 (3.4)	14 (3.2)	1.05 (0.51–2.19)	0.89	3 (1.8)
Urgent revascularization	7 (1.6)	49 (11.1)	0.13 (0.06–0.30)	<0.001	4 (2.4)
Death or myocardial infarction	15 (3.4)	17 (3.9)	0.61 (0.28–1.35)	0.22	3 (1.8)
Cardiac death	1 (0.2)	1 (0.2)	0.96 (0.06–15.17)	0.98	0
Revascularization					
Any	14 (3.1)	86 (19.5)	0.14 (0.08–0.26)	<0.001	6 (3.6)
Nonurgent revascularization	7 (1.6)	38 (8.6)	0.17 (0.08–0.39)	<0.001	2 (1.2)
Stroke	1 (0.2)	2 (0.5)	0.49 (0.04–5.50)	0.56	1 (0.6)
Definite or probable stent thrombosis	5 (1.1)	1 (0.2)	4.98 (0.59–42.25)	0.10	1 (0.6)

urgent revascularization in the medical-therapy group. In the case of half of these urgent revascularizations, the need for the procedure was triggered by an increase in biomarker levels, ischemic changes on ECG, or both. When we performed a landmark analysis, we found that the strategy of PCI plus the best available medical therapy was more beneficial 8 days or more after randomization than 7 days or less after randomization, with interactions between time and treatment with respect to the primary end point, as well as with respect to death and myocardial infarction, suggesting that the benefit of PCI plus the best available medical therapy might become more pronounced with an increasing duration of follow-up. The percentage of patients with angina of CCS class II to IV was markedly lower among patients in the PCI group than among patients in the medical-therapy group. Moreover, in 25% of the patients in whom PCI was considered, none of the stenoses that were visible on an angiogram were hemodynamically significant as assessed by means of the measurement of FFR. Among these patients, the strategy of providing the best available medical therapy alone was associated with a very low event rate.

Several factors may explain the differences between results in the present study and those in previous trials involving patients with stable coronary disease.[3,4] First, in previous trials in which various revascularization methods were compared with the best available medical therapy, patient enrollment was based primarily on angiographic findings, with or without noninvasive documentation of ischemia. It is likely that a sizable proportion of the patients had only limited ischemia. Even in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which noninvasive testing was performed in 85% of the patients,[3] less than one third of the patients had more than 10% ischemia on myocardial perfusion imaging.[8] In daily clinical practice, less than half of patients undergo noninvasive stress testing before elective PCI.[22] In the current trial, all the patients who underwent randomization had at least one functionally significant stenosis. Moreover, a mean FFR value of 0.68 in large epicardial arteries suggests that there were large areas of myocardium that were at risk for ischemia. The low-risk patients with nonischemic FFR values were not randomly assigned to a study group but were followed in a registry — a study design that was unlike that of previous trials.

Second, among patients in the PCI group who had several stenoses, PCI was performed only in

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End Point	PCI	Medical Therapy	Relative Risk (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Primary end point					<0.001
≤7 days	9/447 (2.0)	4/441 (0.9)	2.24 (0.69–7.31)	0.17	
8 days to maximum follow-up	10/427 (2.3)	52/428 (12.1)	0.17 (0.09–0.35)	<0.001	
Death or myocardial infarction					0.003
≤7 days	8/447 (1.8)	1/441 (0.2)	7.99 (0.99–64.57)	0.04	
8 days to maximum follow-up	7/428 (1.6)	16/431 (3.7)	0.42 (0.17–1.04)	0.053	
Death					—
≤7 days	0/447	0/441			
8 days to maximum follow-up	1/436 (0.2)	3/432 (0.7)	0.33 (0.03–3.17)	0.37	
Myocardial infarction					0.007
≤7 days	8/447 (1.8)	1/441 (0.2)	7.99 (0.99–64.57)	0.04	
8 days to maximum follow-up	7/428 (1.6)	13/431 (3.0)	0.52 (0.21–1.32)	0.16	
Urgent revascularization					0.09
≤7 days	2/447 (0.4)	4/441 (0.9)	0.49 (0.09–2.70)	0.45	
8 days to maximum follow-up	5/434 (1.2)	45/428 (10.5)	0.10 (0.04–0.26)	<0.001	

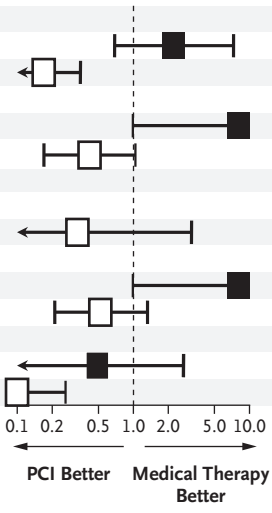

Figure 2. Landmark Analysis of the Primary End Point and Its Components.

The relative risk of the primary end point of death, myocardial infarction, or urgent revascularization and of components of the primary end point are shown, according to the time from randomization (7 days or less vs. 8 days or more). The solid boxes represent relative-risk estimates for 7 days or less after randomization, and the open boxes represent relative-risk estimates for 8 days to the maximum follow-up. Arrows indicate that the lower end of the confidence interval is less than 0.1. (The lower end of the confidence interval for urgent revascularization at 8 days to maximum follow-up, which could not be shown on the plot, was 0.04.) P values were calculated with the use of a log-rank test, except for the following, which were calculated with the use of Fisher's exact test: death or myocardial infarction at 7 days or less; death at 8 days to maximum follow-up; myocardial infarction at 7 days or less; and urgent revascularization at 7 days or less. P values for the interaction between time and treatment with respect to the end points were calculated with the use of the Mantel–Cox method. A total of 10 patients randomly assigned to PCI plus the best available medical therapy and 8 patients assigned to the best available medical therapy alone underwent randomization during the week before January 15, 2012, and their data were censored for the analysis of 8 days to maximum follow-up. In addition, 1 patient in each of those groups withdrew consent during the first week of follow-up, and their data were also censored in the analysis of the subsequent period.

lesions with an FFR of 0.80 or less. This FFR-guided approach is associated with a better clinical outcome than that with PCI performed on the basis of angiographic results alone.[10] These features probably explain the similarity of event rates between patients who were treated with PCI plus the best available medical therapy and patients with equivalent baseline characteristics but no functionally significant lesions who were enrolled in the registry and treated with the best available medical therapy alone.

Third, we used drug-eluting stents in patients who underwent PCI, a strategy that resulted in a low number of repeat revascularizations.[18-20] The use of anti-ischemic medication was similar to that reported in the COURAGE trial[23] and was most likely much higher than that in routine clinical practice.[24] Nevertheless, receipt of the best available medical therapy did not preclude a significantly higher number of unplanned hospitalizations with urgent revascularization among patients randomly assigned to the best available medical therapy alone than among those assigned to PCI plus the best available medical therapy.

Finally, the primary end point of the present study included not only death and myocardial infarction but also urgent revascularization, a component that was not included in the primary end point of previous trials. The definition of urgent revascularization was stringent in order to distinguish it from nonurgent — albeit clinically justified — revascularizations. Among patients who underwent urgent revascularization, the clinical presentation met the criteria of an acute coronary syndrome as assessed by an independent clinical events committee whose members were unaware of the treatment assignments. In half the patients who underwent an urgent revascularization, the unstable nature of the symp-

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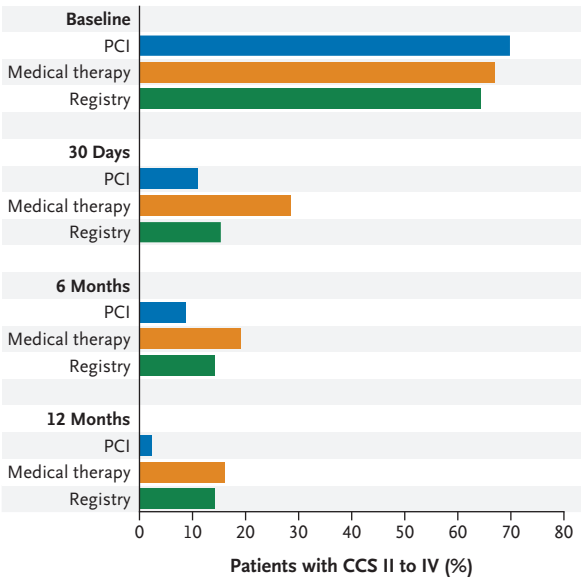

	Randomly Assigned Groups			Randomly Assigned Groups vs. Registry	
	No. of events/ total no.	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Baseline			0.42		
PCI	312/447	1.04 (0.95–1.13)		1.08 (0.95–1.23)	0.22
Medical therapy	296/440	Reference		1.04 (0.92–1.19)	0.52
Registry	107/166	—		Reference	
			<0.001		
30 Days					
PCI	46/413	0.39 (0.28–0.53)		0.72 (0.45–1.15)	0.17
Medical therapy	119/412	Reference		1.87 (1.25–2.81)	0.002
Registry	23/149	—		Reference	
6 Months			0.002		
PCI	21/238	0.46 (0.28–0.74)		0.62 (0.33–1.19)	0.16
Medical therapy	46/239	Reference		1.36 (0.77–2.40)	0.29
Registry	13/92	—		Reference	
12 Months			0.07		
PCI	1/41	0.15 (0.02–1.19)		0.17 (0.01–2.42)	0.19
Medical therapy	6/37	Reference		1.14 (0.16–8.03)	0.90
Registry	1/7	—		Reference	

Figure 3. Patients with Angina Class II to IV and Corresponding Relative Risks.

The percentage of patients with angina of class II to IV on the Canadian Cardiovascular Society (CCS) scale (which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina) and the corresponding relative risks are shown at various time points for the group that was randomly assigned to PCI and the best available medical therapy (PCI), the group that was randomly assigned to the best available medical therapy alone (medical therapy), and the group that did not undergo randomization and was enrolled in a registry (registry). A total of 414 patients in the PCI group, 417 in the medical-therapy group, and 151 in the registry cohort were eligible for follow-up at 30 days; the corresponding numbers at 6 months were 238, 241, and 92, and the corresponding numbers at 1 year were 41, 38, and 7.

toms was evidenced by ST-segment depression, biomarker elevation, or both. The occurrence of an acute coronary syndrome necessitates hospitalization and is associated with an unfavorable prognosis, and it should therefore be considered to be a treatment failure. More important, revascularization has been shown to improve the rate of survival and decrease the risk of myocardial infarction among high-risk patients with an acute coronary syndrome.[25-27]

The trial has several limitations. First, because of the premature termination of enrollment, there was an unusually short follow-up period — too short to see restenosis emerge as a complication of PCI. Differences in the rates of death and myocardial infarction between the strategies of PCI and medical therapy alone that were seen in one recent registry study[28] could not be confirmed. However, the difference in the primary outcome between the two treatment groups was large and was steadily increasing over time; therefore, the data and safety monitoring board believed that exposing more patients with functionally significant stenoses to the risk of urgent revascularization was inappropriate. Second, although randomization was concealed,[29] it is possible that the awareness of the presence of a stenosis influenced decisions regarding revascularization. Third, even though the adherence to medications was high, the best available medical therapy did not include interventions by nurse case managers that were aimed at lifestyle changes and risk-factor reduction, interventions that were included as part of the best available medical therapy in the COURAGE trial.[23] Fourth, the strategic nature of the trial meant that we followed contemporary guidelines,[30] which require dual antiplatelet treatment only for patients who undergo stenting. It is unlikely that this difference in drug regimen between the two groups could explain the magnitude of the observed difference with respect to the primary end point.

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In conclusion, among patients with stable coronary artery disease and at least one stenosis with an FFR of 0.80 or less, FFR-guided PCI with drug-eluting stents plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the rate of urgent revascularization. Among patients with stenoses that were not functionally significant, the best available medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenoses.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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