ORIGINAL ARTICLE

Five-Year Outcomes with PCI Guided by Fractional Flow Reserve

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ABSTRACT

BACKGROUND

We hypothesized that fractional flow reserve (FFR)–guided percutaneous coronary intervention (PCI) would be superior to medical therapy as initial treatment in patients with stable coronary artery disease.

METHODS

Among 1220 patients with angiographically significant stenoses, those in whom at least one stenosis was hemodynamically significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus medical therapy or to medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy and were entered into a registry. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

RESULTS

A total of 888 patients underwent randomization (447 patients in the PCI group and 441 in the medical-therapy group). At 5 years, the rate of the primary end point was lower in the PCI group than in the medical-therapy group (13.9% vs. 27.0%; hazard ratio, 0.46; 95% confidence interval [CI], 0.34 to 0.63; P<0.001). The difference was driven by urgent revascularizations, which occurred in 6.3% of the patients in the PCI group as compared with 21.1% of those in the medical-therapy group (hazard ratio, 0.27; 95% CI, 0.18 to 0.41). There were no significant differences between the PCI group and the medical-therapy group in the rates of death (5.1% and 5.2%, respectively; hazard ratio, 0.98; 95% CI, 0.55 to 1.75) or myocardial infarction (8.1% and 12.0%; hazard ratio, 0.66; 95% CI, 0.43 to 1.00). There was no significant difference in the rate of the primary end point between the PCI group and the registry cohort (13.9% and 15.7%, respectively; hazard ratio, 0.88; 95% CI, 0.55 to 1.39). Relief from angina was more pronounced after PCI than after medical therapy.

CONCLUSIONS

In patients with stable coronary artery disease, an initial FFR-guided PCI strategy was associated with a significantly lower rate of the primary composite end point of death, myocardial infarction, or urgent revascularization at 5 years than medical therapy alone. Patients without hemodynamically significant stenoses had a favorable long-term outcome with medical therapy alone. (Funded by St. Jude Medical and others; FAME 2 ClinicalTrials.gov number, NCT01132495.)

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Among patients with acute coronary syndromes, early percutaneous coronary intervention (PCI) increases the survival rate and decreases the rate of recurrent myocardial infarction.[1-5] In contrast, in patients with stable coronary artery disease, there is persistent controversy about the role and timing of PCI to improve clinical outcomes and provide symptomatic relief.[6,7] Since the potential benefit of revascularization depends on the extent and severity of ischemia, careful identification of stenoses capable of inducing ischemia is essential.[8,9] Current guidelines recommend the measurement of the coronary fractional flow reserve (FFR) for this purpose.[10-12]

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) 2 trial was designed to target stenoses capable of inducing ischemia (FFR, ≤0.80) in a large myocardial territory and to refrain from PCI in patients with hemodynamically nonsignificant stenoses (FFR, >0.80). We hypothesized that an initial strategy of FFR-guided PCI plus medical therapy would provide better long-term outcomes than an initial strategy of medical therapy alone. Here, we describe the prespecified 5-year follow-up of the trial.

Methods

Trial Design

We conducted this randomized, multicenter trial to compare FFR-guided PCI plus medical therapy with medical therapy alone in patients with stable coronary artery disease. The short-term outcomes (mean follow-up, 7 months) have been reported previously.[13] The trial was sponsored by St. Jude Medical; the sponsor did not provide support for the current analysis. The academic members of the steering committee designed the trial protocol (available with the full text of this article at NEJM.org), which was approved by all the relevant local review boards. An independent data and safety monitoring board oversaw the trial.

The sponsor was involved in the collection of the data during the first 3 years of the trial but not in the trial design or conduct, the subsequent data collection, the writing and review of the manuscript, or the decision to submit it for publication. The two first authors and two last authors had full access to all the data in the trial and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Participants and Randomization

Patients with stable coronary artery disease were enrolled at 28 sites in Europe and North America.[13] Patients with stable angina or documented silent ischemia who had at least one stenosis with a 50% diameter in a large epicardial artery that was suitable for PCI were eligible. The full list of the inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

Measurements of FFR were made for all angiographically significant lesions. Each patient with at least one hemodynamically significant stenosis (FFR, ≤0.80) was randomly assigned in a 1:1 ratio to receive either FFR-guided PCI plus medical therapy (PCI group) or medical therapy alone (medical-therapy group). The randomization schedule was computer-generated, stratified according to site, blocked (with randomly varied block sizes), and concealed with the use of central randomization. Patients in whom all angiographically significant stenoses were hemodynamically nonsignificant (FFR, >0.80) did not undergo randomization but received medical therapy and were included in a registry. Written informed consent was obtained from all the patients.

Treatment

Patients who were assigned to the PCI group received a loading dose of clopidogrel (at a dose of 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- or third-generation drug-eluting stents. All the patients who underwent PCI received clopidogrel at a dose of 75 mg daily for at least 12 months.

Trial End Points and Follow-up

The primary end point was a composite of death from any cause, myocardial infarction, or urgent revascularization. Urgent revascularization was defined as any unplanned hospital admission that was due to symptoms that led to revascularization during the same hospitalization. Secondary end points included the components of the primary end point as well as death from cardiac

causes, any revascularization, stroke, and stent thrombosis. End-point definitions are provided in the Supplementary Appendix. 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.

Follow-up was originally scheduled at 1 month, 6 months, and 1, 2, 3, 4, and 5 years. A total of 50% of the patients in the registry cohort were randomly selected and followed in the same manner as the trial patients. In November 2014, the sponsor decided to close out the trial once all the included patients had completed their 3-year visit. The reason indicated by the sponsor was that results were unlikely to change substantially with longer patient follow-up, particularly in view of the high rate of crossover of patients who had been assigned to medical therapy alone. The academic steering committee subsequently invited all 28 sites to participate in an additional 5-year follow-up, and 19 sites participated (Table S1 in the Supplementary Appendix).

Throughout the trial, detailed narratives were obtained for each potential event. Events that were ascertained before the original trial close-out were adjudicated by an independent clinical events committee whose members were unaware of the trial group assignments. Events that were ascertained after the close-out were adjudicated by two cardiologists who were not involved in the trial and who were unaware of the trial group assignments.

STATISTICAL ANALYSIS

The trial was powered to determine the superiority of FFR-guided PCI over medical therapy alone with respect to the primary end point at 2 years. However, recruitment of the patients was stopped prematurely after the randomization of 888 of the originally intended 1632 patients. Recruitment was discontinued at the recommendation of the data and safety monitoring board because of a significant difference in the rate of the primary end point in favor of the PCI group.[13] Details of the original sample-size calculation are provided in the Supplementary Appendix.

Between-group comparisons of the end points were performed with the Mantel–Cox method for the calculation of hazard ratios and 95% confidence intervals and with the log-rank test for corresponding P values. Kaplan–Meier curves were constructed. Landmark analyses were performed according to landmark time points at 7 days and 3 years, with hazard ratios calculated separately for events that occurred before and after these time points. Landmark analyses were accompanied by tests for interaction between treatment and time.

There was no prespecified adjustment for multiple testing of secondary end points. However, because it was considered to be of importance to formally examine the components of the primary end point separately in this follow-up analysis, we informally adopted a post hoc Bonferroni correction, which allowed for the three components of the primary end point to be tested at an alpha level of 0.0167 (0.05÷3). Since the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects. All the analyses were performed according to the intention-to-treat principle by an author who is a statistician in an academic clinical trials unit (Clinical Trials Unit Bern, University of Bern, Switzerland).

RESULTS

PARTICIPANTS AND FOLLOW-UP

Between May 15, 2010, and January 15, 2012, a total of 1220 patients were enrolled, including 888 in the randomized trial. Of these, 447 patients were assigned to PCI plus medical therapy and 441 to medical therapy alone. The remaining 332 patients, who had an FFR more than 0.80 in all lesions, were enrolled in the registry, and half these patients (166 patients) were randomly selected for follow-up. The characteristics of the patients at baseline were similar in the PCI group and the medical-therapy group (Table 1). Tables S2 through S5 in the Supplementary Appendix present comparisons of the baseline characteristics between patients in the randomized trial and those in the registry cohort and according to site participation in the 5-year follow-up (yes or no).

Figure S1 and Table S6 in the Supplementary Appendix present the flow of patients through the different phases of the trial. In the PCI group, 435 of 447 patients underwent the planned pro-

Table 1. Demographic and Clinical Characteristics at Baseline of the Patients Who Underwent Randomization.*

Characteristic	PCI Group (N=447)	Medical-Therapy Group (N=441)
Age — yr	63.5±9.4	63.9±9.6
Age >60 yr — no. (%)	282 (63.1)	279 (63.3)
Male sex — no. (%)	356 (79.6)	338 (76.6)
Body-mass index†	28.3±4.3	28.4±4.5
Family history of coronary artery disease — no./total no. (%)	216/446 (48.4)	207/441 (46.9)
Current smoking — no. (%)	89 (19.9)	90 (20.4)
Hypertension — no. (%)	347 (77.6)	343 (77.8)
Hypercholesterolemia — no. (%)	330 (73.8)	348 (78.9)
Diabetes mellitus — no. (%)		
Any	123 (27.5)	117 (26.5)
Insulin-dependent	39 (8.7)	39 (8.8)
Renal insufficiency — no. (%)‡	8 (1.8)	12 (2.7)
Peripheral vascular disease — no. (%)	43 (9.6)	47 (10.7)
History of stroke or TIA — no. (%)	33 (7.4)	28 (6.3)
History of myocardial infarction — no. (%)	164 (36.7)	165 (37.4)
History of PCI in target vessel — no. (%)	80 (17.9)	76 (17.2)
Angina — no./total no. (%)§		
No angina or asymptomatic	53/447 (11.9)	46/440 (10.5)
CCS class I	82/447 (18.3)	98/440 (22.3)
CCS class II	204/447 (45.6)	197/440 (44.8)
CCS class III	80/447 (17.9)	65/440 (14.8)
CCS class IV	28/447 (6.3)	34/440 (7.7)
Silent ischemia — no. (%)	73 (16.3)	73 (16.6)
Left ventricular ejection fraction <50% — no. (%)	83 (18.6)	56 (12.7)

* Plus–minus values are means ±SD. There were no significant differences between the two randomly assigned groups, with the exception of left ventricular ejection fraction of less than 50% (P=0.02). PCI denotes percutaneous coronary intervention, and TIA transient ischemic attack.
† 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 (177 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.

cedure; the remaining 12 patients were treated with balloon angioplasty, coronary-artery bypass grafting, or medical therapy alone (Fig. S1 in the Supplementary Appendix). In the medical-therapy group, 439 of 441 patients received the planned treatment; the remaining 2 patients erroneously underwent PCI. In the registry, 165 of 166 patients received medical therapy, and 1 underwent PCI. Details of the medical therapy in each group are provided in Table S7 in the Supplementary Appendix.

In the 19 sites that participated in the 5-year follow-up, the median length of follow-up was 60.5 months (interquartile range [IQR], 59.8 to 61.7) in the PCI group, 60.5 months (IQR, 59.8 to 61.7) in the medical-therapy group, and 60.6 months (IQR, 59.9 to 62.5) in the registry cohort, with complete follow-up information available through 5 years for 371 of 395 patients (93.9%) in the PCI group, 362 of 389 (93.1%) in the medical-therapy group, and 133 of 147 (90.5%) in the registry. In the 9 sites that did not

Table 2. Clinical End Points at 5-Year Follow-up.*

End Points	PCI Group (N=447)	Medical-Therapy Group (N=441)	Hazard Ratio (95% CI)	Registry Cohort (N=166)
	no. of patients (%)			*no. of patients (%)*
Primary composite end point	62 (13.9)	119 (27.0)	0.46 (0.34–0.63)	26 (15.7)
Components of primary end point				
Death from any cause	23 (5.1)	23 (5.2)	0.98 (0.55–1.75)	7 (4.2)
Myocardial infarction	36 (8.1)	53 (12.0)	0.66 (0.43–1.00)	14 (8.4)
Urgent revascularization	28 (6.3)	93 (21.1)	0.27 (0.18–0.41)	14 (8.4)
Death or myocardial infarction	53 (11.9)	71 (16.1)	0.72 (0.50–1.03)	20 (12.0)
Death from cardiac causes	11 (2.5)	7 (1.6)	1.54 (0.60–3.98)	3 (1.8)
Death from cardiac causes or myocardial infarction	43 (9.6)	59 (13.4)	0.70 (0.48–1.04)	16 (9.6)
Revascularization				
Any revascularization	60 (13.4)	225 (51.0)	0.19 (0.14–0.26)	29 (17.5)
Nonurgent revascularization	34 (7.6)	155 (35.1)	0.18 (0.12–0.26)	17 (10.2)
Stroke	12 (2.7)	7 (1.6)	1.69 (0.67–4.31)	1 (0.6)
Definite or probable stent thrombosis	7 (1.6)	2 (0.5)	3.46 (0.72–16.70)	1 (0.6)

* The primary end point was a composite of death from any cause, myocardial infarction, or urgent revascularization. The 95% confidence intervals for secondary end points were not adjusted for multiple testing, and any inferences drawn from the intervals as reported may not be reproducible.

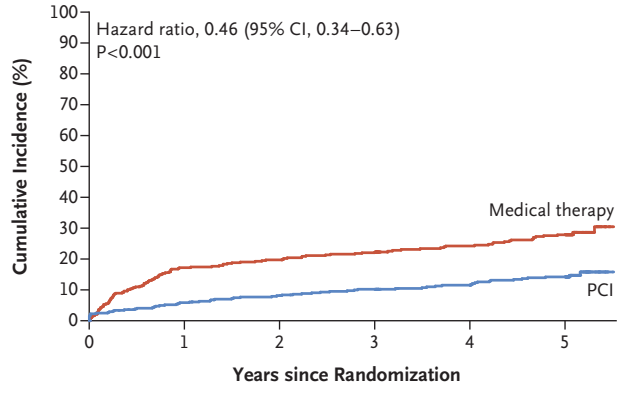


Figure 1. Kaplan–Meier Curves for the Primary End Point.

Shown is the cumulative incidence of the primary end point (a composite of death from any cause, myocardial infarction, or urgent revascularization) in the two groups in the trial. A hazard ratio below 1.00 denotes a lower incidence of the primary end point in the group that underwent fractional flow reserve–guided percutaneous coronary intervention (PCI) than in the medical-therapy group.

participate in the 5-year follow-up, the median length of follow-up was 35.7 months (IQR, 34.9 to 36.3) in the PCI group, 35.6 months (IQR, 35.0 to 36.0) in the medical-therapy group, and 35.3 months (IQR, 34.9 to 36.0) in the registry, with complete follow-up information available through 3 years for 46 of 52 patients (88%), 44 of 52 patients (85%), and 15 of 19 patients (79%), respectively. Details are provided in Table S6 in the Supplementary Appendix.

END POINTS

At least one primary end-point event (death, myocardial infarction, or urgent revascularization) occurred in 62 patients (13.9%) in the PCI group, as compared with 119 (27.0%) in the medical-therapy group (hazard ratio, 0.46; 95% confidence interval [CI], 0.34 to 0.63; P<0.001) (Table 2). The Kaplan–Meier curves for the primary end point are shown in Figure 1, and in Figure S2 in the Supplementary Appendix. In the registry cohort, 26 patients (15.7%) had at least one primary end-point event; the rates in the PCI group and the registry cohort did not differ sig-

nificantly (hazard ratio, 0.88; 95% CI, 0.55 to 1.39), but the rate was significantly higher in the medical-therapy group than in the registry cohort (hazard ratio, 1.91; 95% CI, 1.25 to 2.91) (Fig. S2 in the Supplementary Appendix).

The rates and causes of death did not differ significantly between the two trial groups (Table 2 and Fig. 2A, and Table S8 in the Supplementary Appendix). After Bonferroni correction, the rate of myocardial infarction was not significantly lower in the PCI group than in the medical-therapy group (Table 2 and Fig. 2B). The difference in the rates of primary end-point events between the PCI group and the medical-therapy group was driven by a lower rate of urgent revascularizations in the PCI group ($P<0.001$), a difference that was significant after Bonferroni correction (Table 2 and Fig. 2C).

The rates of spontaneous and periprocedural myocardial infarctions are reported in Table S9 and Figure S3 in the Supplementary Appendix. The rate of the composite of myocardial infarction or death from any cause tended to be lower in the PCI group than in the medical-therapy group, but the difference was not significant (Table 2, and Fig. S4 in the Supplementary Appendix). At the end of follow-up, 225 patients (51.0%) in the medical-therapy group had crossed over to undergo at least one PCI, whereas 60 patients (13.4%) in the PCI group had undergone repeat revascularization (hazard ratio for any revascularization, 0.19; 95% CI, 0.14 to 0.26) (Table 2, and Fig. S5 in the Supplementary Appendix). Time-to-event curves for the remaining secondary composite end points are provided in Figures S6 and S7 in the Supplementary Appendix.

The results of the landmark analyses are provided in Figure S8 in the Supplementary Appendix. The hazard ratio for the primary end point within 7 days after randomization in the PCI group versus the medical-therapy group was 2.49 (95% CI, 0.78 to 8.00); between 8 days and 3 years, the hazard ratio was 0.34 (95% CI, 0.23 to 0.51); and between 3 years and 5 years, the hazard ratio was 0.60 (95% CI, 0.32 to 1.13). The P values for interaction were less than 0.001 between the first and second periods and 0.13 between the second and third periods.

Figure S9 in the Supplementary Appendix presents the results of the originally specified subgroup analyses, and Table S10 in the Supplementary Appendix shows a post hoc subgroup analysis according to site participation in the 5-year follow-up. No significant treatment-by-subgroup interactions were identified. Figure S10 in the Supplementary Appendix shows that the variation in risk ratios across centers was not greater than would be expected by chance ($P=0.93$ for heterogeneity between sites).

The percentage of patients with angina of CCS grade II, III, or IV was lower among patients in the PCI group than among those in the medical-therapy group at all time points during the first 3 years of follow-up. However, this difference was no longer significant at 5 years (Fig. 3).

DISCUSSION

This 5-year follow-up of the FAME 2 trial showed that, among patients with stable angina, FFR-guided PCI led to a significantly lower rate of the prespecified primary composite end point of death, myocardial infarction, or urgent revascularization than medical therapy alone. This difference was driven by a significantly lower rate of urgent revascularization in the PCI group than in the medical-therapy group. Patients in whom all coronary stenoses were hemodynamically nonsignificant had an event rate with medical therapy alone that did not differ significantly from the rate among patients with hemodynamically significant stenoses who underwent FFR-guided PCI. There was no evidence of convergence of event rates between groups in the long term. Patients who had originally been assigned to undergo FFR-guided PCI reported significantly less angina up to 3 years after randomization than did patients who had been assigned to receive medical therapy alone. However, this difference was no longer significant at 5 years, by which time 51% of the patients who had been initially assigned to medical therapy alone had undergone revascularization.

Guidelines recommend that revascularization be considered in patients with stable coronary disease when signs of reversible myocardial ischemia are present.[10-12] In routine clinical practice, however, a minority of patients undergo

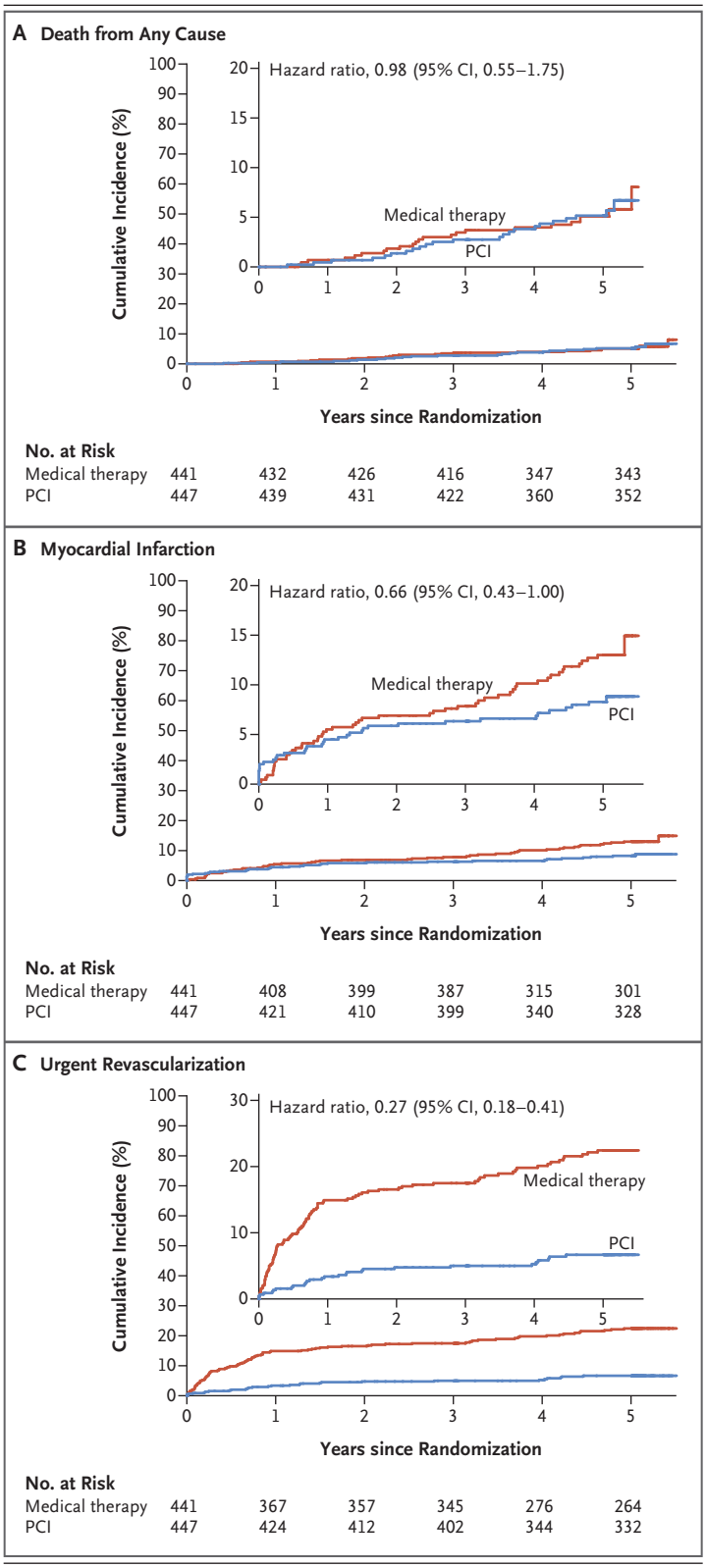


Figure 2. Kaplan–Meier Curves for Death from Any Cause, Myocardial Infarction, and Urgent Revascularization.

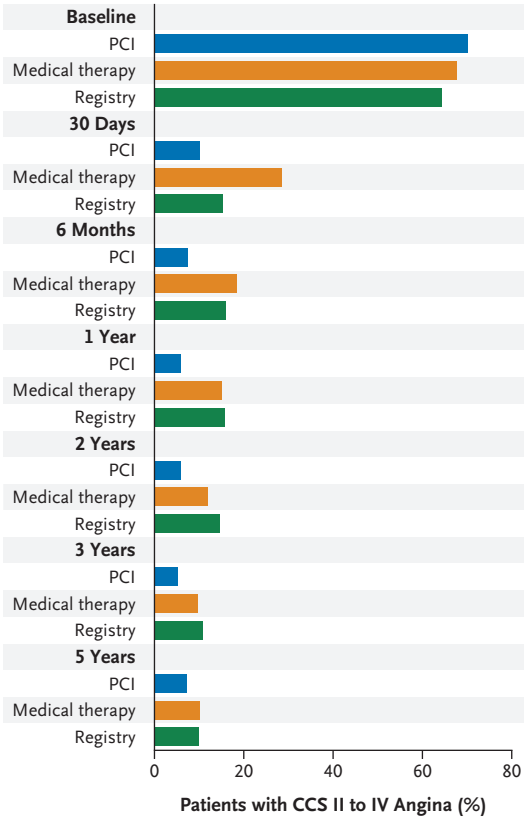
Hazard ratios below 1.00 denote a lower incidence of events in the PCI group than in the medical-therapy group. The 95% confidence intervals for secondary end points were not adjusted for multiple testing, and any inferences drawn from the intervals as reported may not be reproducible. Insets show the same data on an enlarged y axis.

noninvasive functional testing before elective PCI.[14] FFR quantifies the impediment of myocardial flow with a higher spatial resolution than noninvasive testing and is currently the reference standard to guide revascularization. In the FAME 2 trial, patients underwent randomization only if they had at least one hemodynamically significant stenosis (FFR, ≤0.80) in a large artery. In addition, multivessel disease was observed on angiography in almost 45% of the patients who had undergone randomization, and more than 60% of the patients had a hemodynamically significant stenosis in the proximal or middle left anterior descending artery (Table S3 in the Supplementary Appendix). Patients in whom all angiographically significant stenoses were found to be hemodynamically nonsignificant were not included in the randomized trial, given that no benefit regarding the end points was expected in such patients.[15]

In previous trials comparing PCI with medical therapy in patients with stable coronary artery disease, patients were included mainly on the basis of symptoms and angiography without measurement of FFR.[6,7] A sizable proportion of these patients had no objective signs of reversible ischemia. Such patients would not be expected to benefit from revascularization.

Our results contradict the general belief that abrupt coronary occlusions occur predominantly at sites of mild stenosis and hence that the treatment of severe lesions may not prevent myocardial infarction. This belief was also questioned in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, which showed that the main determinants of future events in stable lesions were a small luminal area and a large plaque burden.[16]

In the FAME 2 trial, the physicians, who were



	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					
PCI	314/447	1.04 (0.95–1.13)	0.42	1.09 (0.96–1.24)	0.17
Medical therapy	298/440	Reference		1.05 (0.92–1.20)	0.45
Registry	107/166	—		Reference	
30 Days					
PCI	45/440	0.36 (0.26–0.49)	<0.001	0.66 (0.42–1.04)	0.077
Medical therapy	123/431	Reference		1.85 (1.25–2.73)	0.001
Registry	25/162	—		Reference	
6 Months					
PCI	33/440	0.41 (0.28–0.60)	<0.001	0.47 (0.29–0.76)	0.002
Medical therapy	80/434	Reference		1.16 (0.77–1.73)	0.48
Registry	26/163	—		Reference	
1 Year					
PCI	26/437	0.39 (0.25–0.61)	<0.001	0.38 (0.23–0.64)	<0.001
Medical therapy	65/429	Reference		0.96 (0.63–1.47)	0.86
Registry	25/159	—		Reference	
2 Years					
PCI	25/425	0.49 (0.31–0.77)	0.002	0.40 (0.23–0.69)	0.001
Medical therapy	51/424	Reference		0.82 (0.52–1.30)	0.40
Registry	23/157	—		Reference	
3 Years					
PCI	22/420	0.54 (0.33–0.89)	0.014	0.48 (0.26–0.88)	0.016
Medical therapy	40/413	Reference		0.89 (0.52–1.52)	0.67
Registry	17/156	—		Reference	
5 Years					
PCI	26/352	0.72 (0.45–1.18)	0.19	0.73 (0.39–1.38)	0.34
Medical therapy	35/343	Reference		1.01 (0.55–1.85)	0.97
Registry	13/129	—		Reference	

Figure 3. Angina Class in Patients in the Trial Groups and Registry Cohort over Time.

Shown are the numbers of patients in the two trial groups and the registry cohort who 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) at various time points. The 95% confidence intervals for secondary end points were not adjusted for multiple testing, and any inferences drawn from the intervals as reported may not be reproducible.

aware of the treatment assignments, might have been more likely to recommend a subsequent PCI procedure for patients in the medical-therapy group than for those in the PCI group, thus introducing a risk of bias for the end point of any revascularization. To limit the risk of such bias, the FAME 2 trial included only urgent revascularizations in the primary end point. Revascularization was considered to be urgent if a patient was readmitted to the hospital unexpectedly and revascularization was performed during that same admission. The majority of urgent revascularizations were triggered by worsening angina, ischemic changes observed on electrocardiography, or myocardial infarction.[17] After 5 years, 225 patients (51.0%) who had originally been assigned to receive medical therapy alone had undergone revascularization. Given the high rate of crossover to PCI among patients who had been originally assigned to medical therapy, an intention-to-treat analysis may underestimate the potential benefit of PCI as compared with medical therapy with regard to death, myocardial infarction, and severity of angina.

Some limitations must be taken into account. First, enrollment was stopped prematurely by

the data and safety monitoring board because of a large excess of primary end-point events in the medical-therapy group. The early termination of clinical trials has been shown to exaggerate treatment effects.[18] Second, the sponsor of the trial decided to close the trial after completion of the 3-year follow-up. The academic steering committee subsequently invited all 28 sites to participate in an additional 5-year follow-up, but only 19 sites participated. Taken together, these two points resulted in a relatively low number of events with limited statistical precision. Third, patients, physicians, and nurses were aware of the assigned treatment. Even though the blinded adjudication of clinical events may have reduced the risk of detection bias, we cannot rule out that between-group differences in clinical management biased our results regarding urgent revascularization. Fourth, in stenoses that were estimated to be less than 50% in diameter, no FFR measurements were performed. A sizable number of stenoses with a 30 to 50% diameter are associated with FFR values below 0.80, especially in proximal segments of large coronary arteries.[19,20] Therefore, it is possible that some stenoses that were deemed to be nonsignificant at angiography (and therefore left untreated) might have been hemodynamically significant.

In conclusion, in patients with stable coronary artery disease, an initial FFR-guided PCI strategy resulted in a sustained clinical benefit, as compared with medical therapy alone, with regard to the composite primary end point of death, myocardial infarction, or urgent revascularization at 5 years. Patients without hemodynamically significant stenoses had a favorable long-term outcome with medical therapy alone.

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

APPENDIX

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