

ORIGINAL ARTICLE

Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND

We hypothesized that in patients with stable coronary artery disease and stenosis, percutaneous coronary intervention (PCI) performed on the basis of the fractional flow reserve (FFR) would be superior to medical therapy.

METHODS

In 1220 patients with stable coronary artery disease, we assessed the FFR in all stenoses that were visible on angiography. Patients who had at least one stenosis with an FFR of 0.80 or less were randomly assigned to undergo FFR-guided PCI plus medical therapy or to receive medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy alone and were included in a registry. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization within 2 years.

RESULTS

The rate of the primary end point was significantly lower in the PCI group than in the medical-therapy group (8.1% vs. 19.5%; hazard ratio, 0.39; 95% confidence interval [CI], 0.26 to 0.57; $P < 0.001$). This reduction was driven by a lower rate of urgent revascularization in the PCI group (4.0% vs. 16.3%; hazard ratio, 0.23; 95% CI, 0.14 to 0.38; $P < 0.001$), with no significant between-group differences in the rates of death and myocardial infarction. Urgent revascularizations that were triggered by myocardial infarction or ischemic changes on electrocardiography were less frequent in the PCI group (3.4% vs. 7.0%, $P = 0.01$). In a landmark analysis, the rate of death or myocardial infarction from 8 days to 2 years was lower in the PCI group than in the medical-therapy group (4.6% vs. 8.0%, $P = 0.04$). Among registry patients, the rate of the primary end point was 9.0% at 2 years.

CONCLUSIONS

In patients with stable coronary artery disease, FFR-guided PCI, as compared with medical therapy alone, improved the outcome. Patients without ischemia had a favorable outcome with medical therapy alone. (Funded by St. Jude Medical; FAME 2 ClinicalTrials.gov number, NCT01132495.)

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*A complete list of investigators and committee members in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial is provided in the Supplementary Appendix, available at NEJM.org.

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THE BENEFIT OF PERCUTANEOUS CORONARY intervention (PCI) as an initial treatment strategy in patients with stable coronary artery disease remains controversial.¹⁻³ The potential result from revascularization depends on the extent and the degree of myocardial ischemia.^{4,5} A fractional flow reserve (FFR) value of 0.80 or less (i.e., a drop in maximal blood flow of 20% or more caused by stenosis), as measured with the use of a coronary pressure wire during catheterization, indicates the potential of a stenosis to induce myocardial ischemia.⁶⁻⁸

In such cases, robust clinical-outcome data favor FFR-guided revascularization, as compared with revascularization guided by angiography alone.⁹⁻¹⁶ In previous trials comparing PCI with medical therapy alone in patients with stable coronary artery disease,^{1,2} investigators did not use FFR guidance or contemporary drug-eluting stents.

In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial, we investigated whether contemporary PCI plus medical therapy would be superior to medical therapy alone in patients with stable coronary artery disease and functionally significant stenoses, as determined by the FFR. This report describes the prespecified 2-year results for the primary outcome.

METHODS

PATIENTS

We enrolled patients with clinically stable coronary artery disease involving up to three vessels (as determined on angiography) that was suitable for treatment with PCI. The inclusion and exclusion criteria have been described previously.¹⁷ Using a centralized randomization method, we assigned patients who had at least one stenosis in a major coronary artery with an FFR of 0.80 or less to undergo FFR-guided PCI (with the use of the PressureWire Certus or PressureWire Aeris, St. Jude Medical) plus medical therapy (PCI group) or to receive medical therapy alone (medical-therapy group). Patients with an FFR of more than 0.80 in all stenoses received medical therapy alone and were included in a registry. All patients provided informed written consent. The study protocol is available with the full text of this article at NEJM.org.

STUDY DESIGN AND OVERSIGHT

We conducted this open-label, randomized trial at 28 sites in Europe and North America. The trial was approved by the institutional review board at each participating center. The members of the steering committee 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. An independent data and safety monitoring board oversaw the trial. The members of the steering committee had full access to all the data in the study, wrote the manuscript, and made the decision to submit it for publication.

STUDY TREATMENTS

Patients were prescribed daily aspirin, a beta-blocker (alone or in combination with a calcium-channel blocker, a long-acting nitrate, or both), an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker, and atorvastatin alone or in combination with ezetimibe to achieve a low-density lipoprotein cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter). Among patients in the medical-therapy group and the registry patients, the prescription of clopidogrel was left to the discretion of the treating clinician. Among patients in the PCI group, all stenoses with an FFR of 0.80 or less were treated with second-generation drug-eluting stents. These patients received clopidogrel (at a dose of 75 mg per day) for at least 12 months in addition to standard medical therapy. Smokers were counseled regarding smoking cessation, and patients with diabetes were referred to a specialist in order to optimize their treatment.

STUDY END POINTS AND FOLLOW-UP

The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization within 2 years. Fifty percent of registry patients were randomly selected to be followed up in the same manner as the study patients. For each outcome event, a detailed narrative was produced. All events were adjudicated by an independent clinical-events committee whose members were unaware of the assigned treatment.

Revascularization was considered to be urgent when a patient was admitted to the hospital

with persistent or increasing symptoms (with or without changes in the ST segment or T wave or elevated biomarker levels) and the revascularization procedure was performed during the same hospitalization. All urgent revascularizations were adjudicated by two independent cardiologists, who were unaware of the assigned treatment, to determine the type of trigger (myocardial infarction, electrocardiographic evidence of ischemic changes, or clinical features only) and the severity of angina (according to the criteria of the Canadian Cardiovascular Society [CCS]) that led to the procedure.

ADVERSE EVENTS

Serious adverse events were defined as any event that resulted in death or was life-threatening, required hospitalization or prolongation of a hospital stay, or resulted in persistent or substantial disability. Also included were all protocol-specified clinical end-point events.

STATISTICAL ANALYSIS

The trial was powered to determine the superiority of FFR-guided PCI plus medical therapy over medical therapy alone with respect to the primary end point at 2 years. We estimated that the cumulative incidence of the primary end point would be 12.6% in the PCI group¹⁸⁻²⁰ and 18.0% in the medical-therapy group,¹ which would correspond to a relative risk reduction of 30% in the PCI group. We determined that the enrollment of 816 patients in each study group would provide a power of more than 84% to detect a relative risk reduction of 30% at a two-sided type I error rate of 0.05.

We used the Mantel–Cox method to calculate hazard ratios and 95% confidence intervals for between-group comparisons of clinical outcomes and the log-rank test to calculate corresponding P values. All patients were included in the intention-to-treat analysis. We constructed Kaplan–Meier curves for the primary end point and its components. In exploratory analyses, we separately plotted cumulative urgent-revascularization events triggered by myocardial infarction, unstable angina with evidence of ischemia on electrocardiography, or clinical features only, stratified according to the CCS class, and used the Mantel–Cox method to calculate hazard ratios with 95 confidence intervals and log-rank tests to calculate P values.

We performed separate analyses according to a landmark (cutoff) point of 7 days after randomization, with hazard ratios calculated separately for events that occurred within 7 days and those that occurred between 8 days and the end of follow-up at 2 years. For each type of event, data for patients were censored at the time of the first event — for example, data for a patient who had an event that contributed to the primary composite end point during the first 7 days were censored at the time of the event and excluded from the analysis of subsequent years after the landmark point. Landmark analyses were accompanied by a chi-square test for interaction between treatment effect and time (first 7 days vs. subsequent period). All analyses were performed by two independent statisticians at an academic clinical-trials unit (CTU Bern, University of Bern).

RESULTS

PATIENTS

Among 1220 patients who were enrolled between May 15, 2010, and January 15, 2012, a total of 888 had at least one stenosis with an FFR of 0.80 or less in a large epicardial artery. These patients were randomly assigned to undergo FFR-guided PCI plus medical therapy (447 patients) or to receive medical therapy alone (441 patients). In the remaining 332 registry patients, all stenoses that were visible on angiography had an FFR of more than 0.80. On the basis of the highly significant between-group difference in the primary end point, patient recruitment was halted on January 15, 2012, after the randomization of 54% of the patients in the initially planned study sample (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The characteristics of the patients at baseline, which have been described previously,¹⁷ were well balanced between the two treatment groups (Table S1 in the Supplementary Appendix). Among the 888 patients, 1601 stenoses were eligible for PCI on the basis of angiography, whereas 1304 stenoses were eligible for PCI on the basis of an FFR of 0.80 or less, with a mean (\pm SD) FFR of 0.64 ± 0.13 (range, 0.19 to 0.80).

PRIMARY END POINT

At 2 years, at least one primary outcome event had occurred in 36 patients (8.1%) in the PCI group and in 86 patients (19.5%) in the medical-therapy group (hazard ratio in the PCI group,

Table 1. Clinical Events and Triggers of Urgent Revascularization.*

Variable	PCI (N=447)	Medical Therapy (N=441)	Hazard Ratio (95% CI)†	P Value‡
	no. (%)			
Primary end point	36 (8.1)	86 (19.5)	0.39 (0.26–0.57)	<0.001
Death from any cause	6 (1.3)	8 (1.8)	0.74 (0.26–2.14)	0.58
Myocardial infarction	26 (5.8)	30 (6.8)	0.85 (0.50–1.45)	0.56
Urgent revascularization	18 (4.0)	72 (16.3)	0.23 (0.14–0.38)	<0.001
Death or myocardial infarction	29 (6.5)	36 (8.2)	0.79 (0.49–1.29)	0.35
Other end points				
Death from cardiac causes	3 (0.7)	3 (0.7)	0.99 (0.20–4.90)	0.99
Revascularization				
Any	36 (8.1)	179 (40.6)	0.16 (0.11–0.22)	<0.001
Nonurgent	18 (4.0)	117 (26.5)	0.13 (0.08–0.22)	<0.001
Stroke	7 (1.6)	4 (0.9)	1.74 (0.51–5.94)	0.37
Definite or probable stent thrombosis	7 (1.6)	2 (0.5)	3.48 (0.72–16.8)	0.10
Triggers of urgent revascularization according to Canadian Cardiovascular Society class§				
Any trigger				
All classes	18 (4.0)	72 (16.3)	0.23 (0.14–0.38)	<0.001
0, I, or II	4 (0.9)	7 (1.6)	0.56 (0.16–1.93)	0.35
III	3 (0.7)	20 (4.5)	0.14 (0.04–0.49)	<0.001
IV	11 (2.5)	47 (10.7)	0.22 (0.11–0.42)	<0.001
Myocardial infarction or changes on ECG				
All classes	15 (3.4)	31 (7.0)	0.47 (0.25–0.86)	0.01
0, I, or II	3 (0.7)	4 (0.9)	0.74 (0.17–3.31)	0.69
III	2 (0.4)	7 (1.6)	0.28 (0.06–1.35)	0.09
IV	10 (2.2)	21 (4.8)	0.46 (0.22–0.98)	0.04
Clinical features only				
All classes	3 (0.7)	43 (9.8)	0.07 (0.02–0.21)	<0.001
0, I, or II	1 (0.2)	3 (0.7)	0.33 (0.03–3.17)	0.31
III	1 (0.2)	14 (3.2)	0.07 (0.01–0.53)	0.001
IV	1 (0.2)	27 (6.1)	0.03 (0.00–0.26)	<0.001

* ECG denotes electrocardiography, and PCI percutaneous coronary intervention.

† Hazard ratios are for the PCI group as compared with the medical-therapy group.

‡ P values were calculated with the use of the log-rank test.

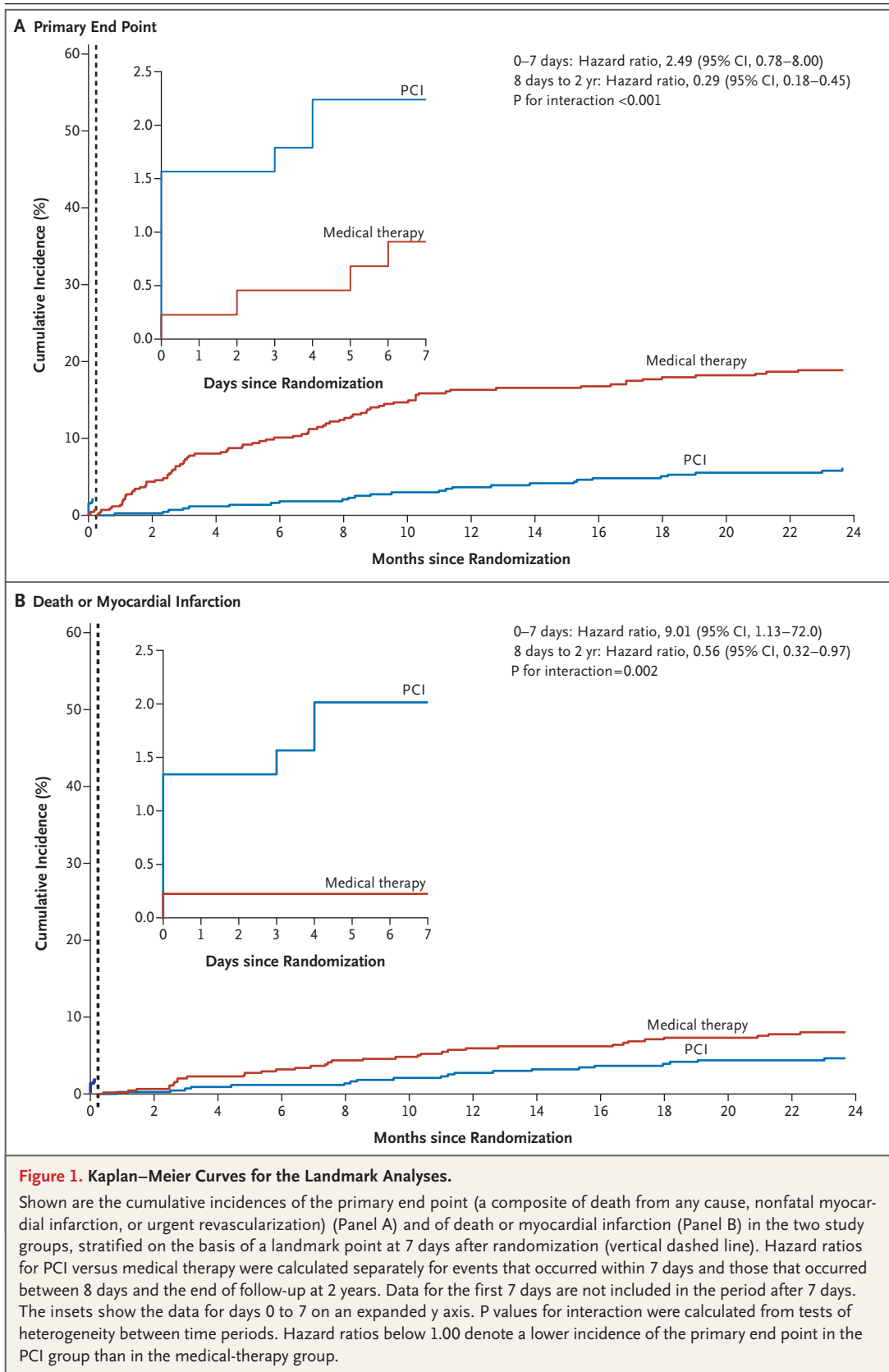
§ Patients could have more than one event. The Canadian Cardiovascular Society grades the severity of angina as follows: class I, angina only during strenuous or prolonged physical activity; class II, slight limitation, with angina only during vigorous physical activity; class III, symptoms with activities of everyday living (moderate limitation); and class IV, inability to perform any activity without angina or angina at rest (severe limitation).

0.39; 95% confidence interval [CI], 0.26 to 0.57; P<0.001) (Table 1, and Table S2 in the Supplementary Appendix). In the registry group, at least one event in the primary end point occurred in 15 patients (9.0%), with little difference between the PCI group and registry patients (hazard ratio, 0.90; 95% CI, 0.49 to 1.64; P=0.72) but a large difference between the medical-therapy group

and registry patients (hazard ratio, 2.34; 95% CI, 1.35 to 4.05; P=0.002) (Table S2 and Fig. S2 in the Supplementary Appendix).

LANDMARK ANALYSES

Within 7 days after randomization, there were more primary end-point events in the PCI group than in the medical-therapy group (2.2% vs.

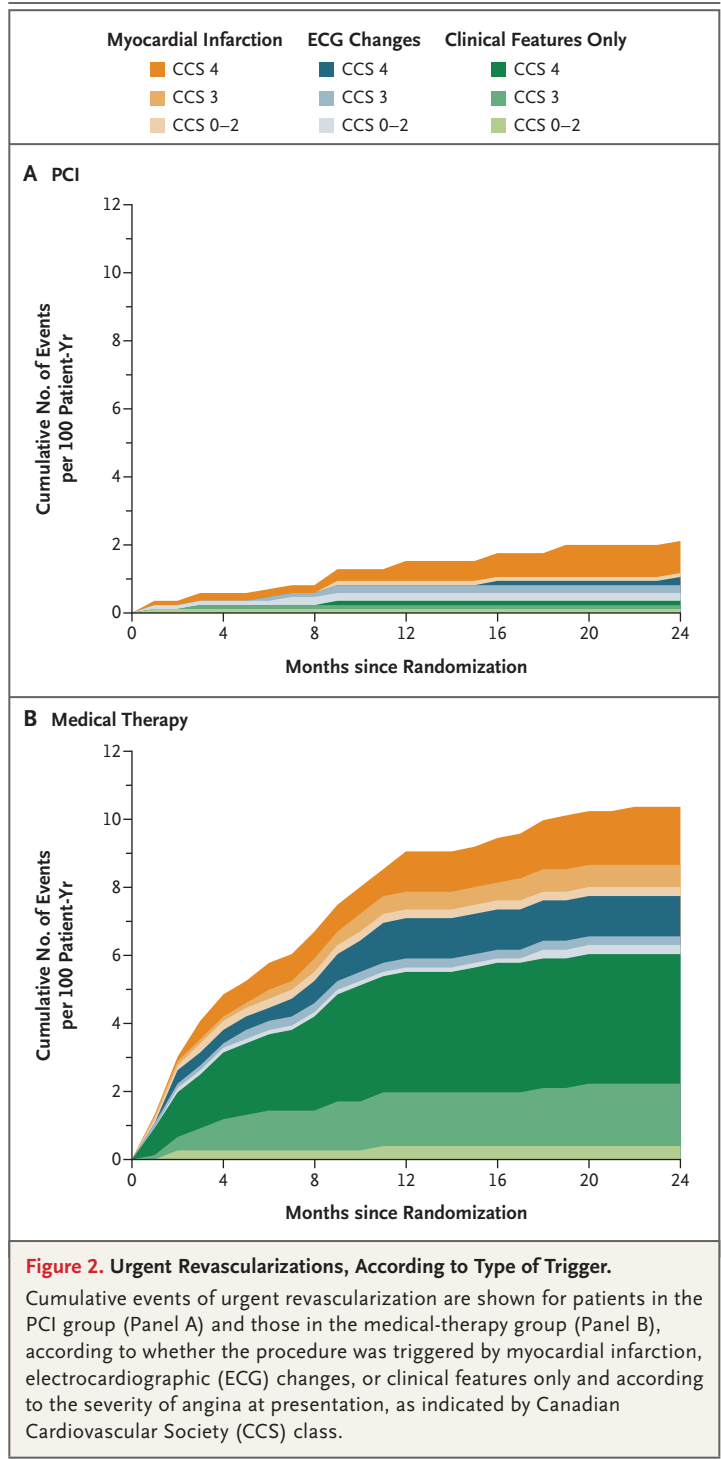


0.9%; hazard ratio, 2.49; 95% CI, 0.78 to 8.00; $P=0.11$) (Fig. 1A, and Table S3 in the Supplementary Appendix). Six out of 10 primary end-point events in the PCI group were periprocedural myocardial infarctions. During the period from 8 days to 2 years after randomization, patients undergoing PCI had a 44% relative risk reduction for the composite of death or myocardial infarction (4.6% vs. 8.0%; hazard ratio, 0.56; 95% CI, 0.32 to 0.97; $P=0.04$) (Fig. 1B) and a 79% relative risk reduction for urgent revascularization (3.6% vs. 15.6%; hazard ratio, 0.21; 95% CI, 0.12 to 0.37; $P<0.001$), with a significant interaction between treatment and time for the composite of death or myocardial infarction ($P=0.002$ for interaction) but not for urgent revascularization ($P=0.34$ for interaction).

URGENT REVASCUARIZATION

The between-group difference in the primary end point was driven by a 77% reduction in the need for urgent revascularization in the PCI group, as compared with the medical-therapy group (4.0% vs. 16.3%; hazard ratio, 0.23; 95% CI, 0.14 to 0.38; $P<0.001$) (Table 1). Figure 2 shows the cumulative numbers of unplanned rehospitalizations with urgent revascularization according to the type of trigger and angina class over time. Eighteen urgent revascularizations were performed in 18 patients in the PCI group (2.1 events per 100 patient-years), whereas 79 revascularizations were performed in 72 patients in the medical-therapy group (10.4 events per 100 patient-years).

In these 90 patients in the two study groups, revascularizations were triggered by a myocardial infarction in 28 patients (31%), by unstable angina with ischemic changes on electrocardiography in 18 patients (20%), and by clinical features only in the remaining 44 patients (49%), with a predominance of CCS class IV angina, regardless of the trigger. There were significant differences between the PCI group and the medical-therapy group with respect to urgent revascularizations triggered by a myocardial infarction or ischemic electrocardiographic changes (3.4% vs. 7.0%; hazard ratio, 0.47; 95% CI, 0.25 to 0.86; $P=0.01$) and those triggered by CCS class IV angina (2.5% vs. 10.7%; hazard ratio, 0.22; 95% CI, 0.11 to 0.42; $P<0.001$). Figure 3 shows the cumulative incidence of revascularization for any reason.



OTHER END POINTS

After 2 years, 179 patients (40.6%) in the medical-therapy group had crossed over to undergo PCI, whereas 36 patients (8.1%) in the PCI group had undergone repeat revascularization (hazard

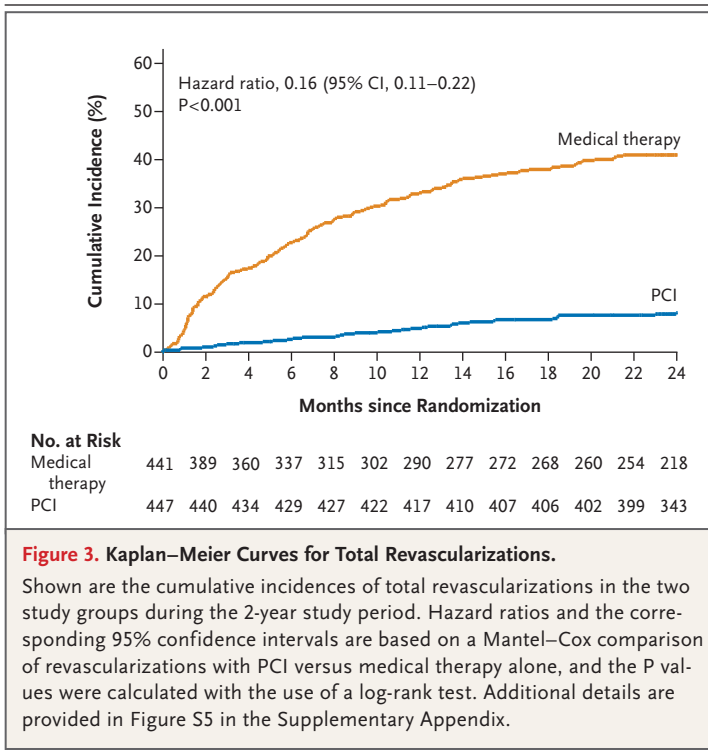


Figure 3. Kaplan–Meier Curves for Total Revascularizations.

Shown are the cumulative incidences of total revascularizations in the two study groups during the 2-year study period. Hazard ratios and the corresponding 95% confidence intervals are based on a Mantel–Cox comparison of revascularizations with PCI versus medical therapy alone, and the P values were calculated with the use of a log-rank test. Additional details are provided in Figure S5 in the Supplementary Appendix.

ratio, 0.16; 95% CI, 0.11 to 0.22; $P < 0.001$). Table S2 in the Supplementary Appendix presents a comparison of end points for patients in the two study groups and the 166 registry patients who were followed for up to 2 years; 20 registry patients (12.0%) crossed over to undergo PCI. Figure S3 in the Supplementary Appendix presents stratified analyses of the primary end point according to the characteristics of the patients at baseline. The reduction from baseline in the percentage of patients with angina of CCS grade II, III, or IV was greater among patients in the PCI group than among those in the medical-therapy group and those in the registry group at all time points during 2 years of follow-up (Fig. S4 in the Supplementary Appendix). After 2 years, 69% of patients were still receiving a combination of aspirin, beta-blockers, and statins (Table S4 in the Supplementary Appendix).

SERIOUS ADVERSE EVENTS

At least one clinical event or other serious adverse event was reported in 151 patients (33.8%) in the PCI group and in 232 patients (52.6%) in the medical-therapy group (hazard ratio, 0.55; 95% CI, 0.44 to 0.67; $P < 0.001$) (Table 1, and Table S5 in the Supplementary Appendix). The same percentage

of patients in the two groups (17.2%) had noncardiovascular serious adverse events, including clinical events (hazard ratio, 1.00; 95% CI, 0.73 to 1.38; $P = 0.98$), whereas serious cardiovascular adverse events (defined as death from cardiac causes, myocardial infarction, stent thrombosis, any revascularization, or any other cardiovascular serious adverse event) were reported in 110 patients in the PCI group as compared with 204 patients in the medical-therapy group (24.6% vs. 46.3%; hazard ratio, 0.45; 95% CI, 0.36 to 0.57; $P < 0.001$).

DISCUSSION

In our study involving patients with stable coronary artery disease and stenosis, the rate of the primary end point (death, myocardial infarction, or urgent revascularization at 2 years) among those who underwent FFR-guided PCI with contemporary drug-eluting stents was less than half the rate among patients who received medical therapy alone. Urgent revascularizations triggered by a myocardial infarction or ischemic changes on electrocardiography were half as frequent in the PCI group as in the medical-therapy group. Although there was no significant between-group difference in the overall rate of death or myocardial infarction, patients who underwent PCI, as compared with those who received medical therapy alone, had a significant reduction in the rate of death or myocardial infarction after the initial 7 days following randomization.

More than 25% of patients with stable coronary artery disease who were scheduled to undergo PCI on the basis of clinical and angiographic data had no stenosis with an FFR value of 0.80 or less and were thus unlikely to have had ischemia. These patients had a favorable clinical outcome at 2 years with medical therapy alone, a finding that is similar to results in patients with at least one clinically significant stenosis who were treated with PCI plus medical therapy. The degree of angina at 2 years was significantly lower in the PCI group than in the medical-therapy group, even though almost 50% of patients who were initially assigned to the medical-therapy group had died, had had a myocardial infarction, or had undergone revascularization.

In daily clinical practice, less than half of patients undergo noninvasive stress testing be-

fore elective PCI,²¹ and the decision to perform revascularization is based primarily on the angiographic appearance of a stenosis. There is a growing awareness of the poor accuracy of coronary angiography for identifying lesions responsible for myocardial ischemia and the inaccuracy of noninvasive stress testing in patients with multivessel coronary artery disease.^{22,23} In our randomized trial, we enrolled only patients with an FFR of 0.80 or less in at least one large epicardial artery. In contrast to all previous trials comparing PCI with medical therapy in patients with stable coronary artery disease, this FFR-driven selection process excluded patients without clinically significant ischemia, who are known to be at lower risk than are those with ischemia. The inclusion of these low-risk patients in previous trials limited the potential for showing any benefit from PCI. In our study, the measurement of FFR in patients with multivessel coronary artery disease allowed for the determination of which lesions were hemodynamically significant. Such lesions were shown to benefit from PCI, as compared with hemodynamically nonsignificant stenoses, for which PCI is unnecessary or even harmful.^{9,10} The resolution of ischemia in the patients treated with FFR-guided PCI probably explains the similar event rates among registry patients who had coronary artery disease and similar baseline characteristics but who received medical therapy alone because they had no ischemia-producing lesions.

Multiple studies have suggested that periprocedural infarctions rarely have an effect on the long-term prognosis for patients undergoing PCI,^{24,25} whereas spontaneous infarctions are predictive of an increased risk of death. In our study, the rate of death or myocardial infarction was significantly higher in the medical-therapy group than in the PCI group after the initial 7 days following randomization because of a higher rate of spontaneous myocardial infarction in the medical-therapy group.

The primary end point of our study included not only death and myocardial infarction but also unplanned hospitalization for urgent revascularization. The definition of urgent revascularization was stringent in order to distinguish urgent from nonurgent procedures. Severe angina was present in more than 90% of patients who underwent urgent revascularization, and in more than 40% of these patients, there was an

increase in biomarkers or dynamic changes on electrocardiography, which are criteria for performing PCI according to both American and European guidelines.^{26,27} Therefore, urgent revascularization in our study should be considered a failure of the treatment to which the patient has been assigned.

In contrast to previous trials comparing PCI with medical therapy,^{1,2} we used second-generation drug-eluting stents.¹⁸⁻²⁰ This factor may partially explain the improved outcome in patients with stable coronary artery disease who were treated with PCI as compared with the outcome in the medical-therapy group.^{28,29}

Our trial has several limitations. First, enrollment was interrupted early after interim analyses by the data and safety monitoring board disclosed a large excess of primary end-point events in the medical-therapy group. Second, patients and treating physicians were aware of study-group assignments. It is possible that the awareness of the presence of a functionally significant stenosis influenced the decision of the physician or the patient during follow-up. Yet, the fact that the group of registry patients with angiographically significant coronary artery disease had a lower number of events than those in the medical group suggests that the awareness of having an unstented coronary blockage cannot explain the high event rates among patients in the medical-therapy group. Moreover, the significantly higher rates of death and myocardial infarction that occurred more than 7 days after randomization in the medical-therapy group than in the PCI group and the registry group cannot be explained by the lack of blinding. Third, stenoses were located in large coronary arteries and the mean FFR value was 0.64, which suggests both profound and extensive ischemia. Thus, these results should not be extended to patients with smaller vascular areas at risk.

In conclusion, among patients with stable coronary artery disease and ischemia, as shown by the presence of at least one stenosis with an FFR of 0.80 or less in a large epicardial artery, the clinical outcome at 2 years was improved by FFR-guided PCI with second-generation drug-eluting stents plus the best available medical therapy, as compared with medical therapy alone. In patients without hemodynamically significant stenosis, the best available medical therapy alone

was associated with an excellent 2-year clinical 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.

APPENDIX

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