

## ORIGINAL ARTICLE

# Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction

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## ABSTRACT

**BACKGROUND**

In patients with ST-elevation myocardial infarction (STEMI) who have multivessel disease, percutaneous coronary intervention (PCI) for nonculprit lesions (complete revascularization) is superior to treatment of the culprit lesion alone. However, whether complete revascularization that is guided by fractional flow reserve (FFR) is superior to an angiography-guided procedure is unclear.

**METHODS**

In this multicenter trial, we randomly assigned patients with STEMI and multivessel disease who had undergone successful PCI of the infarct-related artery to receive complete revascularization guided by either FFR or angiography. The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization at 1 year.

**RESULTS**

The mean ( $\pm$ SD) number of stents that were placed per patient for nonculprit lesions was  $1.01 \pm 0.99$  in the FFR-guided group and  $1.50 \pm 0.86$  in the angiography-guided group. During follow-up, a primary outcome event occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 patients (4.2%) in the angiography-guided group (hazard ratio, 1.32; 95% confidence interval, 0.78 to 2.23;  $P=0.31$ ). Death occurred in 9 patients (1.5%) in the FFR-guided group and in 10 (1.7%) in the angiography-guided group; nonfatal myocardial infarction in 18 (3.1%) and 10 (1.7%), respectively; and unplanned hospitalization leading to urgent revascularization in 15 (2.6%) and 11 (1.9%), respectively.

**CONCLUSIONS**

In patients with STEMI undergoing complete revascularization, an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with respect to the risk of death, myocardial infarction, or urgent revascularization at 1 year. However, given the wide confidence intervals for the estimate of effect, the findings do not allow for a conclusive interpretation. (Funded by the French Ministry of Health and Abbott; FLOWER-MI ClinicalTrials.gov number, NCT02943954.)

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\*A list of the FLOWER-MI study investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**I**N PATIENTS WITH CHRONIC CORONARY syndrome or acute coronary syndrome without ST-segment elevation, the use of fractional flow reserve (FFR) measurement during percutaneous coronary intervention (PCI) to assess the functional severity of coronary lesions results in a lower risk of major cardiovascular events than myocardial revascularization guided by angiography.<sup>1-6</sup> Among patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease, complete revascularization of nonculprit lesions that is guided by FFR or angiography results in a lower frequency of repeat revascularization than revascularization of only the culprit lesion.<sup>7-9</sup> However, it is unclear whether an FFR-guided approach results in better clinical outcomes than an angiography-guided approach for complete revascularization in patients with STEMI and multivessel disease.

We designed the Flow Evaluation to Guide Revascularization in Multivessel ST-Elevation Myocardial Infarction (FLOWER-MI) trial to investigate whether the use of FFR in complete revascularization results in a better clinical outcome than the use of angiography in patients with STEMI and multivessel disease.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

From December 18, 2016, to December 6, 2018, we conducted this investigator-initiated, randomized, open-label, multicenter trial with blinded end-point evaluation at 41 sites in France.<sup>10</sup> The trial protocol (available with the full text of this article at NEJM.org) was approved by the Comité de Protection de Personnes Ile de France XI. A data and safety monitoring committee provided oversight and assessed the safety profile of the trial. Independent clinical research associates monitored the sites and gathered the data. All the events were analyzed and adjudicated by an independent clinical evaluation committee whose members were unaware of trial-group assignments.

The trial was funded by a grant from the Programme Hospitalier de Recherche Clinique issued by the French Ministry of Health. The trial was sponsored by Assistance Publique-Hôpitaux de Paris, with an unrestricted grant from St. Jude Medical (now Abbott), which provided the coronary pressure guidewires (Radi

Medical Systems). None of the funders had a role in the design or conduct of the trial, data collection, or management. The steering committee vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

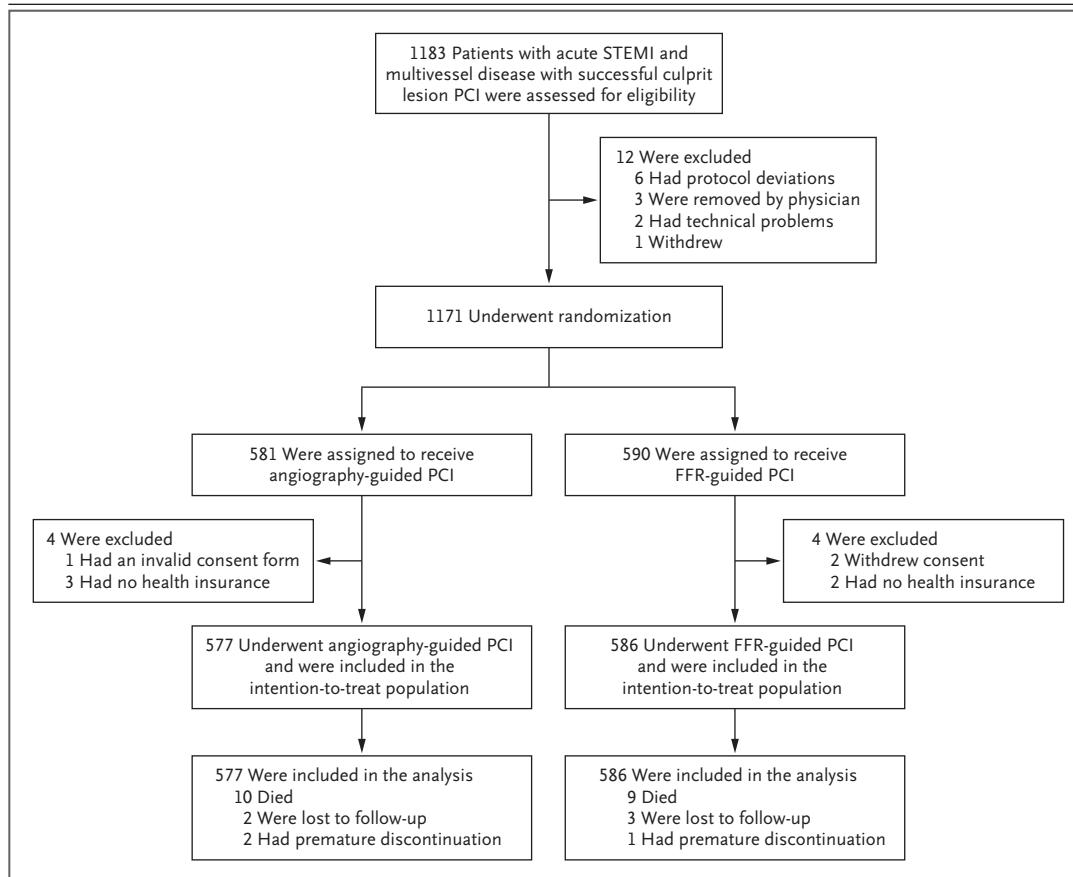
### PATIENTS

All adult patients ( $\geq 18$  years of age) with STEMI who had undergone successful PCI of an infarct-related artery (primary PCI, rescue PCI, or pharmacoinvasive PCI) were candidates for enrollment. Successful PCI of the infarct-related artery was defined as having a Thrombolysis in Myocardial Infarction (TIMI) score of at least 2 and a residual stenosis measure of less than 30% for the culprit lesion as well as for any additional substantial stenoses in the infarct-related artery. Additional key eligibility criteria were multivessel disease in which at least one nonculprit coronary artery (i.e., major epicardial coronary artery or major side branch measuring  $\geq 2.0$  mm in diameter) had at least one lesion with stenosis of 50% or more in diameter (by visual assessment) that was judged to be amenable to PCI by the interventional cardiologist performing the procedure. Lesions were identified as not being infarct-related by comparison with the infarct territory as determined on diagnostic electrocardiography (ECG).

Key exclusion criteria were single-vessel disease, hemodynamic instability (i.e., cardiogenic shock), previous coronary-artery bypass grafting (CABG) surgery, coronary-artery calcification or chronic total occlusion, failed culprit-lesion PCI, and referral for CABG. A full list of the inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

### CONSENT AND RANDOMIZATION

Informed consent was obtained after completion of the procedure on the infarct-related artery, either orally (with subsequent signature) in the case of immediate PCI of the nonculprit arteries, or in writing after the initial procedure had been completed in the case of delayed (staged) PCI of the nonculprit arteries. Randomization was performed in a 1:1 ratio with the use of randomly permuted blocks of 2 or 4 and was stratified according to the trial site and timing of the procedure (immediate or staged). Randomization was performed immediately after consent was



**Figure 1. Enrollment and Outcomes.**

Among the patients who were excluded from the primary analysis were five patients who did not have health insurance, since such patients are prohibited by French law from inclusion in interventional randomized clinical trials. At the 1-year follow-up, these patients had not had any clinical events. Two patients withdrew their consent after randomization to the group assigned to undergo percutaneous coronary intervention (PCI) guided by fractional flow reserve (FFR). The first one withdrew before the index PCI. The second withdrew 1 month after randomization and stopped participating in the trial. These two patients declined to have their previously collected personal data included in the trial, so these patients were excluded from all the analyses. Three other patients (one in the FFR-guided group and two in the angiography-guided group) stopped participating in the trial before the 12-month follow-up visit but consented to the use of their data. Therefore, their data were kept in the analyses until the date of their withdrawal. These three withdrawals occurred 1 day, 183 days, and 280 days after PCI. STEMI denotes ST-elevation myocardial infarction.

obtained through an Internet-based centralized system (CleanWEB software, Telemedicine Technologies).

#### INTERVENTIONS

All operators were experienced in the use of the FFR technique in other clinical settings. (Details regarding this pressure-wire–based technique for assessing the functional severity of coronary lesions are provided in the Supplementary Appendix.) In the FFR-guided group, operators measured FFR in all lesions that were judged to

have stenosis of at least 50% on visual estimation by means of a Radi Medical Systems wire (Abbott).

An FFR value of 0.80 or less was considered to be clinically important, with a recommendation that PCI on the corresponding lesion be performed. Repeating FFR measurement after completion of the PCI was encouraged. An FFR value of more than 0.80 was not considered to be clinically important, and PCI on the corresponding lesion was not to be performed.

In both groups, complete revascularization

<b>Table 1. Characteristics of the Patients at Baseline.*</b>		
<b>Characteristic</b>	<b>FFR-Guided Group (N = 586)</b>	<b>Angiography-Guided Group (N = 577)</b>
<b>Age — yr</b>		
Mean	62.5±11.0	61.9±11.4
Median (IQR)	61.0 (54.3–70.0)	62.0 (54.0–70.0)
Median body-mass index (IQR) †	26.7 (24.2–29.1)	26.6 (24.4–29.7)
Male sex — no. (%)	498 (85.0)	468 (81.1)
<b>Medical history — no./total no. (%)</b>		
Hypertension	253/586 (43.2)	262/577 (45.4)
Diabetes mellitus	107/586 (18.3)	82/577 (14.2)
Hypercholesterolemia‡	232/586 (39.6)	237/577 (41.1)
Current smoker	235/586 (40.1)	210/577 (36.4)
Family history of CAD	173/579 (29.9)	153/573 (26.7)
Previous myocardial infarction	45/586 (7.7)	31/577 (5.4)
Previous PCI	59/586 (10.1)	44/577 (7.6)
Previous stroke	16/586 (2.7)	17/573 (3.0)
Peripheral-artery disease	16/586 (2.7)	23/577 (4.0)
Chronic renal insufficiency	11/586 (1.9)	12/577 (2.1)
Cancer§	23/586 (3.9)	17/577 (3.0)
<b>Location of infarct — no./total no. (%) ¶</b>		
Anterior	173/580 (29.8)	197/570 (34.6)
Inferior	359/580 (61.9)	319/570 (56.0)
Posterior	9/580 (1.6)	17/570 (3.0)
Posterolateral	36/580 (6.2)	31/570 (5.4)
Left bundle-branch block	3/580 (0.5)	6/570 (1.1)
<b>Arteries with stenosis — no./total no. (%)</b>		
1	7/582 (1.2)	11/573 (1.9)
2	424/582 (72.9)	447/573 (78.0)
3	151/582 (25.9)	115/573 (20.1)
Killip class ≥II — no./total no. (%)	37/556 (6.7)	29/549 (5.3)
<b>Glycated hemoglobin</b>		
Median value (IQR) — %	5.8 (5.5–6.2)	5.7 (5.5–6.1)
Missing data — no. of patients	110	98
<b>Low-density lipoprotein cholesterol</b>		
Median value (IQR) — mmol/liter	1.2 (0.9–1.5)	1.3 (1.0–1.6)
Missing data — no. of patients	43	28
<b>Peak creatinine</b>		
Median value (IQR) — μmol/liter	88.0 (77.8–100.0)	87.0 (75.0–101.0)
Missing data — no. of patients	2	1
<b>Left ventricular ejection fraction</b>		
Median value (IQR) — %	50 (45–58)	50 (45–60)
Missing data — no. of patients	26	20

\* Plus–minus values are means ±SD. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. CAD denotes coronary artery disease, FFR fractional flow reserve, IQR interquartile range, and PCI percutaneous coronary intervention.

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

‡ Hypercholesterolemia was defined as the receipt of treatment with cholesterol-lowering medication or an elevated level of total cholesterol (>200 mg per deciliter [5.2 mmol per liter]).

§ A diagnosis of cancer did not include nonmelanoma skin cancer.

¶ The location of the infarct was determined on diagnostic electrocardiography.

|| In patients with single-vessel disease, the infarct-related lesion and the nonculprit lesion were in different major side branches of the same main coronary artery.

during the index procedure was encouraged. However, complete revascularization could also be performed during a separate staged procedure as early as possible, before hospital discharge and within 5 days after the initial procedure. The use of drug-eluting stents was encouraged.<sup>10</sup> Patients in both groups received guideline-directed medical therapy.<sup>1</sup>

#### **FOLLOW-UP**

Follow-up was conducted during outpatient clinic visits scheduled at 30 days and at 6, 12, and 36 months after primary revascularization. Patients for whom no outpatient visit was possible were contacted by mail or telephone. All the patients who were enrolled in the trial were monitored for adherence to the protocol, and all critical data reported in the case report form were monitored.

#### **TRIAL OUTCOMES**

The primary outcome was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization at 1 year. Secondary outcomes were as follows: procedure time; total amount of contrast agent used during the initial hospital stay and at 1, 6, 12, and 36 months; individual components of the primary outcome; any revascularization (urgent or elective); urgent revascularization of any target lesion in a nonculprit artery; rehospitalization for angina or for acute heart failure; any rehospitalization in a cardiology department or service; functional class according to the Canadian Cardiovascular Society (CCS) classification of angina; health-related quality of life, as measured by the score on the European Quality of Life–5 Dimensions (EQ-5D) scale<sup>11</sup>; the number of antianginal medications; and cost-effectiveness and cost-utility analyses at 1 year. (Results of the economic analyses are not included in this report.) Definitions of the trial outcomes are provided in the Supplementary Appendix.

#### **STATISTICAL ANALYSIS**

We calculated that a sample size of 1170 patients would provide the trial with a power of at least 80% (at a two-sided alpha of 5%) to reject the null hypothesis of no between-group difference,

assuming that the incidence of the primary outcome was 9.5% with the FFR-guided strategy and 15% with the angiography-guided strategy, given an anticipated 5% loss to follow-up at 1 year. These estimates were based on the results of previous studies, as described in the Supplementary Appendix.<sup>12-16</sup> No interim analysis was planned.

All analyses were performed on an intention-to-treat basis. The incidence of clinical events and other categorical data are summarized as percentages. Continuous data are presented as means ( $\pm$ SD) or as medians and interquartile ranges.

Kaplan–Meier plots were constructed for time-to-event outcomes, with treatment effects estimated with the use of Cox models and results presented as hazard ratios with 95% confidence intervals.<sup>17</sup> A Schoenfeld test was used to check the proportional-hazards assumption. To take into account any deaths early in the trial, we performed sensitivity analyses using Fine and Gray models.<sup>18</sup> For the numbers of antianginal medications at 12 months, a negative binomial model was used to estimate the mean number of medications in each group. Treatment effect was estimated with the use of the ratio of the two means. For the CCS classification of angina ( $\geq$ I vs. asymptomatic), a logistic-regression model was used to estimate the treatment effect. All the models were adjusted for the timing of the procedure (stratification factor).

Planned subgroup analyses of the primary outcome were performed according to age (<65 years vs.  $\geq$ 65 years), sex, presence of risk factors (diabetes, hypertension, dyslipidemia, and family history of coronary artery disease), history of cardiovascular disease, and clinical presentation (Killip class I vs.  $\geq$ II).

For the primary outcome, a two-sided P value of less than 0.05 was considered to indicate statistical significance. Secondary outcomes are presented with effect-size estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, and any inferences drawn from these intervals may not be reproducible. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute), and R software, version 4.0.2 (R Core Team).

<b>Table 2. Procedural Data.*</b>		
<b>Variable</b>	<b>FFR-Guided Group (N = 586)</b>	<b>Angiography-Guided Group (N = 577)</b>
<b>Lesion location and characteristics†</b>		
Location of culprit lesion — no. of patients (%)		
Left main coronary artery	3 (0.5)	4 (0.7)
Left anterior descending artery	182 (31.1)	196 (34.0)
Circumflex artery	124 (21.2)	127 (22.0)
Right coronary artery	281 (48.0)	260 (45.1)
Total no. of lesions in infarct-related arteries	718	706
Location of nonculprit lesion — no. of patients (%)		
Left main coronary artery	7 (1.2)	9 (1.6)
Left anterior descending artery	351 (59.9)	316 (54.8)
Circumflex artery	239 (40.8)	222 (38.5)
Right coronary artery	179 (30.5)	172 (29.8)
Total no. of nonculprit lesions	980	891
Stenosis in nonculprit lesion on visual estimation — no./total no. of lesions (%)		
<50%	29/980 (3.0)	18/891 (2.0)
50–69%	414/980 (42.2)	265/891 (29.7)
70–90%	466/980 (47.6)	559/891 (62.7)
>90%	52/980 (5.3)	40/891 (4.5)
Missing data	19/980 (1.9)	9/891 (1.0)
<b>PCI of nonculprit lesion‡</b>		
Staged intervention of nonculprit lesion — no. of patients (%)	566 (96.6)	553 (95.8)
FFR procedures attempted — no. of patients (%)	561 (95.7)	NA
FFR before PCI of nonculprit lesion		
Mean value	0.79±0.11	NA
Missing data — no./total no. of lesions	154/980	
FFR after PCI of nonculprit lesion		
Mean value	0.90±0.06	NA
Missing data — no./total no. of lesions	802/980	
Lesions with FFR		
≤0.80 — no./total no. (%)	460/826 (55.7)	NA
>0.80 — no./total no. (%)	366/826 (44.3)	NA
Lesions with PCI — no./total no. of lesions (%)	546/980 (55.7)	806/891 (90.5)
Patients with ≥1 PCI — no./total no. of patients (%)	388/586 (66.2)	560/577 (97.1)
<b>Procedural characteristics</b>		
Procedure duration for culprit lesion		
Median (IQR) — min	31 (21–45)	32 (20–46)
Missing data — no. of patients	45	47
Procedure duration for nonculprit lesion		
Median (IQR) — min	35 (22–50)	30 (20–44)
Missing data — no./total no. of patients	74/566	59/553

Variable	FFR-Guided Group (N=586)	Angiography-Guided Group (N=577)
Volume of contrast agent used for culprit lesion		
Median (IQR) — ml	148.0 (109.5–180.0)	140.0 (110.0–171.5)
Missing data — no. patients	82	77
Volume of contrast agent used for nonculprit lesion		
Median (IQR) — ml	110.0 (71.8–170.0)	110.0 (80.0–150.0)
Missing data — no./total no. of patients	78/566	69/553
Median length of hospital stay (IQR) — days	5 (4–6)	5 (4–6)

\* Plus–minus values are means  $\pm$ SD. Percentages may not total 100 because of rounding. NA denotes not applicable.

† Data were obtained at the angiographic core laboratory.

‡ In 25 patients in the FFR-guided group, nonculprit coronary artery lesions were also treated because no FFR measurement was obtained; in 4 patients, these lesions were treated even though the FFR was higher than 0.80. The decision to treat was based on the angiographic results.

## RESULTS

### PATIENTS

A total of 1171 patients with STEMI and multivessel disease were enrolled and underwent randomization (590 to the FFR-guided group and 581 to the angiography-guided group). Although screening logs were not maintained for the trial, screening data for the largest recruiting center are presented in Table S1 in the Supplementary Appendix. Four patients in each group withdrew consent or were excluded for violations of the inclusion criteria. In addition, 5 patients were lost to follow-up, and 3 patients withdrew from the trial during follow-up (Fig. 1).

The characteristics of the patients at baseline were similar in the two groups, with a mean age of  $62.2 \pm 11.2$  years (Table 1). Infarct location as determined by ECG was seen mostly in the inferior leads. Baseline angiographic characteristics were also well balanced (Table 2 and Tables S2 and S3). The mean number of lesions in the infarct-related artery (including the culprit lesion) was  $1.2 \pm 0.5$  (median, 1; interquartile range, 1 to 1) in both groups. Medications that were administered during the procedure, at discharge, and at 1 year are described in Table S4.

### NONCULPRIT LESION INTERVENTION

Staged intervention for nonculprit lesions was used in more than 95% of the patients in each group. The mean time delay between the interventions was  $2.6 \pm 1.4$  days in the FFR-guided

group and  $2.7 \pm 3.3$  days in the angiography-guided group.

In the FFR-guided group, FFR measurement was attempted in 561 of 586 patients (95.7%) and failed in 13 patients with no severe adverse event (Table 2 and Table S3). PCI was performed in 388 of 586 patients (66.2%) in the FFR-guided group and in 560 of 577 patients (97.1%) in the angiography-guided group. (Owing to the stricter criteria for performing PCI with FFR, more patients in the angiography-guided group than in the FFR-guided group underwent the procedure.)

The mean number of stents used per patient for nonculprit lesions was  $1.01 \pm 0.99$  in the FFR-guided group and  $1.50 \pm 0.86$  in the angiography-guided group. Drug-eluting stents were used in 99% of all the patients. The median procedural time related to treatment of nonculprit lesions was 35 minutes in the FFR-guided group and 30 minutes in the angiography-guided group.

### PRIMARY OUTCOME

Clinical outcomes are summarized in Table 3. At 1 year, the primary outcome had occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 (4.2%) in the angiography-guided group (hazard ratio, 1.32; 95% confidence interval [CI], 0.78 to 2.23;  $P=0.31$ ) (Fig. 2). The  $P$  value for the Schoenfeld test was 0.25, thus confirming the proportional hazards. The results of a post hoc analysis performed with the use of an extended Cox model that included a time-dependent coefficient with a cutoff at

**Table 3. Prespecified Clinical Outcomes at 1 Year.\***

Outcomes	FFR-Guided Group (N=586)	Angiography-Guided Group (N=577)	Hazard Ratio or Difference (95% CI) <sup>†</sup>	P Value
<b>Primary outcome</b>				
Composite outcome — no. (%) <sup>‡</sup>	32 (5.5)	24 (4.2)	1.32 (0.78–2.23)	0.31
Death from any cause	9 (1.5)	10 (1.7)	0.89 (0.36–2.20)	
Nonfatal myocardial infarction <sup>§</sup>	18 (3.1)	10 (1.7)	1.77 (0.82–3.84)	
Unplanned hospitalization leading to urgent revascularization				
Patients with condition — no. (%)	15 (2.6)	11 (1.9)	1.34 (0.62–2.92)	
Treatment of target lesions in nonculprit artery by urgent revascularization — no./total no. (%)	8/15 (53.3)	3/11 (27.3)	—	
<b>Secondary outcomes</b>				
Key outcomes — no. (%)				
Stent thrombosis	4 (0.7)	6 (1.0)	0.65 (0.19–2.32)	
Any revascularization <sup>¶</sup>	38 (6.5)	26 (4.5)	1.45 (0.88–2.38)	
Hospitalization for heart failure	9 (1.5)	11 (1.9)	0.82 (0.34–1.98)	
Hospitalization for recurrent ischemia	32 (5.5)	19 (3.3)	1.68 (0.95–2.97)	
Any hospitalization in a cardiology department or service	68 (11.6)	46 (8.0)	1.49 (1.03–2.17)	
<b>Functional status</b>				
Mean no. of antianginal medications used per patient <sup>  </sup>	1.0±0.5	1.0±0.5	1.01 (0.90–1.14)**	
QALY based on EQ-5D-5L score <sup>††</sup>	0.86±0.19	0.87±0.18	0.01 (0.00–0.01)**	
Recurrent ischemia				
Patients with condition — no. (%)	32 (5.5)	19 (3.3)	0.82 (0.21–3.24) <sup>‡‡</sup>	
Patients with CCS class ≥II — no./total no. (%) <sup>§§</sup>	20/32 (62.5)	13/19 (68.4)	—	

\* Plus-minus values are means ±SD.

<sup>†</sup> The widths of the confidence intervals for the hazard ratios have not been adjusted for multiplicity, and any inferences drawn from these intervals may not be reproducible. A dash indicates that no between-group statistical comparison was performed, since data are presented for information only.

<sup>‡</sup> The composite primary outcome was death from any cause, nonfatal myocardial infarction, and unplanned hospitalization leading to urgent revascularization at 1 year.

<sup>§</sup> Periprocedural myocardial infarction was reported in 7 patients in the FFR-guided group and in 2 patients in the angiography-guided group.

<sup>¶</sup> Any revascularization includes all first revascularization procedures that were elective or urgent, whether clinically indicated or not, between the time of the index procedure and follow-up at 1 year.

<sup>||</sup> Antianginal medications included beta-blockers, calcium antagonists, and nitrates. The mean number of medications per patient was estimated by means of a negative binomial model.

\*\* This value is the absolute between-group difference in effect.

<sup>††</sup> The quality-adjusted life-year (QALY) represents a patient's survival time weighted by the quality of life represented by utility. Utility was derived from the European Quality of Life–5 Dimensions 5-Levels questionnaire (EQ-5D-5L) health-related quality-of-life questionnaire, with scores ranging from –0.5 to 1.0, with higher scores indicating a better quality of life. The between-group difference in QALYs was estimated by bootstrapping.

<sup>‡‡</sup> This comparison is reported as an odds ratio, as estimated by a logistic-regression model.

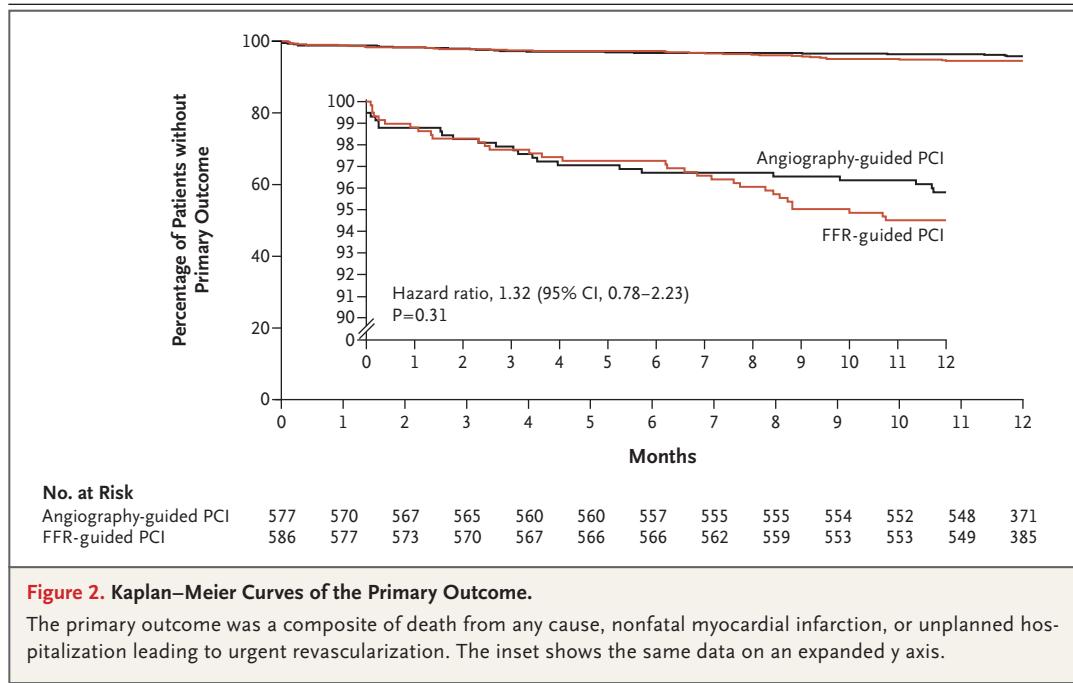
<sup>§§</sup> Angina was assessed according to the Canadian Cardiovascular Society (CCS) Functional Classification of Angina Pectoris as follows: angina only with strenuous exertion, class I; angina with moderate exertion, class II; angina with mild exertion, class III; and angina at rest, class IV.

7 months are provided in the Supplementary Appendix. The lack of benefit of FFR with respect to the primary outcome was consistent across the prespecified subgroups (Fig. S1). In the FFR-guided group, a primary outcome event occurred in 16 of 388 patients (4.1%) who had undergone

PCI as compared with 16 of 198 (8.1%) who had not undergone PCI (Table S5).

#### SECONDARY CLINICAL OUTCOMES

Death from any cause occurred in 9 patients in the FFR-guided group and in 10 patients in the



angiography-directed group (hazard ratio, 0.89; 95% CI, 0.36 to 2.20). Nonfatal reinfarction occurred in 18 and 10 patients, respectively (hazard ratio, 1.77; 95% CI, 0.82 to 3.84), and unplanned hospitalization leading to urgent revascularization in 15 and 11 patients, respectively (hazard ratio, 1.34; 95% CI, 0.62 to 2.92). Kaplan–Meier curves for these three components of the primary outcome are shown in Figure S2. Causes of death are shown in Table S6. For clinical outcomes that did not include death, competing-risks analyses were performed, which showed results similar to those in the main analyses (Table S7).

## DISCUSSION

Among patients with STEMI and multivessel disease who had undergone successful PCI of the infarct-related artery, an FFR-guided strategy for complete revascularization was not superior to an angiography-guided strategy for reducing the risk of the composite primary outcome (death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization at 1 year). The individual components of the primary outcome, as well as all other clinical outcomes, did not differ significantly between the two groups.

In patients with STEMI and multivessel disease, investigators in the Third Danish Study of Optimal Acute Treatment of Patients with ST-Elevation Myocardial Infarction (DANAMI-3)<sup>7</sup> and the Compare-Acute trial<sup>8</sup> found that FFR-guided revascularization of nonculprit arteries was associated with a lower incidence of major adverse cardiac events than revascularization of culprit lesions only, a difference that was driven by a lower number of subsequent PCI procedures. Likewise, in the large Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial,<sup>9</sup> complete revascularization was superior to revascularization of only the culprit lesion, with respect not only to the number of subsequent PCI procedures but also to a composite outcome of cardiovascular death or myocardial infarction. Hence, current guidelines recommend that routine complete revascularization in patients with STEMI and multivessel disease be considered before hospital discharge.<sup>1,19</sup> In this context, a comparison of an FFR-guided approach with an angiography-guided approach for the use of PCI in nonculprit lesions in patients with STEMI and multivessel disease was appropriate.

In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial,<sup>3</sup> routine measurement of FFR during PCI in pa-

tients with stable multivessel disease resulted in a lower incidence of major adverse events than angiography-guided PCI at 1 year. It is not clear why the findings of the FAME trial differ from those of our trial, although the results of one previous trial suggest that the use of FFR may actually be disadvantageous in patients with STEMI.<sup>20</sup>

In our trial, the event-rate curves for the primary outcome diverged after 6 months. Although this divergence may constitute an artifact in view of the limited number of events, it is also possible that some lesions that had been left untreated in the FFR-guided group worsened during follow-up, which led to the occurrence of clinical events. Such a pattern has been observed after 5 years among patients with stable disease.<sup>21</sup>

For the treatment of nonculprit lesions, we encouraged investigators to perform complete revascularization during the index procedure. In practice, however, this was rarely done, since only 4% of the patients had an immediate nonculprit-lesion intervention, which suggests that FFR measurement that is performed at the same time as PCI of the infarct-related artery may be unrealistic under routine clinical conditions. Our results should therefore be interpreted as pertaining to patients who are undergoing staged multivessel procedures. Staged procedures expose the patient to a second procedure with its associated risks, and in some instances the second procedure proves unnecessary since no intervention will be performed. The performance of FFR during the initial procedure, which would result in fewer additional procedures, could save exposure to radiation and contrast materials. However, there is concern that prolonging the index procedure could lead to a higher risk during a period of acute vulnerability (active prothrombotic state, acute inflammation, and risks of hemodynamic instability and arrhythmia) than repeating the procedure 48 hours later when the patient's condition is more stable. Also, assessment of nonculprit lesions may be uncertain during the acute event, when vasospasm may lead to an overestimate of stenosis severity. Finally, the validity of FFR in patients with acute myocardial infarction, and particularly anterior myocardial infarction, is debated.<sup>22,23</sup> Only a randomized trial comparing immediate with staged PCI

will resolve the question of the most effective timing of multivessel procedures in patients with STEMI.

Our trial has several limitations. Only limited information was captured regarding patients who had undergone screening but were not eligible to participate in the trial. Because of the lower-than-expected incidence of events, our trial had less statistical power than intended. As a consequence, although we found no significant benefit of the FFR-guided strategy, the confidence intervals for the hazard ratio for the primary outcome are quite wide and compatible with either a 22% relative benefit or a 123% relative harm associated with the FFR-guided strategy. Given the low incidence of events observed, more than 8000 patients would be needed to show a 15% lower relative risk of the composite outcome; this reduction would correspond to a lower absolute risk of 0.6 percentage points for the FFR-guided strategy, a difference of doubtful clinical significance. These considerations may make any attempt at future comparisons between these two strategies difficult. Finally, for logistic reasons, the evaluation of the completeness of revascularization was not performed by a core laboratory and relied on the investigators' evaluations.

In patients with STEMI and multivessel disease undergoing PCI, we found no significant benefit of an FFR-guided strategy as compared with an angiography-guided strategy in the management of nonculprit lesions with respect to the risk of death, myocardial infarction, or urgent revascularization at 1 year. However, given the wide confidence intervals for the estimate of effect, the findings do not allow for a conclusive interpretation.

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## APPENDIX

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