

ORIGINAL ARTICLE

Fractional Flow Reserve–Guided Multivessel Angioplasty in Myocardial Infarction

Pieter C. Smits, M.D., Ph.D., Mohamed Abdel-Wahab, M.D., Franz-Josef Neumann, M.D., Bianca M. Boxma-de Klerk, Ph.D., Ketil Lunde, M.D., Carl E. Schotborgh, M.D., Zsolt Piroth, M.D., David Horak, M.D., Adrian Wlodarczak, M.D., Paul J. Ong, M.D., Rainer Hambrecht, M.D., Oskar Angerås, M.D., Gert Richardt, M.D., Ph.D., and Elmir Omerovic, M.D., for the Compare-Acute Investigators*

ABSTRACT

BACKGROUND

In patients with ST-segment elevation myocardial infarction (STEMI), the use of percutaneous coronary intervention (PCI) to restore blood flow in an infarct-related coronary artery improves outcomes. The use of PCI in non–infarct-related coronary arteries remains controversial.

METHODS

We randomly assigned 885 patients with STEMI and multivessel disease who had undergone primary PCI of an infarct-related coronary artery in a 1:2 ratio to undergo complete revascularization of non–infarct-related coronary arteries guided by fractional flow reserve (FFR) (295 patients) or to undergo no revascularization of non–infarct-related coronary arteries (590 patients). The FFR procedure was performed in both groups, but in the latter group, both the patients and their cardiologist were unaware of the findings on FFR. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, revascularization, and cerebrovascular events at 12 months. Clinically indicated elective revascularizations performed within 45 days after primary PCI were not counted as events in the group receiving PCI for an infarct-related coronary artery only.

RESULTS

The primary outcome occurred in 23 patients in the complete-revascularization group and in 121 patients in the infarct-artery-only group that did not receive complete revascularization, a finding that translates to 8 and 21 events per 100 patients, respectively (hazard ratio, 0.35; 95% confidence interval [CI], 0.22 to 0.55; $P < 0.001$). Death occurred in 4 patients in the complete-revascularization group and in 10 patients in the infarct-artery-only group (1.4% vs. 1.7%) (hazard ratio, 0.80; 95% CI, 0.25 to 2.56), myocardial infarction in 7 and 28 patients, respectively (2.4% vs. 4.7%) (hazard ratio, 0.50; 95% CI, 0.22 to 1.13), revascularization in 18 and 103 patients (6.1% vs. 17.5%) (hazard ratio, 0.32; 95% CI, 0.20 to 0.54), and cerebrovascular events in 0 and 4 patients (0 vs. 0.7%). An FFR-related serious adverse event occurred in 2 patients (both in the group receiving infarct-related treatment only).

CONCLUSIONS

In patients with STEMI and multivessel disease who underwent primary PCI of an infarct-related artery, the addition of FFR-guided complete revascularization of non–infarct-related arteries in the acute setting resulted in a risk of a composite cardiovascular outcome that was lower than the risk among those who were treated for the infarct-related artery only. This finding was mainly supported by a reduction in subsequent revascularizations. (Funded by Maasstad Cardiovascular Research and others; Compare-Acute ClinicalTrials.gov number, NCT01399736.)

From the Department of Cardiology, Maasstad Ziekenhuis, Rotterdam (P.C.S., B.M.B.-K.), and the Department of Cardiology, Haga Ziekenhuis, The Hague (C.E.S.) — both in the Netherlands; the Department of Cardiology, Heart Center, Segeberger Kliniken, Bad Segeberg (M.A.-W., G.R.), the Department of Cardiology, University Heart Center Freiburg–Bad Krozingen, Bad Krozingen (F.-J.N.), and the Department of Cardiology, Klinikum Links der Weser, Bremen (R.H.) — all in Germany; the Department of Cardiology, Rigshospitalet, University of Oslo, Oslo (K.L.); the Department of Cardiology, György Hungarian Institute of Cardiology, Budapest, Hungary (Z.P.); the Department of Cardiology, Liberec Regional Hospital, Liberec, Czech Republic (D.H.); the Department of Cardiology, Miedziove Centrum Zdrowia, Lubin, Poland (A.W.); the Department of Cardiology, Tan Tock Seng Hospital, Singapore (P.J.O.); and the Department of Cardiology, Gothenburg University Hospital, Gothenburg, Sweden (O.A., E.O.). Address reprint requests to Dr. Smits at the Department of Cardiology, Maasstad Hospital, Maasstadweg 21, 3079 DZ Rotterdam, the Netherlands, or at smitsp@maasstadziekenhuis.nl.

*A complete list of investigators in the Compare-Acute study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 18, 2017, at NEJM.org.

N Engl J Med 2017;376:1234–44.

DOI: 10.1056/NEJMoa1701067

Copyright © 2017 Massachusetts Medical Society.

PATIENTS PRESENTING WITH ACUTE ST-segment elevation myocardial infarction (STEMI) are best treated with percutaneous coronary intervention (PCI) of the infarct-related coronary artery and the implantation of stents.^{1,2} Approximately 50% of these patients have additional, severe stenotic lesions in non-infarct-related coronary arteries.³⁻⁶ The need for a high-quality, evidence-directed treatment strategy for non-infarct-related coronary artery lesions remains.

On the basis of nonrandomized clinical trials, a conservative approach to non-infarct-related coronary artery lesions has been advocated previously.^{1,2,7} Two randomized clinical trials challenged this concept by showing that the preventive use of stents for non-infarct-related coronary artery lesions in the acute phase reduced the risk of subsequent adverse events.^{8,9} In both trials, the decision to use stents for these lesions was based on angiographic appearance, irrespective of whether the lesions were causing ischemia or symptoms. The question of whether preventive stenting is always needed is debatable, because coronary angiography may both underestimate and overestimate the functional severity of a lesion and may lead to overtreatment, with additional costs and risks.¹⁰⁻¹²

Fractional flow reserve (FFR) is a well-established pressure-wire-based technique that is used to assess the functional severity of coronary lesions.¹³⁻¹⁵ The use of FFR to guide decisions regarding the use of PCI in patients with stable coronary artery disease has been shown to reduce the risk of serious adverse events as compared with angiography-guided PCI or conservative treatment.^{12,16}

A recent randomized trial that evaluated an FFR-guided approach to justify the use of PCI for non-infarct-related coronary artery lesions among patients presenting with STEMI and multivessel disease showed that patients who had complete staged (FFR-guided) revascularization had significantly fewer repeat revascularizations than those who received treatment for the infarct-related coronary artery only.¹⁷ The aim of the Compare-Acute trial was to examine whether the strategy of FFR-guided treatment of non-infarct-related coronary artery lesions in the acute setting is superior to the strategy of infarct-related, coronary-artery-only treatment in patients with STEMI and multivessel disease.

METHODS

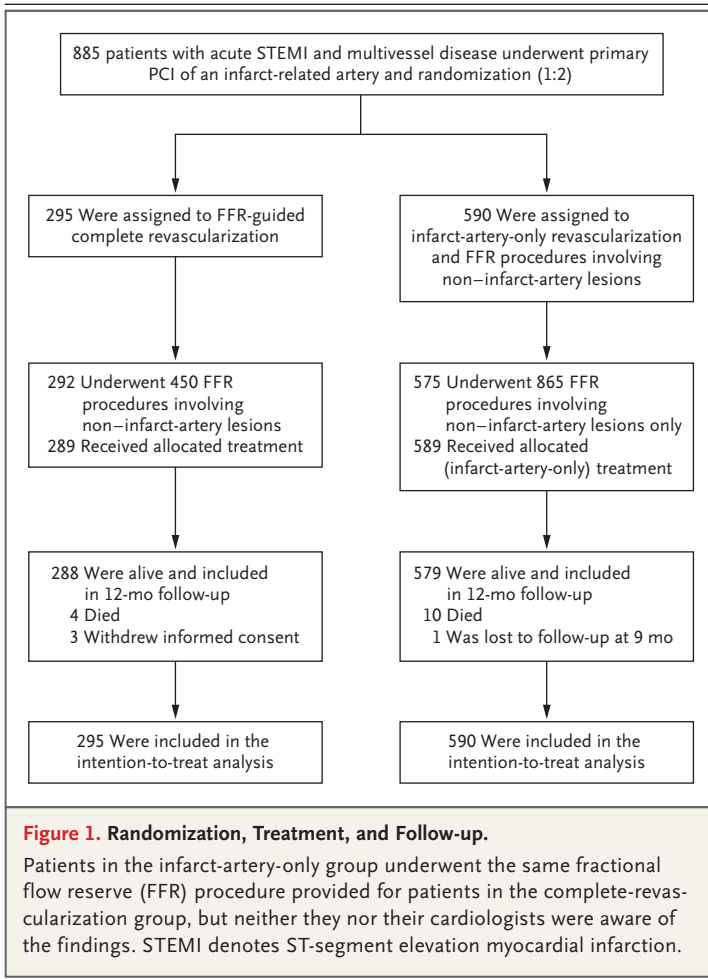
STUDY DESIGN AND OVERSIGHT

The Compare-Acute trial was an investigator-initiated, prospective, multicenter, randomized trial in which FFR-guided, complete revascularization in the acute setting of primary PCI was compared with infarct-related, coronary-artery-only revascularization in patients with STEMI. Patients in the infarct-artery-only group underwent the FFR procedure but were not aware of the findings. We enrolled 885 patients with STEMI and multivessel disease in 24 participating centers in Europe and Asia.¹⁸

All patients 18 through 85 years of age who presented with STEMI within 12 hours after symptom onset and who had an indication for primary PCI were eligible for enrollment if the non-infarct-related coronary arteries (or their major side branches of at least 2.0 mm in diameter) showed lesions with stenosis of 50% or more according to quantitative coronary angiography or visual assessment and were determined to be appropriate candidates for PCI by the interventional cardiologist (who performed the PCI). Non-infarct-related coronary artery lesions were those identified as not being responsible for the acute myocardial infarction on the basis of their appearance on electrocardiography (ECG) and angiography.

A detailed study outline, a list of the criteria used for exclusion or inclusion in the study (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and definitions of end points have been published previously.¹⁸ The most important criteria for study exclusion were left main coronary artery disease, chronic total occlusion, severe stenosis, with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or less in the non-infarct-related coronary artery, a suboptimal result or complications after treatment of an infarct-related coronary artery, severe valve dysfunction, and Killip class III or IV.

The ethics committee at each participating site approved the study. A steering committee provided trial oversight, and a data and safety monitoring committee provided advice as to whether the trial should be stopped because of clear evidence of benefit or harm. Independent clinical research associates monitored the sites and gathered the data. All events were analyzed and adjudicated by an independent clinical evaluation com-



mittee at a clinical research organization (Diagram). All recurrent revascularizations were evaluated by the clinical evaluation committee for both the extent of need (urgent or elective) and indication (clinically indicated or not). A revascularization was considered to be clinically indicated if quantitative coronary angiography revealed a stenosis of 50% or more and one of the following criteria was met: a history of recurrent angina pectoris, presumably related to the target vessel; ischemic changes on ECG at rest or during exercise testing (or the equivalent), presumably related to the target vessel; abnormal results on any invasive functional diagnostic test (e.g., a Doppler pattern of flow velocity reserve or fractional flow reserve during follow-up); or stenosis of 70% or more on quantitative coronary angiography in the absence of signs or symptoms of ischemia.

The companies providing grant support had some comments on the proposed protocol and minor modifications were made. They had no involvement in the collection, analysis, or interpretation of the data or in the writing of the manuscript. The steering committee vouches for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, available at NEJM.org.

TREATMENT

Informed consent was obtained before the procedure in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. To avoid delay in treatment, patients provided oral consent in the presence of a third person not involved in the study either before or during primary PCI. Written consent was obtained after the procedure.

After successful primary PCI of the infarct-related coronary artery (preferably with placement of everolimus-eluting stents), eligible patients who had provided informed consent underwent randomization and FFR measurements in the non-infarct-related coronary artery containing lesions with an angiographic stenosis of 50% or more. Only hemodynamically stable patients with non-infarct-related lesions for which FFR and PCI were deemed appropriate were eligible for randomization.

Patients were randomly assigned in a ratio of 1:2 with the use of closed, opaque envelopes to FFR-guided complete revascularization or treatment of the infarct artery only. Figure 1 shows the randomization and follow-up of patients.

In the complete-revascularization group, FFR measurements were used to guide the decision as to whether percutaneous revascularization was appropriate. In the case of non-infarct-related coronary arteries with flow-limiting lesions (FFR, ≤ 0.80), PCI — preferably with everolimus-eluting stents — was performed, generally during the same intervention; this step could be delayed at the operator's discretion (e.g., for complex lesions or logistical problems) but had to be performed during the index hospitalization and preferably within 72 hours.

In patients receiving infarct-related-artery treatment only (the infarct-artery-only group), the procedure was stopped after FFR measurements were obtained. Each patient was referred to his or her treating cardiologist. Both the patient and the

treating cardiologist were unaware of the findings on FFR but were aware of the angiography. A management plan based on current practice guidelines was recommended, but further investigations and management of care were carried out at the discretion of the treating cardiologist. Thus, the treating cardiologist could decide whether revascularization of non-infarct-related coronary arteries was needed on the basis of tests conducted to detect ischemia, symptoms, or clinical judgment. Elective, clinically indicated revascularizations performed within 45 days after the primary intervention were not counted as events, in accordance with the protocol. Urgent revascularizations performed within 45 days or further revascularizations performed thereafter were counted as events. Additional patient care, including the implementation of anticoagulant and antithrombotic regimens, was performed in accordance with contemporary guidelines.

FFR MEASUREMENT

Sites that were obstructed by 50% or more were identified during angiography. A commercially available pressure wire (St. Jude Medical) was used to measure the Pa/Pd ratio at rest and during maximally induced hyperemia. Hyperemia was achieved through intravenous administration of 140 μg of adenosine per kilogram of body weight per minute or through repeated, dose-increasing, intracoronary injections of adenosine boluses (40 to 100 μg for the right coronary artery and 60 to 100 μg for the left coronary artery).

FOLLOW-UP

Follow-up was conducted during outpatient clinic visits that took place 30 days and 12, 24, and 36 months after primary revascularization. Patients for whom no outpatient visit was scheduled were contacted through the postal service or by telephone. The first five patients enrolled in the study at each study center were monitored for adherence to the protocol and provided data on variables listed in the case report form; thereafter, random monitoring was performed. All reported events were monitored.

END POINTS

The primary end point was defined as the composite of all-cause mortality, nonfatal myocardial infarction, any revascularization, and cerebrovas-

cular events (MACCE) at 12 months for the complete-revascularization group versus the infarct-artery-only group. Secondary end points included the primary end point as adjudicated at 24 and 36 months in addition to the following outcomes, which were assessed at 12, 24, and 36 months: each component of the primary end point; the composite of all-cause mortality and myocardial infarction; the composite of cardiac death, myocardial infarction, any revascularization, stroke, and major bleeding; the composite of hospitalization for heart failure and unstable angina pectoris; any revascularization; stent thrombosis; and treatment costs. Bleeding at 48 hours and at 12 months were also secondary outcomes. In this article we report clinical outcomes up to 12 months. Three subgroup analyses of the primary outcome were prespecified: a comparison of patients in both groups with treated lesions with an FFR of 0.80 or less versus patients with untreated lesions with an FFR of 0.80 or less, a comparison of acute versus staged treatment for lesions with an FFR of 0.80 or less, and a comparison of patients with treated lesions with an FFR of more than 0.80 (see the Supplementary Appendix for details).

STATISTICAL ANALYSIS

As reviewed elsewhere,¹⁸ we calculated that a sample size of 858 patients would obtain a power of at least 80%, with a two-sided alpha of 5% for the rejection of the null hypothesis of no difference when the end-point difference was 8% in the complete-revascularization group and 14.5% in the infarct-artery-only group. Given the anticipation of a 3% loss to follow-up, a sample size of 885 patients was needed.

All analyses were performed on an intention-to-treat basis. A post hoc, per-protocol analysis that included only patients who received the allocated treatment was also performed.

Clinical event rates and other categorical data have been summarized according to treatment group with the use of percentages. Continuous data are presented as means with standard deviations for normally distributed variables and as medians with minimum and maximum values for variables that were not normally distributed. Differences between both groups for continuous data were assessed with the use of an unpaired T-test when data were normally distributed and with

the Mann–Whitney U test when not. Categorical data were analyzed with the use of the chi-square test or Fisher's exact test. A two-sided P value of ≤ 0.05 was considered to indicate significance. Kaplan–Meier time-to-event plots were constructed for clinical events, and treatment groups were compared with the use of the log-rank test. Patients were censored from Kaplan–Meier plots when any event that contributed to the composite end point occurred or at the time of their last follow-up visit. Cox proportional-hazard models were fitted to estimate hazard ratios with 95% confidence intervals for treatment comparisons.¹⁹ Analysis was performed with the use of SPSS software, version 23.0 (SPSS).

RESULTS

PATIENTS

Between July 2011 and October 2015, a total of 885 patients with STEMI and multivessel disease were enrolled in the trial. Among them, 295 patients were randomly assigned to receive FFR-guided complete revascularization and 590 to receive treatment of an infarct-related coronary artery only (Fig. 1).

The baseline characteristics of the patients were similar in the two groups, with the exception of the fact that there were significantly more smokers in the infarct-artery-only group (Table 1). The angiographic and procedural data (Table 2, and Tables S2 and S3 in the Supplementary Appendix) were similar in the two groups, but in the complete revascularization group the procedural time was an average of 6 minutes longer and the volume of contrast material used was an average of 22 ml greater. Drug-eluting stents were used to treat infarct-related coronary artery lesions in 97% of all patients, with everolimus-eluting stents used in 75% of patients in both groups. The medications administered during the procedure and at discharge were also similar in the two groups (Table S4 in the Supplementary Appendix). All but four patients (three of whom withdrew consent and one who was lost to follow-up) underwent follow-up at 1 year (Fig. 1).

FFR-RELATED OUTCOMES

No FFR values were obtained for 18 of the 885 patients (3 in the complete-revascularization group and 15 in the infarct-artery-only group) (Table 2). According to FFR measurements, the distribution

of significant flow-limiting lesions in non–infarct-related coronary arteries was similar in the two groups (Table 2, and Table S3 in the Supplementary Appendix).

In the complete-revascularization group, 158 of 292 patients (54.1%) had one or more lesions in non–infarct-related coronary arteries, with an FFR of 0.80 or less, and underwent PCI of these lesions. Five additional patients had PCI of non–infarct-related coronary artery lesions that were not based on FFR values. In 136 of these 163 patients (83.4%), additional PCIs were performed during the primary PCI; the remainder of these patients had staged, in-hospital PCI (mean waiting time, 2.1 days) (Table 2).

In the infarct-artery-only group, 275 of 575 patients (47.8%) had one or more lesions in non–infarct-related coronary arteries with an FFR 0.80 or less. These patients were initially treated conservatively, with the exception of 1 patient who underwent PCI for one non–infarct-related coronary artery lesion during the index procedure. There were 59 patients who underwent staged elective revascularizations within 45 days after primary PCI, and 44 of these patients had one or more non–infarct-related coronary artery lesions with an FFR of 0.80 or less.

In two patients (0.2%), both in the infarct-artery-only group, a serious adverse event related to FFR occurred. In one patient, the FFR wire caused a dissection in the non–infarct-related right coronary artery, with subsequent occlusion, infarction, and in-hospital death. In the other patient, after withdrawal of the FFR wire, the non–infarct-related left anterior descending coronary artery became occluded and the patient had ST-segment elevation and recurrent chest pain. PCI of the artery was performed successfully. Apart from brief episodes of atrioventricular conduction delay and moderate drops in blood pressures, no other adverse events occurred during measurements of FFR.

PRIMARY OUTCOME

Clinical outcomes are summarized in Table 3. At 1 year, the primary outcome had occurred in 23 patients (7.8%) in the complete-revascularization group and in 121 patients (20.5%) in the infarct-artery-only group (hazard ratio, 0.35; 95% confidence interval [CI], 0.22 to 0.55; $P < 0.001$) (Fig. 2). The difference was driven mainly by the greater number of revascularizations performed in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Complete Revascularization (N = 295)	Infarct-Artery-Only Treatment (N = 590)	P Value
Age — yr	62±10	61±10	0.22
BMI†			0.79
Median	27.2	27.1	
Range	18.0–44.1	17.7–54.3	
Male sex — no. (%)	233 (79.0)	450 (76.3)	0.37
White race — no./total no. (%)	263/295 (89.2)	545/589 (92.5)	0.09
Medical history			
Diabetes — no. (%)	43 (14.6)	94 (15.9)	0.60
Hypertension — no. (%)	136 (46.1)	282 (47.8)	0.63
Current smoker — no./total no. (%)	120/294 (40.8)	287/589 (48.7)	0.03
Hypercholesterolemia — no. (%)‡	95 (32.2)	176 (29.8)	0.47
Family history of premature coronary artery disease — no./total no. (%)	103/294 (35.0)	223/590 (37.8)	0.42
Previous stroke — no. (%)	10 (3.4)	26 (4.4)	0.47
Previous myocardial infarction — no. (%)	22 (7.5)	48 (8.1)	0.73
Previous PCI — no. (%)	25 (8.5)	44 (7.5)	0.60
Renal impairment — no. (%)§	3 (1.0)	7 (1.2)	0.82
Peripheral-vessel disease — no. (%)	10 (3.4)	23 (3.9)	0.71
Location of infarct — no. (%)¶			
Posterior	53 (18.0)	96 (16.3)	0.53
Anterior	105 (35.6)	206 (34.9)	0.84
Inferior	149 (50.5)	307 (52.0)	0.67
Lateral	41 (13.9)	86 (14.6)	0.79
Impossible to determine	3 (1.0)	4 (0.7)	0.59
Time from symptom onset to primary PCI — no. (%)			0.58
<6 hr	225 (76.3)	462 (78.3)	
6–12 hr	47 (15.9)	84 (14.2)	
>12 hr	23 (7.8)	44 (7.5)	
Arteries with stenosis — no. (%)			0.54
2	204 (69.2)	396 (67.1)	
3	91 (30.8)	194 (32.9)	
Killip class ≥2 — no. (%)	15 (5.1)	30 (5.1)	1.00
Maximum creatine kinase level (IU/liter)			0.62
Median	1040	1125	
Range	102–8182	112–11,052	

* Plus–minus values are means ±SD. FFR denotes fractional flow reserve, and PCI percutaneous coronary intervention.

† Measurements for BMI (body-mass index; the weight in kilograms divided by the square of the height in meters) were available for 290 patients in the group undergoing complete revascularization and for 581 patients in the group undergoing infarct-artery-only revascularization.

‡ Patients described as having hypercholesterolemia were either receiving treatment with cholesterol-lowering medications or were known to have elevated levels of cholesterol (>200 mg per deciliter [5.2 mmol per liter]).

§ Patients described as having renal impairment had a creatinine level of more than 1.5 mg per deciliter (133 μmol per liter) or were receiving dialysis.

¶ The location of the infarct was determined with the use of electrocardiography.

|| The P value applies to all three sets of comparisons in accordance with the Mantel–Haenszel test of trend (or linear-by-linear association).

Type of Data	Complete Revascularization (N=295)	Infarct-Artery-Only Treatment (N=590)	P Value
Mean time for index procedure — min	65±31	59±28	0.001
Mean volume of contrast material used during index PCI — ml	224±104	202±75	0.007
FFR procedure successful — no. (%)	292 (99.0)	575 (97.5)	0.13
Reason for FFR procedure failure — no. (%)			
Failure to cross lesion	2 (0.7)	7 (1.2)	
Logistic and technical problems	1 (0.3)	3 (0.5)	
Patient with asthma	0	2 (0.3)	
Unknown	0	3 (0.5)	
Patients with lesions — no./total no. (%)			
FFR ≤0.80	158/292 (54.1)	275/575 (47.8)	0.08
FFR >0.80	134/292 (45.9)	300/575 (52.2)	
Mean FFR value	0.78±0.12	0.79±0.12	0.42
Patients with treated (FFR-guided) non–infarct-related coronary artery lesions — no./total no. (%)	163/295 (55.3) †	NA	
During index PCI procedure	136/163 (83.4)		
Delayed during index hospitalization ‡	27/163 (16.6)		
Treatment method — no./total no. (%)		NA	
Drug-eluting stent only	161/163 (98.8)		
Bare-metal stent only	1/163 (0.6)		
Balloon dilation only	1/163 (0.6)		
Mean no. of stents used per patient	1.6±0.9	NA	
Dimensions of stents — mm			
Mean length	34.3±21.0	NA	
Mean diameter	2.9±0.4	NA	
Length of hospital stay — days			0.36
Median	4	4	
Range	1–35	1–71	
Patients receiving predischARGE noninvasive stress tests — no./total no. (%)	21/294 (7.1)	71/590 (12.0)	0.03

* Plus–minus values are means ±SD, and NA denotes not applicable.

† In four patients, non–infarct-related coronary artery lesions were also treated because no measurement was obtained for FFR, and in one patient these lesions were treated even though the FFR was higher than 0.80. The decision to treat was based on the angiographic results.

‡ There was a mean delay of 2.1±1.0 days after the primary PCI procedure.

latter group. Approximately one third of these revascularizations were conducted for the treatment of unstable angina and approximately one third for stable angina; more than 80% of these revascularizations were considered to be clinically indicated according to the protocol (see also Table S5 in the Supplementary Appendix). The hazard ratios for the comparison of the in-

Table 3. Prespecified Clinical End Points at 1 Year.

End Point	Complete Revascularization (N=295)	Infarct-Artery-Only Treatment (N=590)	Hazard Ratio (95% CI)	P Value
	<i>number (percent)</i>			
Primary				
MACCE*	23 (7.8)	121 (20.5)	0.35 (0.22–0.55)	<0.001
Death from any cause	4 (1.4)	10 (1.7)	0.80 (0.25–2.56)	0.70
Cardiac event	3 (1.0)	6 (1.0)	1.00 (0.25–4.01)	1.00
Myocardial infarction	7 (2.4)	28 (4.7)	0.50 (0.22–1.13)	0.10
Spontaneous event	5 (1.7)	17 (2.9)	0.59 (0.22–1.59)	0.29
Periprocedural event	2 (0.7)	11 (1.9)	0.36 (0.08–1.64)	0.19
Revascularization	18 (6.1)	103 (17.5)	0.32 (0.20–0.54)	<0.001
PCI	15 (5.1)	98 (16.6)	0.37 (0.24–0.57)	<0.001
Coronary-artery bypass graft	3 (1.0)	5 (0.8)	1.20 (0.29–5.02)	0.80
Cerebrovascular event	0	4 (0.7)	NA	NA
Secondary				
NACE (any first event)	25 (8.5)	174 (29.5)	0.25 (0.16–0.38)	<0.001
Death from any cause) or myocardial infarction	11 (3.7)	38 (6.4)	0.57 (0.29–1.12)	0.10
Major bleeding	3 (1.0)	8 (1.4)	0.75 (0.20–2.84)	0.67
Any bleeding				
At 12 mo	9 (3.1)	28 (4.7)	0.64 (0.30–1.36)	0.25
At 48 hr	5 (1.7)	8 (1.4)	1.25 (0.41–3.83)	0.69
Hospitalization for heart failure, unstable angina, or chest pain	13 (4.4)	47 (8.0)	0.54 (0.29–0.99)	0.04
Any revascularization†	19 (6.4)	161 (27.3)	0.47 (0.29–0.76)	0.002
Stent thrombosis	2 (0.7)	1 (0.2)	0.58 (0.12–2.80)	0.50

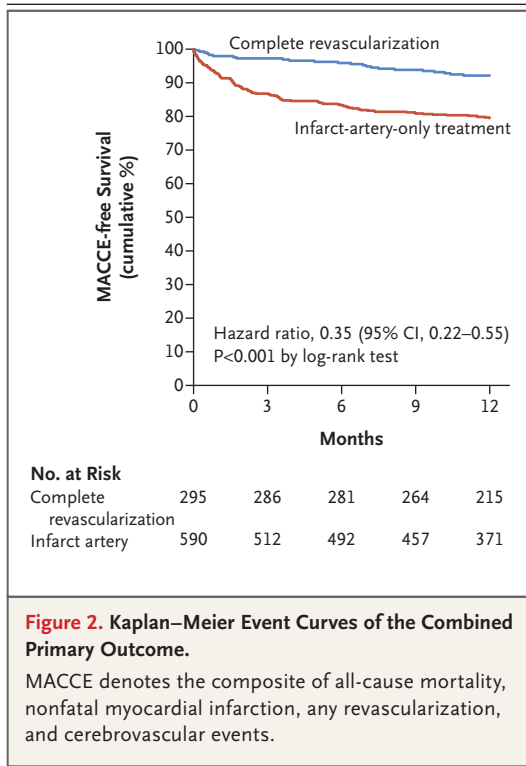
* MACCE denotes the composite of all-cause mortality, nonfatal myocardial infarction, any revascularization, and cerebrovascular events; NA not available because there were too few events to compute a reliable hazard ratio; and NACE net adverse clinical events (the composite of cardiac death, myocardial infarction, any revascularization, stroke, and major bleeding).

† Any revascularization includes all first revascularizations that were elective or urgent and that were clinically indicated or not between the time of the index procedure and follow-up at 12 months.

dividual components of the composite end point in the two groups were as follows: for all-cause mortality, 0.80 (95% CI, 0.25 to 2.56; $P=0.70$); for nonfatal reinfarction, 0.50 (95% CI, 0.22 to 1.13; $P=0.10$); and for revascularization, 0.32 (95% CI, 0.20 to 0.54; $P<0.001$). (The hazard ratio for cerebrovascular events was not calculated because there were no such events in the group undergoing FFR-guided revascularization.)

The results of the per-protocol analysis were consistent with those of the intention-to-treat

analysis (Fig. S1 in the Supplementary Appendix). Prespecified subgroup comparisons showed a significantly lower rate of MACCE among patients with treated lesions than among patients with untreated lesions with an FFR of 0.80 or less (8.9% vs. 30.7%, $P<0.001$). In the other two subgroup comparisons, there were no significant differences between groups, but these analyses were underpowered. The results of these analyses and the outcomes for various subgroups are included in the Supplementary Appendix.



DISCUSSION

The Compare-Acute trial showed that the addition of FFR-guided revascularization of non–infarct-related coronary arteries at the time of primary PCI in patients with STEMI and multivessel disease resulted in a lower rate of a composite cardiovascular outcome that included death from any cause, nonfatal myocardial infarction, revascularization, and cerebrovascular events. This reduction was driven mainly by decreased need for subsequent revascularizations. The Compare-Acute trial also showed that approximately half the lesions in non–infarct-related arteries that were considered to be significant on coronary angiography had an FFR value of more than 0.80 and were therefore not physiologically significant.

Two randomized clinical trials of angiography-guided revascularization have reported a decrease in major adverse cardiac events after routine revascularization of non–infarct-related coronary arteries in patients with STEMI during primary PCI.^{8,9} The DANAMI-3–PRIMULTI trial (Complete Revascularisation versus Treatment of the Culprit Lesion Only in Patients with ST-Segment Elevation Myocardial Infarction and Multivessel Dis-

ease),¹⁷ which staged FFR-guided treatment of non–infarct-related coronary artery lesions 2 days after PCI, also reported a reduction in major adverse cardiac events, a finding driven by a reduction in the number of PCI procedures conducted during follow-up.

Although FFR-guided PCI is increasingly used in patients with stable angina, it has not been frequently used in patients with an acute coronary syndrome, mainly owing to concerns that disturbed microvascular function in the early stage of acute myocardial infarction might affect the reliability of the technique. However, the evidence supports the reliability of FFR assessment of non–infarct-related coronary arteries in this context.²⁰ The use of an FFR-guided strategy for complete revascularization during STEMI has the potential to substantially decrease the number of unnecessary interventions during primary PCI and the number of subsequent revascularizations. The percentage of angiographically significant, non–infarct-related coronary artery lesions with an FFR greater than 0.80 was 31% in the DANAMI-3–PRIMULTI trial and 50% in the present trial. The generally favorable outcomes of patients who had untreated lesions with an FFR of more than 0.80 in the complete-revascularization group support the idea that deferral of treatment of these FFR-negative, non–infarct-related coronary artery lesions is safe, although analyses of this subgroup were not prespecified.

In contrast with the DANAMI-3–PRIMULTI trial, in our trial the FFR-guided revascularizations were performed during primary PCI. This strategy limits the need for sequential catheterizations and has the potential to limit costs, given the significantly lower frequency of predischARGE stress tests and recurrent hospital admissions for chest pain and heart failure in the group receiving FFR-guided revascularization.

Elective revascularization of non–infarct-related coronary arteries — pursued on the basis of clinical evaluation that included noninvasive imaging — was performed in 59 patients in the group receiving PCI of infarct-related coronary arteries only within the first 45 days after the first procedure was performed and was not included as an end point in this trial. This strategy, which is in keeping with the current European Society of Cardiology guidelines, was not allowed in the previously mentioned trials.^{8,9,17} Even with the ex-

clusion of these 59 revascularizations, the beneficial effect of complete FFR-guided revascularization over treatment of infarct-related coronary arteries only was substantial.

Our study has limitations. No information was captured on screened and eligible patients who were not enrolled. Given the open-label design, it is possible that there was a bias among patients and physicians toward subsequent revascularization among persons assigned to the group receiving treatment of the infarct-related coronary artery only, on the basis of their knowledge of the angiographic results. Two thirds of the revascularizations performed, although adjudicated as clinically indicated, were not performed to address an acute coronary syndrome but to address less definitive indications, for which the effect on mortality remains questionable. Our study was not powered to detect differences in low-frequency events, such as death, reinfarction, and stroke. Because we performed FFR in both groups, the between-group difference in procedure time and

the volume of contrast material used underestimates the differences that would be expected between an FFR-guided strategy for non-infarct-related coronary artery revascularization and for an infarct-related coronary artery only.

In conclusion, among patients presenting with STEMI and multivessel disease, FFR-guided complete revascularization of non-infarct-related lesions in the acute phase of primary PCI reduced the risk of a composite cardiovascular outcome as compared with a strategy of treatment of the infarct-related artery only. This reduction was mainly driven by the decreased need for subsequent revascularization.

Supported by Maasstad Cardiovascular Research, which received unconditional grants from Abbott Vascular and St. Jude Medical.

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

We thank the cardiologists of Maasstad Hospital for their support of the trial, Ria van Vliet and Niklas Svensson for assistance with the conduct of the trial, Elvin Kedhi for assistance with the trial design, and the Gothia Forum at Sahlgrenska University for data management.

REFERENCES

1. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. *Eur Heart J* 2012;33:2569-619.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:529-55.
3. Corpus RA, House JA, Marso SP, et al. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. *Am Heart J* 2004;148:493-500.
4. Hanratty CG, Koyama Y, Rasmussen HH, Nelson GI, Hansen PS, Ward MR. Exaggeration of nonculprit stenosis severity during acute myocardial infarction: implications for immediate multivessel revascularization. *J Am Coll Cardiol* 2002;40:911-6.
5. Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J* 2007;28:1709-16.
6. Park D-W, Clare RM, Schulte PJ, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. *JAMA* 2014;312:2019-27.
7. Vlaar PJ, Mahmoud KD, Holmes DR Jr, et al. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J Am Coll Cardiol* 2011;58:692-703.
8. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115-23.
9. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;65:963-72.
10. Fischer JJ, Samady H, McPherson JA, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. *Am J Cardiol* 2002;90:210-5.
11. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995;92:2333-42.
12. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213-24.
13. Pijls NHJ, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. *N Engl J Med* 1996;334:1703-8.
14. De Bruyne B, Baudhuin T, Melin JA, et al. Coronary flow reserve calculated from pressure measurements in humans: validation with positron emission tomography. *Circulation* 1994;89:1013-22.
15. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007;49:2105-11.
16. De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
17. Engström T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMUMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665-71.
18. Smits PC, Assaf A, Richardt G, Omerovic E, Abdel-Wahab M, Neumann

- F-J. Design and rationale of the Compare-Acute trial: fractional flow reserve-guided primary multivessel percutaneous coronary intervention to improve guideline indexed actual standard of care for treatment of ST-elevation myocardial infarction in patients with multivessel coronary disease. *Am Heart J* 2017;186:21-8.
19. Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.
20. Ntalianis A, Sels JW, Davidavicius G, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010;3:1274-81.

Copyright © 2017 Massachusetts Medical Society.