

ORIGINAL ARTICLE

Randomized Trial of Preventive Angioplasty in Myocardial Infarction

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ABSTRACT

BACKGROUND

In acute ST-segment elevation myocardial infarction (STEMI), the use of percutaneous coronary intervention (PCI) to treat the artery responsible for the infarct (infarct, or culprit, artery) improves prognosis. The value of PCI in noninfarct coronary arteries with major stenoses (preventive PCI) is unknown.

METHODS

From 2008 through 2013, at five centers in the United Kingdom, we enrolled 465 patients with acute STEMI (including 3 patients with left bundle-branch block) who were undergoing infarct-artery PCI and randomly assigned them to either preventive PCI (234 patients) or no preventive PCI (231 patients). Subsequent PCI for angina was recommended only for refractory angina with objective evidence of ischemia. The primary outcome was a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina. An intention-to-treat analysis was used.

RESULTS

By January 2013, the results were considered conclusive by the data and safety monitoring committee, which recommended that the trial be stopped early. During a mean follow-up of 23 months, the primary outcome occurred in 21 patients assigned to preventive PCI and in 53 patients assigned to no preventive PCI (infarct-artery-only PCI), which translated into rates of 9 events per 100 patients and 23 per 100, respectively (hazard ratio in the preventive-PCI group, 0.35; 95% confidence interval [CI], 0.21 to 0.58; $P < 0.001$). Hazard ratios for the three components of the primary outcome were 0.34 (95% CI, 0.11 to 1.08) for death from cardiac causes, 0.32 (95% CI, 0.13 to 0.75) for nonfatal myocardial infarction, and 0.35 (95% CI, 0.18 to 0.69) for refractory angina.

CONCLUSIONS

In patients with STEMI and multivessel coronary artery disease undergoing infarct-artery PCI, preventive PCI in noninfarct coronary arteries with major stenoses significantly reduced the risk of adverse cardiovascular events, as compared with PCI limited to the infarct artery. (Funded by Barts and the London Charity; PRAMI Current Controlled Trials number, ISRCTN73028481.)

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PATIENTS WITH ACUTE ST-SEGMENT ELEVATION myocardial infarction (STEMI) are effectively treated with emergency angioplasty, hereafter called percutaneous coronary intervention (PCI), to restore blood flow to the coronary artery that is judged to be causing the myocardial infarction (infarct artery, also known as culprit artery).¹⁻⁵ These patients may have major stenoses in coronary arteries that were not responsible for the myocardial infarction,⁶ but the value of performing PCI in such arteries for the prevention of future cardiac events is not known.

Some physicians have taken the view that stenoses in noninfarct arteries may cause serious adverse cardiac events that could be avoided by performing preventive PCI during the initial procedure.⁷⁻¹² Others have suggested that medical therapy with antiplatelet, lipid-lowering, and blood-pressure-lowering drugs is sufficient and that the risks of preventive PCI outweigh the benefits.^{2-4,13-17}

The aim of our single-blind, randomized study, called the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial, was to determine whether performing preventive PCI as part of the procedure to treat the infarct artery would reduce the combined incidence of death from cardiac causes, nonfatal myocardial infarction, or refractory angina.

METHODS

STUDY DESIGN

From 2008 through 2013, we enrolled 465 patients at five coronary care centers in the United Kingdom: the London Chest Hospital, Golden Jubilee National Hospital in Glasgow, Morriston Hospital in Swansea, Freeman Hospital in Newcastle, and Norfolk and Norwich University Hospital. The study was approved by the East London Research Ethics Committee. A steering committee provided oversight of the trial, and a data and safety monitoring committee advised on whether the trial should be stopped because of clear evidence of benefit or harm.

The members of the steering committee designed the study and gathered and analyzed the data. The writing committee prepared the manuscript and together with their coauthors made the decision to submit the manuscript for publication. The steering committee members vouch for the accuracy of the data and the analyses and for the fidelity of this report to the trial proto-

col, which is available with the full text of this article at NEJM.org.

STUDY PARTICIPANTS

The trial enrolled consecutive patients of any age with acute STEMI and multivessel coronary disease detected at the time of emergency PCI. The trial was limited to patients with STEMI (including three patients with left bundle-branch block) because unlike patients with non-STEMI, such patients usually have a clearly identifiable infarct artery (often occluded) that is easily distinguished from noninfarct coronary arteries.⁶

Patients were considered for eligibility after undergoing PCI in the infarct artery while they were in the catheterization laboratory. They were deemed to be eligible if the infarct artery had been treated successfully and there was stenosis of 50% or more in one or more coronary arteries other than the infarct artery and the stenosis was deemed to be treatable by PCI. The treating cardiologist had to consider that both infarct-artery-only PCI and preventive PCI would be acceptable treatment options.

Patients were ineligible if they were in cardiogenic shock, were unable to provide consent for any other reason, had undergone previous coronary-artery bypass grafting (CABG), had a noninfarct-artery stenosis of 50% or more in the left main stem or the ostia of both the left anterior descending and circumflex arteries (because these are indications for CABG), or if the only noninfarct stenosis was a chronic total occlusion (because it was felt that PCI in such circumstances was contraindicated owing to a low success rate). Patients provided written informed consent.

STUDY PROCEDURES AND FOLLOW-UP

After the completion of PCI in the infarct artery, eligible patients were randomly assigned to undergo no further PCI procedures or to undergo immediate preventive PCI in noninfarct arteries with more than 50% stenoses (preventive PCI). The randomization schedule was computer-generated in blocks of four at each study center.

All other decisions regarding the treatment of patients were left to the discretion of the responsible clinicians. Staged PCI (i.e., treatment of stenoses that were not treated during the initial procedure) in patients without angina was discouraged. Any patient with subsequent symptoms of angina that were not controlled with the use of

medical therapy was required to undergo an objective assessment of ischemia to secure a diagnosis of refractory angina, and the intention of the investigators was that further PCI for angina should be performed only in cases of refractory angina that were so defined.

We collected follow-up information at 6 weeks and then yearly, usually at clinic visits but sometimes during telephone calls with patients. At each visit, patients were examined and underwent electrocardiography, and investigators obtained information regarding the occurrence of trial outcomes, including the date of occurrence (as confirmed by hospital records). Patients were registered with the Medical Research Information Service, and death certificates were automatically sent to investigators.

STUDY OUTCOMES

The primary outcome was a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina, and each of the components was also assessed individually. Secondary outcomes were death from noncardiac causes and repeat revascularization procedures (PCI or CABG).

Myocardial infarction was defined as symptoms of cardiac ischemia and a troponin level above the 99th centile. For patients with a recurrent myocardial infarction within 14 days after randomization, the definition required new electrocardiographic evidence of ST-segment elevation or left bundle-branch block and angiographic evidence of coronary-artery occlusion. Refractory angina was defined as angina despite medical therapy supported by objective evidence of ischemia (either electrocardiographic changes during a spontaneous episode of pain or abnormal results on exercise electrocardiography, stress echocardiography, stress nuclear perfusion scan, stress magnetic resonance perfusion scan, or pressure-wire assessment).

An independent cardiologist and cardiac surgeon who were not notified about study-group assignments examined specified primary and secondary outcomes. These clinicians reviewed outcome events separately and then together for the five participating sites. Recorded entries were agreed on and accepted; in cases of disagreement, a joint decision was reached.

STATISTICAL ANALYSIS

We determined that an enrollment of 600 patients would provide a power of at least 80% to detect a

reduction in risk of 30% in the preventive-PCI group, as compared with the group receiving no preventive PCI, at a 5% level of significance, assuming a 20% annual rate of the primary outcome in the latter group.^{13,14,18} We based all sample-size calculations on survival outcomes using the log-rank test statistic.¹⁹ Stopping criteria included a clear answer to the trial question from the emerging literature or from the results of the trial, showing a primary outcome difference at the 0.001 level of significance. An interim analysis was prespecified after the enrollment of 300 patients. A second interim analysis was performed after a further year of recruitment at the request of the data and safety monitoring committee.

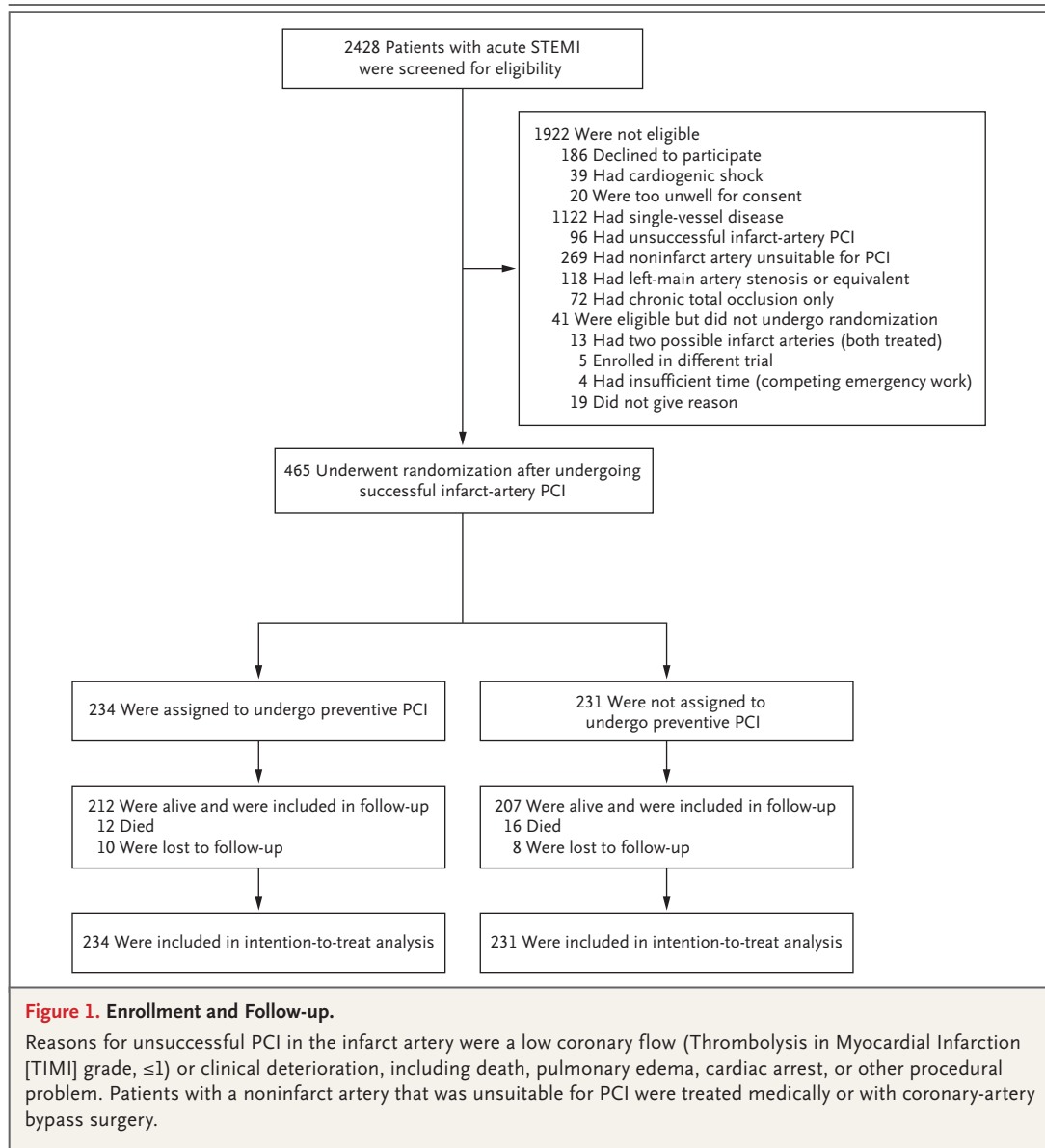
All enrolled patients were included in the analysis of primary and secondary outcomes on an intention-to-treat basis. Baseline variables were compared with the use of chi-square tests for categorical variables, t-tests for continuous variables with gaussian distributions, and Kruskal-Wallis rank-sum tests for continuous variables with non-gaussian distributions. Kaplan-Meier curves were plotted for the time to the occurrence of the clinical outcomes, and Cox proportional-hazard models were fitted to estimate hazard ratios for treatment comparisons. We used Schoenfeld residuals to test the assumptions of proportionality of the hazard ratios for covariates. Subgroup analyses of the primary outcome were performed with five prespecified covariates — age, sex, the presence or absence of diabetes, infarct location on electrocardiography (anterior vs. nonanterior), and the number of coronary arteries with stenosis (two vs. three) — on the basis of a significance level of 0.01 or less. All analyses were performed with Stata software, version 10.

RESULTS

PATIENTS

On January 24, 2013, recruitment was stopped early after a recommendation from the data and safety monitoring committee that was based on a highly significant between-group difference ($P < 0.001$) in the incidence of the primary outcome favoring preventive PCI.

From April 2008 through January 2013, a total of 465 patients were enrolled in the study, with 234 assigned to the preventive-PCI group and 231 to the group receiving no preventive PCI (Fig. 1). The characteristics of the patients at baseline



were similar in the two groups (Table 1), as was the use of bare-metal and drug-eluting stents and medical therapies at hospital discharge (Table 2). Mean follow-up was 23 months; 67% of patients were followed for at least 1 year and 46% for at least 2 years. Ten patients in the preventive-PCI group and 8 in the group receiving no preventive PCI were lost to follow-up.

PRIMARY OUTCOME

At the time of study closure, the primary outcome had occurred in 21 patients in the preventive-PCI group and 53 in the group receiving no preven-

tive PCI, for event rates of 9 per 100 and 23 per 100, respectively, and an absolute risk reduction of 14 percentage points in the preventive-PCI group (hazard ratio, 0.35; 95% confidence interval [CI], 0.21 to 0.58; $P < 0.001$) (Table 3). When the analyses were limited to the two main components of the primary outcome, cardiac death and nonfatal myocardial infarction, the hazard ratio was similar: 0.36 (95% CI, 0.18 to 0.73; $P = 0.004$). In the as-treated analysis, the hazard ratio for the primary outcome in the preventive-PCI group was 0.34 (95% CI, 0.20 to 0.57). Allowing for the two scheduled interim examinations of the data, the

P value remained less than 0.001 (hazard ratio, 0.36; 95% CI, 0.22 to 0.60).

The Kaplan–Meier analysis showed that the risk reduction in the preventive-PCI group was evident within 6 months after the procedure and was maintained thereafter (Fig. 2). The effect size did not vary over the duration of the trial ($P=0.28$ by analysis with Schoenfeld residuals). The reductions in risk were similar for death from cardiac causes, nonfatal myocardial infarction, refractory angina, and repeat revascularization; of these components, only the between-group difference in the rate of cardiac death was not significant ($P=0.07$) (Fig. S1 through S4 in the Supplementary Appendix, available at NEJM.org). The rate of death from noncardiac causes did not differ significantly between the two study groups (hazard ratio, 1.10; 95% CI, 0.38 to 3.18; $P=0.86$).

The results were not materially affected by the five prespecified covariates — age, sex, the presence or absence of diabetes, infarct location, and the number of coronary arteries with stenosis (Table S1 in the Supplementary Appendix) — or study center (Table S2 in the Supplementary Appendix). There were 2 events of STEMI and 5 events of non-STEMI in the preventive-PCI group (2 from stent thrombosis) and 9 and 11 events, respectively, in the group receiving no preventive PCI (3 from stent thrombosis).

PROCEDURE DATA AND FOLLOW-UP THERAPY

The procedure time, fluoroscopy dose, and contrast volume were increased in the preventive-PCI group (Table S3 in the Supplementary Appendix). The rates of complications (procedure-related stroke, bleeding requiring transfusion or surgery, and contrast-induced nephropathy requiring dialysis) were similar in the two groups ($P=0.84$) (Table S3 in the Supplementary Appendix). The proportions of patients receiving medical therapy were similar in the two groups throughout the trial (Table S4 in the Supplementary Appendix). Details regarding the use of medical therapy in patients with refractory angina are provided in Table S5 in the Supplementary Appendix. The median length of hospital stay in the two groups was 2 days, with 95% of patients being discharged within 1 week.

DISCUSSION

The results of this trial show that in patients with acute STEMI, the use of preventive PCI to treat

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Preventive PCI (N=234)	No Preventive PCI (N=231)
Mean age (range) — yr	62 (32–92)	62 (33–90)
Sex — no. (%)		
Male	177 (76)	186 (81)
Female	57 (24)	45 (19)
Medical history — no. (%)		
Diabetes	35 (15)	48 (21)
Hypertension	94 (40)	93 (40)
Current smoker	118 (50)	103 (45)
Previous stroke	10 (4)	10 (4)
Previous myocardial infarction	19 (8)	16 (7)
Mean blood pressure — mm Hg		
Systolic	136±26	134±26
Diastolic	81±14	80±15
Infarct location — no. (%)†		
Anterior	67 (29)	89 (39)
Inferior	154 (66)	128 (55)
Lateral	10 (4)	14 (6)
Left bundle-branch block — no. (%)	3 (1)	0
Arteries with stenosis — no. (%)		
2	143 (61)	155 (67)
3	91 (39)	76 (33)
Proximal or mid portion of left anterior descending coronary artery — no. (%)	61 (26)	74 (32)

* Plus–minus values are means ±SD. All patients in the trial underwent infarct-artery percutaneous coronary intervention (PCI) immediately before randomization. There was no significant difference between the two study groups in any characteristic at baseline.

† The location of the infarct was determined on the basis of electrocardiography.

noninfarct coronary-artery stenoses immediately after PCI in the infarct artery conferred a substantial advantage over not performing this additional procedure. The combined rate of cardiac death, nonfatal myocardial infarction, or refractory angina was reduced by 65%, an absolute risk reduction of 14 percentage points over 23 months. The effect was similar in magnitude and remained highly significant when the analysis was limited to cardiac death and nonfatal myocardial infarction.

In this trial, all decisions regarding the treatment of patients, other than the random assignments to the two study groups, were left to the discretion of the clinicians involved. The rates of use of drug-eluting stents and medical therapy

Table 2. Details Regarding PCI and Medical Therapy at Discharge.*

Variable	Preventive PCI (N=234)	No Preventive PCI (N=231)
PCI		
Infarct artery		
No. of stents per artery†	1.56±0.75	1.42±0.70
Stent length — mm	21.8±6.7	21.3±5.6
Stent diameter — mm	3.2±0.4	3.2±0.4
Stent type — no. (%)		
Bare-metal	86 (37)	96 (42)
Drug-eluting	147 (63)	135 (58)
No stenting‡	1 (<1)	0
Noninfarct artery		
No. of arteries treated per patient	1.36±0.77	NA
No. of stents per artery	1.29±0.53	NA
Stent length — mm	19.4±5.8	NA
Stent diameter — mm	3.1±0.9	NA
Stent type — no. (%)		
Bare-metal	58 (25)	NA
Drug-eluting	165 (71)	NA
No stenting§	11 (5)	NA
Use of glycoprotein IIb/IIIa inhibitor or bivalirudin — no. (%)		
Any	185 (79)	181 (78)
Glycoprotein IIb/IIIa inhibitor	178 (76)	176 (76)
Bivalirudin	7 (3)	5 (2)
Medical therapy — no. (%)¶		
Aspirin	233 (100)	229 (100)
Clopidogrel, prasugrel, or ticagrelor	234 (100)	229 (100)
Statin	222 (95)	223 (97)
Beta-blocker	207 (88)	210 (92)
ACE inhibitor or angiotensin-receptor blocker	218 (93)	209 (91)
Calcium-channel blocker	28 (12)	26 (11)
Nitrate	38 (16)	45 (20)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme.

† P<0.05 for this comparison.

‡ One patient received thrombus aspiration only.

§ The assigned treatment was not performed in 11 patients.

¶ Two patients in the group without preventive PCI died before hospital discharge.

were similar in the two groups. In the group receiving no preventive PCI, ischemia testing was performed in about one third of patients: 44 tests in asymptomatic patients (usually ≤6 weeks after the myocardial infarction) and 37 tests in patients with chest pain. In the preventive-PCI group, ischemia testing was performed in about one sixth of

patients: 8 tests in asymptomatic patients and 31 tests in patients with chest pain. Although such testing was not a prespecified trial outcome, these findings suggest that preventive PCI may lead to less ischemia testing and that when such testing is performed, it tends to be in patients with symptoms.

Table 3. Prespecified Clinical Outcomes.*

Outcome	Preventive PCI (N=234)	No Preventive PCI (N=231)	Hazard Ratio (95% CI)	P Value
<i>no. of events</i>				
Primary outcome				
Death from cardiac causes, nonfatal myocardial infarction, or refractory angina†	21	53	0.35 (0.21–0.58)	<0.001
Death from cardiac causes or nonfatal myocardial infarction†	11	27	0.36 (0.18–0.73)	0.004
Death from cardiac causes	4	10	0.34 (0.11–1.08)	0.07
Nonfatal myocardial infarction	7	20	0.32 (0.13–0.75)	0.009
Refractory angina	12	30	0.35 (0.18–0.69)	0.002
Secondary outcomes				
Death from noncardiac causes	8	6	1.10 (0.38–3.18)	0.86
Repeat revascularization	16	46	0.30 (0.17–0.56)	<0.001

* All patients underwent infarct-artery PCI.

† Only the first event per patient is listed.

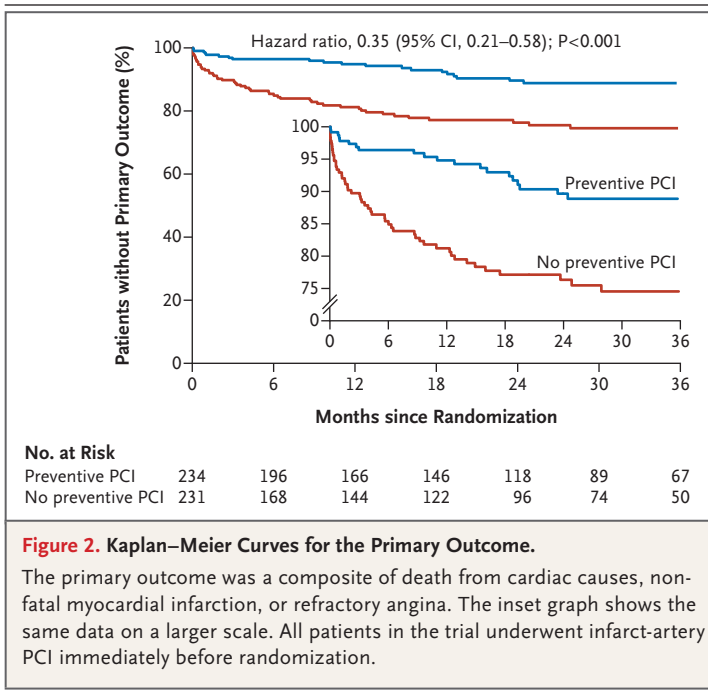
Although refractory angina is a more subjective outcome than myocardial infarction or cardiac death, it was included as a component of the primary outcome because it is a serious symptomatic condition that warrants prevention. We sought to reduce bias in the assessment of this outcome by requiring that the diagnosis be confirmed with objective evidence of ischemia. The benefit of preventive PCI was also evident when the less subjective outcomes of cardiac death and nonfatal myocardial infarction were considered alone.

We decided against using revascularization as a primary outcome, since subsequent revascularization procedures could be prompted by the identification of stenosis in a noninfarct artery in the group receiving no preventive PCI during the initial procedure. This factor would also tend to underestimate the effect of preventive PCI on primary-outcome events by reducing the treatment difference between the two study groups. However, revascularization was retained as a secondary outcome to record the number of subsequent procedures in each group.

In our study, 13 patients did not receive their assigned treatment. In the group receiving no preventive PCI, 2 patients underwent PCI in a noninfarct artery (1 for unknown reasons and 1 because the operator treated what turned out to be a noninfarct right coronary artery and then had to treat the infarct circumflex artery). In the preventive-PCI group, 11 patients underwent PCI only in the infarct artery because the preventive PCI could not be completed owing to insufficient time

(because of competing emergency PCIs) in 3 patients, failure of the noninfarct-artery PCI in 5 patients, and other complications in 3 patients. These deviations from the assigned treatment mean that the intention-to-treat analysis, adopted to ensure comparability of the two study groups, will tend to underestimate the benefit of preventive PCI. However, the results of the as-treated analysis were consistent with those of the intention-to-treat analysis.

In two other randomized trials, investigators have specifically assessed the value of preventive PCI in patients with acute STEMI undergoing PCI in the infarct artery. In one study, 69 patients were randomly assigned (in a 3:1 ratio) to preventive PCI (52 patients) or no preventive PCI (17 patients).²⁰ At 1 year, in the preventive-PCI group, there were nonsignificant reductions in the rates of repeat revascularization (17% and 35%, respectively) and cardiac death or myocardial infarction (4% and 6%, respectively). In the other trial, 214 patients were randomly assigned to one of three groups: no preventive PCI (84 patients), immediate preventive PCI (65 patients), and staged preventive PCI performed during a second procedure about 40 days later (65 patients).⁷ At 2.5 years, the rate of repeat revascularization was less frequent in the immediate- and staged-preventive PCI groups combined, as compared with the group receiving no preventive PCI (11% and 33%, respectively), and there was a nonsignificant decrease in the rate of cardiac death (5% and 12%, respectively). These studies were limited by a lack of sta-



tistical power and a reliance on repeat revascularization as an outcome, which, as indicated above, may be subject to bias. However, the results of these studies are consistent with those of our study.

Current guidelines on the management of STEMI recommend infarct-artery-only PCI in patients with multivessel disease, owing to a lack of evidence with respect to the value of preventive PCI.²⁻⁵ This uncertainty has led to variations in practice, with some cardiologists performing immediate preventive PCI in spite of the guidelines, some delaying preventive PCI until recovery from the acute episode, and others limiting the procedure to patients with recurrent

symptoms or evidence of ischemia. The results of this trial help resolve the uncertainty by making clear that preventive PCI is a better strategy than restricting a further intervention to those patients with refractory angina or a subsequent myocardial infarction. However, our findings do not address the question of immediate versus delayed (staged) preventive PCI, which would need to be clarified in a separate trial.

Several questions remain. First, are the benefits of preventive PCI applicable to patients with non-STEMI?²¹ Such patients tend to be difficult to study because, unlike those with STEMI (in whom the infarct artery is invariably identifiable), there is often uncertainty over which artery is the culprit. Second, do the benefits extend to coronary-artery stenoses of less than 50%? There is uncertainty over the level of stenosis at which the risks of PCI outweigh the benefits. Third, would a physiological measure of blood flow, such as fractional flow reserve,^{22,23} offer an advantage over angiographic visual assessment in guiding preventive PCI? Further research is needed to answer these questions.

In conclusion, in this randomized trial, we found that in patients undergoing emergency infarct-artery PCI for acute STEMI, preventive PCI of stenoses in noninfarct arteries reduced the risk of subsequent adverse cardiovascular events, as compared with PCI limited to the infarct artery.

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Dr. David Wald and Prof. Nicholas Wald report being directors of and having an equity interest in Polypill. No other potential conflict of interest relevant to this article was reported.

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

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