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Coronary Intervention for Persistent Occlusion after Myocardial Infarction

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ABSTRACT

BACKGROUND

It is unclear whether stable, high-risk patients with persistent total occlusion of the infarct-related coronary artery identified after the currently accepted period for myocardial salvage has passed should undergo percutaneous coronary intervention (PCI) in addition to receiving optimal medical therapy to reduce the risk of subsequent events.

METHODS

We conducted a randomized study involving 2166 stable patients who had total occlusion of the infarct-related artery 3 to 28 days after myocardial infarction and who met a high-risk criterion (an ejection fraction of <50% or proximal occlusion). Of these patients, 1082 were assigned to routine PCI and stenting with optimal medical therapy, and 1084 were assigned to optimal medical therapy alone. The primary end point was a composite of death, myocardial reinfarction, or New York Heart Association (NYHA) class IV heart failure.

RESULTS

The 4-year cumulative primary event rate was 17.2% in the PCI group and 15.6% in the medical therapy group (hazard ratio for death, reinfarction, or heart failure in the PCI group as compared with the medical therapy group, 1.16; 95% confidence interval [CI], 0.92 to 1.45; $P=0.20$). Rates of myocardial reinfarction (fatal and nonfatal) were 7.0% and 5.3% in the two groups, respectively (hazard ratio, 1.36; 95% CI, 0.92 to 2.00; $P=0.13$). Rates of nonfatal reinfarction were 6.9% and 5.0%, respectively (hazard ratio, 1.44; 95% CI, 0.96 to 2.16; $P=0.08$); only six reinfarctions (0.6%) were related to assigned PCI procedures. Rates of NYHA class IV heart failure (4.4% vs. 4.5%) and death (9.1% vs. 9.4%) were similar. There was no interaction between treatment effect and any subgroup variable (age, sex, race or ethnic group, infarct-related artery, ejection fraction, diabetes, Killip class, and the time from myocardial infarction to randomization).

CONCLUSIONS

PCI did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up in stable patients with occlusion of the infarct-related artery 3 to 28 days after myocardial infarction. (ClinicalTrials.gov number, NCT00004562.)

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OPTIMAL TREATMENT FOR PATIENTS who have acute myocardial infarction with ST-segment elevation includes early reperfusion with primary percutaneous coronary intervention (PCI) or thrombolytic therapy. However, approximately one third of eligible patients do not receive early reperfusion therapy, in many cases because of late presentation.^{1,2}

The best strategy for the care of patients with persistent total occlusion of the infarct-related artery who are identified after the currently accepted period during which reperfusion is administered for myocardial infarction is unclear. Most observational studies have reported that lower event rates are associated with patency of the infarct-related artery late after myocardial infarction, as compared with persistent occlusion, but the results of a large database study and small clinical trials of routine PCI have been inconclusive.³⁻¹¹

The clinical approach to the occluded infarct-related artery late after myocardial infarction remains variable and controversial, but there is strong bias in favor of PCI, particularly in the United States.¹²⁻¹⁵ Mechanisms by which late PCI of an occluded infarct-related artery might improve outcomes include reduction in adverse left ventricular remodeling with preservation of left ventricular function,^{5,7,16} increased electrical stability, and the provision of collateral vessels to other coronary beds for protection against future events.^{17,18} Late PCI also has the potential for harm from procedure-related complications, distal embolization of atherothrombotic debris resulting in myocardial injury, and loss of recruitable collateral flow to other coronary territories.^{19,20}

We report the results of the Occluded Artery Trial (OAT), which tested the hypothesis that a strategy of routine PCI for total occlusion of the infarct-related artery 3 to 28 days after acute myocardial infarction would reduce the occurrence of a composite end point of death, reinfarction, or New York Heart Association (NYHA) class IV heart failure.

METHODS

The methods used in the trial have been described previously.²¹ Sponsorship and oversight of the trial were provided by the National Heart, Lung, and Blood Institute (NHLBI). Corporate support from several sources accounted for 6% of the total funding and in-kind support for the trial, as

described in the support statement. A data and safety monitoring board appointed by the NHLBI oversaw the conduct of the trial and monitored treatment effects. Institutional review boards at the participating centers approved the study protocol, and all patients provided written informed consent. In the preparation of this report, data management and the statistical analysis were performed by the data coordinating center with oversight by the academic authors, who had full access to the data and vouch for the accuracy and completeness of the data and the analysis. The companies that provided financial support, products, or both had no role in the study design, analysis, or interpretation of the results or in the decision to submit the manuscript for publication.

STUDY POPULATION

Patients were eligible for enrollment if coronary angiography, performed 3 to 28 days after myocardial infarction, showed total occlusion of the infarct-related artery with poor or absent antegrade flow, defined as a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 0 or 1, and if they met a criterion for increased risk, defined as an ejection fraction of less than 50% (assessed by echocardiography, radionuclide ventriculography, or contrast ventriculography), proximal occlusion of a major epicardial vessel with a large risk region, or both.²¹ Qualifying angiograms were reviewed at a core angiography laboratory. The qualifying period of 3 to 28 days was based on calendar days; day 1 was the day of the onset of symptoms. Thus, the minimal time from the myocardial infarction to angiography was just over 24 hours. Exclusion criteria were NYHA class III or IV heart failure, shock, a serum creatinine concentration higher than 2.5 mg per deciliter (221 μ mol per liter), angiographically significant left main or three-vessel coronary artery disease, angina at rest, and severe ischemia on stress testing (which was required if the infarct zone was not akinetic or dyskinetic).²¹

TREATMENT

Patients were randomly assigned to PCI with stent placement and optimal medical therapy or optimal medical therapy alone. Randomization was performed with the use of an interactive automated telephone-response system; a permuted-block design was used to generate random allocations within each study site.

All patients received optimal medical therapy, including aspirin, anticoagulation if indicated, angiotensin-converting-enzyme inhibition, beta-blockade, and lipid-lowering therapy, unless contraindicated. Thienopyridine therapy was initiated before PCI and continued for 2 to 4 weeks in patients who underwent stenting. After reports of the efficacy of prolonged treatment with a thienopyridine,^{22,23} a thienopyridine was recommended in the two study groups for 1 year after myocardial infarction.

Patients assigned to PCI were to undergo the procedure within 24 hours after randomization. Use of glycoprotein IIb/IIIa inhibitors was strongly recommended. Stenting was recommended for the occluded segment as well as for high-grade stenoses in major proximal or distal segments, whenever technically feasible in the PCI group. PCI for stenoses in non-infarct-related arteries was permitted in the two groups.

Images from the PCI were reviewed at the angiography core laboratory.²¹ Successful PCI was defined as an open artery with residual stenosis of less than 50% and a TIMI flow grade of 2 or 3. PCI was also considered to be successful if there was an optimal epicardial result, accompanied by a TIMI antegrade flow grade of 1 presumed to be due exclusively to microvascular obstruction. Cardiac markers (preferably creatine kinase MB [CK-MB] or, if not available, troponin I or T or creatine kinase) were to be measured routinely in both groups three times during the first 48 hours after randomization and within 24 hours after PCI in patients assigned to PCI.

ANCILLARY STUDIES

A subgroup of 124 patients underwent baseline viability scanning with the use of single-photon-emission computed tomography (SPECT) and technetium-99m-labeled sestamibi (after the administration of nitroglycerin and while the patient was at rest) to assess myocardial viability before the patient received the assigned treatment.²¹ In a subgroup of 381 patients, cardiac catheterization was repeated at 1 year.

END POINTS

The study end-point events were adjudicated by an independent mortality and morbidity classification committee, which was unaware of the treatment assignments. The primary end point was a composite of death from any cause, reinfarction,

or NYHA class IV heart failure with hospitalization or admission for a stay in a short-stay unit. Secondary end points included the separate components of the primary end point as well as symptoms and other clinical events.

The prespecified definition of reinfarction required two of the following three criteria: the persistence of symptoms for 30 or more minutes, electrocardiographic changes, and elevated cardiac markers. Elevations were defined as follows: a creatine kinase concentration that was two or more times the upper limit of the normal range used by the local laboratory, a CK-MB fraction that was greater than the upper limit of the normal range, and a troponin I or T level that was two or more times the upper limit of the normal range.

A diagnosis of reinfarction after revascularization also required two of three criteria; elevation of a cardiac marker was defined as more than three times the upper limit of the normal range in patients who had undergone PCI and more than five times the upper limit of the normal range in those who had undergone coronary-artery bypass grafting (CABG). Troponin levels were not used to diagnose reinfarction within 10 days after the index myocardial infarction.

Reinfarction was centrally adjudicated. Site-determined reinfarctions included those locally diagnosed or suspected and those reported in association with hospitalization for other events after central review suggested that reinfarction had occurred (e.g., on the basis of cardiac marker elevations). An additional prespecified end point was recurrent elevation of a cardiac marker within 48 hours after randomization, as reported by the sites.

STATISTICAL ANALYSIS

It was initially estimated that 3200 patients would be required for the study to have 90% power to detect a 25% reduction in the rate of the primary end-point event in patients undergoing PCI, assuming a 3-year event rate of 25% with medical therapy, a 25% crossover rate (including patients who crossed over from medical therapy alone to PCI and those in whom PCI was not attempted or failed), and a 5% loss to follow-up. Subsequently, the study leadership, with the approval of the data and safety monitoring board, reduced the recruitment goal to 2400 patients because of recruitment challenges and a crossover rate that was less than expected. The final enrollment of 2166 patients

Table 1. Baseline Clinical and Angiographic Core Laboratory Characteristics.*

Characteristic	PCI Group (N=1082)	Medical Therapy Group (N=1084)	P Value
Clinical			
Age — yr	58.6±10.8	58.7±11.1	0.78
Sex — no. (%)			0.94
Male	845 (78)	845 (78)	
Female	237 (22)	239 (22)	
Race or ethnic group — no. (%)†			0.55
White	874 (81)	864 (80)	
Black	32 (3)	35 (3)	
Hispanic	137 (13)	133 (12)	
Other	39 (4)	52 (5)	
History — no./total no. (%)			
Angina	236/1081 (22)	252/1084 (23)	0.43
Myocardial infarction	127/1082 (12)	117/1084 (11)	0.49
Cerebrovascular disease	46/1081 (4)	32/1084 (3)	0.10
Peripheral-vessel disease	42/1081 (4)	39/1082 (4)	0.73
Heart failure	26/1081 (2)	24/1082 (2)	0.77
PCI	51/1081 (5)	53/1084 (5)	0.85
CABG	5/1082 (0.5)	4/1084 (0.4)	0.74
Diabetes	200/1082 (18)	246/1084 (23)	0.02
Insulin use	63/1082 (6)	59/1084 (5)	0.70
Hypertension	519/1082 (48)	536/1084 (49)	0.49
Current cigarette smoker — no./total no. (%)	423/1082 (39)	427/1084 (39)	0.89
Highest Killip class II through IV during index MI — no./total no. (%)	219/1077 (20)	194/1076 (18)	0.17
NYHA classification at randomization — no./total no. (%)			0.98
I	898/1079 (83)	900/1081 (83)	
II	181/1079 (17)	181/1081 (17)	
New Q waves	720/1082 (67)	727/1084 (67)	0.80
ST-segment elevation	700/1037 (68)	681/1039 (66)	0.34
ST-segment elevation or Q-wave or R-wave loss	939/1082 (87)	932/1084 (86)	0.58
Glomerular filtration rate — ml/min‡	80.8±21.4	80.6±21.9	0.83
Thrombolytic therapy during first 24 hr after onset of index MI — no./total no. (%)	225/1081 (21)	195/1084 (18)	0.10
Interval between MI and randomization — days§			0.68
Median	8	8	
25th percentile, 75th percentile	5, 16	5, 17	
Stress test performed — no./total no. (%)¶	290/1082 (27)	299/1084 (28)	0.68
Ischemia in infarct-related artery territory — no./total no. (%)			0.22
Severe (ineligible)	0/290 (0)	1/299 (0.3)	
Moderate	27/290 (9)	32/299 (11)	
Mild	98/290 (34)	80/299 (27)	
None	165/290 (57)	186/299 (62)	

Table 1. (Continued.)

Characteristic	PCI Group (N=1082)	Medical Therapy Group (N=1084)	P Value
Angiographic			
Infarct-related artery — no./total no. (%)			0.49
Left anterior descending coronary artery	380/1082 (35)	401/1084 (37)	
Left circumflex coronary artery	173/1082 (16)	156/1084 (14)	
Right coronary artery	529/1082 (49)	527/1084 (49)	
TIMI flow grade in infarct-related artery			0.35
0	888/1072 (83)	892/1074 (83)	
1	177/1072 (17)	180/1074 (17)	
2	5/1072 (0.5)	2/1074 (0.2)	
3	2/1072 (0.2)	0/1074 (0)	
Collateral vessels present — no./total no. (%)	934/1068 (87)	957/1071 (89)	0.17
Multivessel disease — no./total no. (%)	192/1074 (18)	191/1075 (18)	0.95
Ejection fraction			
Mean	47.4±11.3	48.0±11.0	0.22
<50% — no./total no. (%)	597/1075 (56)	554/1075 (52)	0.06
<40% — no./total no. (%)	236/1075 (22)	206/1075 (19)	0.11

* Plus-minus values are means ±SD. MI denotes myocardial infarction.

† Race or ethnic group was self-reported.

‡ The estimated glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease formula: $GFR (ml/min/1.73 m^2 \text{ of body-surface area}) = 186 \times (S_{Cr})^{-1.154} \times (\text{age})^{-0.203}$ ($\times 0.742$ among women and $\times 1.210$ among blacks). S_{Cr} denotes serum creatinine. For this category, 1062 patients in the PCI group and 1056 in the medical therapy group were included.

§ Three hundred twenty-nine patients (15%) underwent randomization at the earliest allowable time (3 calendar days after the index MI).

¶ Stress testing was performed as part of the clinical evaluation for eligibility (as described in the Methods section and by Hochman et al.²¹). Therefore, patients who were not tested did not constitute a random sample of the full study cohort.

|| Investigators at the study site reported the ejection fraction if a left ventriculogram was not obtained.

(90% of the target population) afforded 94% power to detect the anticipated difference in the primary end point. To adjust for interim testing, a two-sided significance level of 0.0456 was specified for the comparison of the primary end point between the two groups and a significance level of 0.01 for the secondary end points.²¹

Estimates of the cumulative event rate were calculated by the Kaplan–Meier product-limit method,²⁴ and treatments were compared with the use of log-rank tests of the 5-year curves.²⁵ The 4-year event rates are presented because the number of patients followed for 5 years was small. Data for patients lost to follow-up were censored as of the time of the last contact. Analyses were performed according to the intention-to-treat principle, except in the as-treated analysis. Categorical variables were compared with the use of the

chi-square test, and continuous variables were compared with the use of Student's t-test.

Prespecified subgroup analyses of the primary outcome were performed by Cox proportional-hazards regression,²⁶ with each test (regression coefficient) performed at an alpha level of 0.01, with tests for interaction. Other, a posteriori subgroup analyses were also performed. To generate the covariate-adjusted hazard ratio, we used a Cox proportional-hazards regression model with eight covariates of interest (six that were preidentified plus the presence or absence of diabetes and the Killip class), with interactions of these covariates with treatment included in the model. The final model included the treatment group, regardless of its significance, and covariates and interactions with a significance level of 0.01 or less were retained. The exponentiation of the coefficient for

the treatment group in this model, adjusted for the other terms in the model, yielded the hazard ratio and, combined with the standard error of the coefficient, the confidence interval (CI).

The protocol specified a significance level of 0.01 or less for secondary end points, including subgroup tests of interactions. At the request of the *Journal* editors, we present 95% CIs, instead of 99% CIs.

RESULTS

BASELINE CHARACTERISTICS

Between February 2000 and December 2005, 2166 patients were enrolled in the trial (as described in detail in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Of these, 1082 were randomly assigned to routine PCI plus optimal medical therapy, and 1084 to optimal medical therapy alone. The baseline characteristics of the patients in the two groups were similar except for a higher prevalence of diabetes in the group assigned to medical therapy (Table 1).

The angiographic core laboratory confirmed the angiographic eligibility of 99% of patients who underwent randomization. Baseline SPECT data from the ancillary study to assess myocardial viability showed at least moderately preserved viability of the infarct zone (>40% of peak tracer uptake) in 69% of the 124 patients.

PCI PROCEDURAL DATA

PCI of the qualifying occlusion was attempted in 1071 of the 1082 patients in the PCI group (99%) and was successful in 937 (87%); 869 of 1056 patients in the PCI group (82%) for whom the TIMI flow was reported after the procedure had a TIMI flow grade of 3. At least one stent was placed in 945 of 1082 patients (87%) in the PCI group, of whom 77 (8%) received drug-eluting stents. Glycoprotein IIb/IIIa antagonists were administered to 72% of the patients in whom PCI was successful. PCI of an artery other than the infarct-related artery was performed in 7% of the patients in this group and in 6% of those in the medical therapy group. Major PCI-related complications were rare (death, 0.2% of patients in the PCI group; centrally adjudicated myocardial reinfarction, 0.6%; NYHA class IV heart failure, 0.2%; cardiac tamponade, 0.2%; and stroke, 0.1%).

Among the 1084 patients in the medical ther-

apy group, 27 (3%) crossed over to PCI within 30 days after randomization, and an additional 63 (6%) crossed over after 30 days. Four patients (0.4%) in each of the two groups underwent CABG within 30 days after randomization.

CONCOMITANT MEDICAL THERAPY

At discharge, the rates of use of medication, as recommended in the guidelines of the American College of Cardiology and the American Heart Association,²⁷ were high (Table 2). A thienopyridine was administered to more than 99% of patients in the PCI group in whom PCI with stenting was successful. Medication use was similar in the two groups, except for higher rates of use of anticoagulant agents, nitrates, and hypoglycemic agents in the medical therapy group (Table 2). Overall, thienopyridines were used more frequently in the PCI group at both 4 months and 1 year than in the medical therapy group.

FOLLOW-UP

In the subgroup of patients who underwent repeated angiography, the infarct-related artery was patent at 1 year in 83% of 173 patients in the PCI group (89% of those in whom PCI was initially successful) and in 25% of 159 patients in the medical therapy group ($P<0.001$). Details of this angiographic substudy are reported elsewhere.²⁸

The mean (\pm SE) follow-up was 1059 ± 11 days, and it was similar in the two groups. Only 1% of patients (15 patients in each of the two groups) were lost to follow-up before the occurrence of a primary end-point event or 12 months of follow-up (see the Supplementary Appendix). Vital status was not ascertained for 20 of these patients (8 in the PCI group and 12 in the medical therapy group).

PRIMARY OUTCOME

The centrally adjudicated primary outcome (death from any cause, nonfatal reinfarction, or NYHA class IV heart failure) occurred in 161 patients in the PCI group as compared with 140 in the medical therapy group (Table 3). The estimated 4-year cumulative primary event rate was 17.2% in the PCI group and 15.6% in the medical therapy group (unadjusted hazard ratio for the PCI group as compared with the medical therapy group, 1.16; 95% CI, 0.92 to 1.45; $P=0.20$; covariate-adjusted hazard ratio, 1.17; 95% CI, 0.93 to 1.47; $P=0.18$) (Fig. 1). In an as-treated analysis comparing 937 patients

Table 2. Medication Use on Discharge.

Medication	PCI Group (N=1071)	Medical Therapy Group (N=1078)	P Value
Aspirin — no. (%)	1037 (97)	1015 (94)	0.003
Clopidogrel — no. (%)	789 (74)	258 (24)	<0.001
Ticlopidine — no. (%)	189 (18)	60 (6)	<0.001
Thienopyridine (clopidogrel or ticlopidine) — no. (%)*	974 (91)	317 (29)	<0.001
Aspirin or thienopyridine — no. (%)	1066 (100)	1047 (97)	<0.001
Aspirin plus thienopyridine — no. (%)*	945 (88)	285 (26)	<0.001
Warfarin — no. (%)	76 (7)	135 (13)	<0.001
One or more of the following: aspirin, warfarin, or thienopyridine — no. (%)	1068 (100)	1068 (99)	0.09
Two or more of the following: aspirin, warfarin, or thienopyridine — no. (%)	962 (90)	378 (35)	<0.001
Beta-blocker — no. (%)	925 (86)	961 (89)	0.05
Calcium-channel blocker — no. (%)	65 (6)	61 (6)	0.69
Long-acting nitrate — no. (%)	202 (19)	283 (26)	<0.001
Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker — no. (%)	860 (80)	866 (80)	0.98
In patients with an ejection fraction of <40% — no./total no. (%)	209/229 (91)	190/205 (93)	0.59
Diuretic agent — no. (%)	173 (16)	183 (17)	0.57
Digoxin — no. (%)	33 (3)	26 (2)	0.34
Spironolactone — no. (%)	50 (5)	65 (6)	0.16
Insulin — no. (%)	66 (6)	63 (6)	0.76
Oral hypoglycemic agent — no. (%)	124 (12)	168 (16)	0.01
Lipid-lowering agent — no. (%)	858 (80)	884 (82)	0.26

* A thienopyridine was prescribed for more than 99% of the patients, and aspirin plus a thienopyridine for 97% of those in the PCI group in whom PCI with stenting was successful.

in the PCI group in whom PCI was successful on angiographic examination with 1057 patients in the medical therapy group who did not cross over to PCI within 30 days after randomization, the hazard ratio for the primary outcome was 1.15 for PCI as compared with medical therapy (95% CI, 0.91 to 1.46; $P=0.26$).

Primary end-point events as determined at the study sites occurred in 170 patients in the PCI group and 142 patients in the medical therapy group (hazard ratio, 1.22; 95% CI, 0.97 to 1.52; $P=0.09$). The lower rates of adjudicated primary end-point events as compared with site-determined events largely reflect lower rates of reinfarction that met the more stringent adjudicated study definition of events.

SECONDARY OUTCOMES

On the basis of the study definition of reinfarction, there was no significant difference in the number of confirmed reinfarctions between the

PCI group and the medical therapy group (Table 3 and Fig. 2). The rate of site-determined reinfarction tended to be higher in the PCI group (hazard ratio, 1.37; 95% CI, 1.00 to 1.89; $P=0.05$). There were no significant differences between the groups for the other components of the primary end point or other secondary end points. There was a trend toward more frequent coronary revascularization in the medical therapy group than in the PCI group.

There were significantly fewer patients with angina in the PCI group at 4 months and at 1 year (see the Supplementary Appendix). Over time, the occurrence of angina declined in both study groups, as did the difference between the two groups, and by 3 years there was no significant difference between the groups.

SUBGROUP ANALYSIS

There was no significant interaction ($P<0.01$) between treatment effect and any subgroup variable

Table 3. Primary and Secondary Outcomes.*

Outcome	PCI Group (N=1082)		Medical Therapy Group (N=1084)		P Value	Hazard Ratio (95% CI)
	No. of Outcomes	Estimated 4-Yr Cumulative Event Rate (%)	No. of Outcomes	Estimated 4-Yr Cumulative Event Rate (%)		
Centrally adjudicated						
Primary end point	161	17.2	140	15.6	0.20	1.16 (0.92–1.45)
Death from all causes	87	9.1	84	9.4	0.83	1.03 (0.77–1.40)
Fatal and nonfatal reinfarction†	59	7.0	44	5.3	0.13	1.36 (0.92–2.00)
Procedure-related	6		1			
Not temporally related to procedure	53		43			
Nonfatal reinfarction	57	6.9	40	5.0	0.08	1.44 (0.96–2.16)
NYHA class IV heart failure‡	43	4.4	44	4.5	0.92	0.98 (0.64–1.49)
Cardiovascular death	58	6.3	52	5.0	0.56	1.12 (0.77–1.63)
Death or nonfatal reinfarction	139	14.9	116	13.2	0.13	1.21 (0.95–1.55)
NYHA class III or IV heart failure‡	57	5.9	61	6.2	0.72	0.94 (0.65–1.34)
Death, reinfarction, or NYHA class III or IV heart failure‡	173	18.2	153	16.9	0.24	1.14 (0.92–1.42)
Stroke	16	1.7	19	2.0	0.62	0.84 (0.43–1.64)
Site-determined						
Primary end point	170	18.2	142	16.2	0.09	1.22 (0.97–1.52)
Fatal and nonfatal reinfarction	89	10.1	66	8.1	0.05	1.37 (1.00–1.89)
Procedure-related	17		7			
Not temporally related to procedure	72		59			
Nonfatal reinfarction	80	9.4	57	7.2	0.04	1.43 (1.02–2.00)
NYHA class III–IV heart failure	61	6.2	67	7.0	0.61	0.91 (0.65–1.29)
Hospitalization or treatment for any class of heart failure	75	7.4	77	8.1	0.89	0.98 (0.71–1.34)
Revascularization (PCI or CABG) ex- cluding protocol-assigned PCI§	170	18.4	205	22.0	0.03	0.81 (0.66–0.99)
CABG	38	4.3	40	4.8	0.81	0.95 (0.61–1.48)
Repeated elevation of cardiac marker						
Within 48 hr after randomization — no./total no. (%)	101/1012 (10.0)		30/918 (3.3)		<0.001¶	

* P values were calculated with the use of the log-rank test for Kaplan–Meier curves through 5 years of follow-up, unless otherwise noted.

† Two of 44 patients in the medical therapy group did not have elevated serum cardiac markers but had pain and changes on electrocardiography.

‡ All patients reaching the end point of heart failure required hospitalization or admission to a short-stay unit. Data on the site-reported functional class of heart failure are available in the Supplementary Appendix.

§ In 58 patients in the PCI group, the procedure was repeated in the infarct-related artery, in 14 of the patients at 1 week or less after the occurrence of an adjudicated reinfarction. In 106 patients assigned to medical therapy, PCI of the infarct-related artery was performed, in 6 of the patients at 1 week or less after the occurrence of an adjudicated reinfarction.

¶ The P value was calculated with the use of the chi-square test.

(Fig. 3). There were also no significant differences for the primary end point according to the country where patients were enrolled (United States or other countries) or according to the enrollment period (before 2002, 2002 to June 2003, or July 2003 to December 2005).

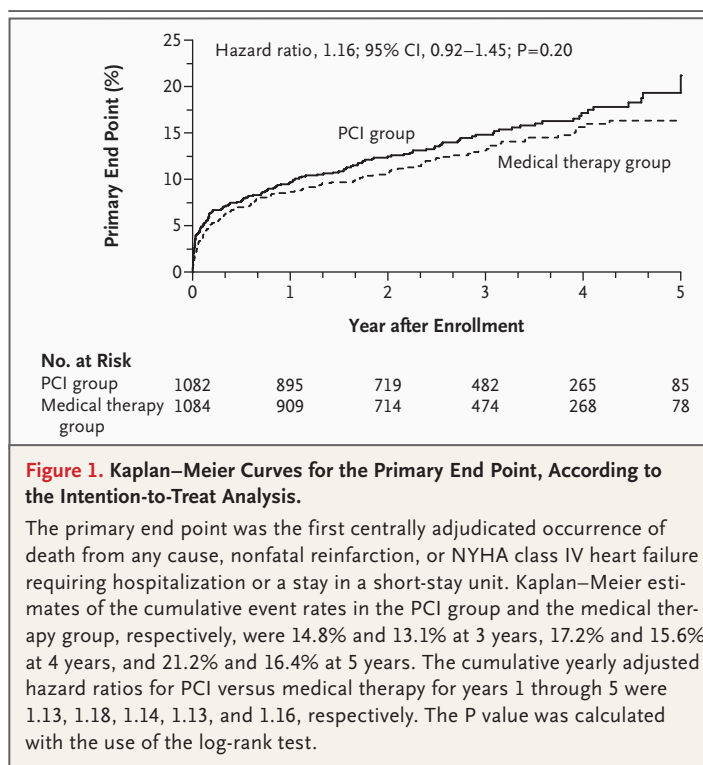
DISCUSSION

The late open-artery hypothesis asserts that the mechanical opening of a persistently occluded infarct-related artery at a time too late for myocardial salvage should improve the long-term outcome. Our study showed high rates of procedural success with PCI and sustained patency but no clinical benefit during an average 3-year follow-up with respect to death, reinfarction, or heart failure, contrary to the hypothesis. Moreover, a trend toward an excess risk of reinfarction in the PCI group aroused concern.

These unexpected results were remarkably consistent among all subgroups, including patients at highest risk for adverse left ventricular remodeling (patients with a low ejection fraction or an anterior myocardial infarction). The trend ($P=0.05$) toward an interaction based on age may be a chance finding. An as-treated analysis that excluded patients in whom PCI failed and patients who crossed over from medical therapy to PCI within 30 days showed no trend toward a benefit from PCI.

There was no statistically significant between-group difference in the rate of reinfarction according to the adjudicated, conservative definition of myocardial infarction. However, the event curves showed a trend that aroused concern. Site-determined reinfarctions better reflect the international consensus document that redefined myocardial infarction, published after the inception of our trial, which relies primarily on cardiac markers.²⁹ Our analysis showed that patients in the PCI group tended to have excess reinfarctions, which were mostly due to events not temporally related to the procedure. There was also a higher rate of release of cardiac markers early after randomization in the PCI group that did not meet the trial criteria for myocardial infarction. The clinical consequences of reinfarction in this circumstance remain to be investigated.

The mechanisms of early and late myocardial damage in this trial may be different. The excess



early release of a cardiac marker may be a consequence of distal atherothrombotic embolization and microvascular plugging related to PCI. Although the risk of reinfarction appeared to be greatest during the first 30 days after PCI, a trend toward an increased risk persisted throughout the 5-year follow-up. These reinfarctions occurred despite thienopyridine use at discharge in more than 99% of patients in whom PCI had been successful. However, information on whether events occurred while these agents were being taken is not available. We speculate that the loss of rapidly recruitable collateral flow after PCI of the total occlusion³⁰ could have predisposed patients in the PCI group to reinfarction in the event of spontaneous reocclusion. Indeed, patients in the nuclear imaging ancillary study had, on average, sufficient viability (69% with moderate retained viability in the infarct zone) to explain reinfarction within the same region.

Experimental studies, with support from observational studies, have shown that late reperfusion reduces infarct expansion and adverse left ventricular remodeling.^{5,16,31-33} A strong association between a patent infarct-related artery at hospital discharge and improved clinical outcomes

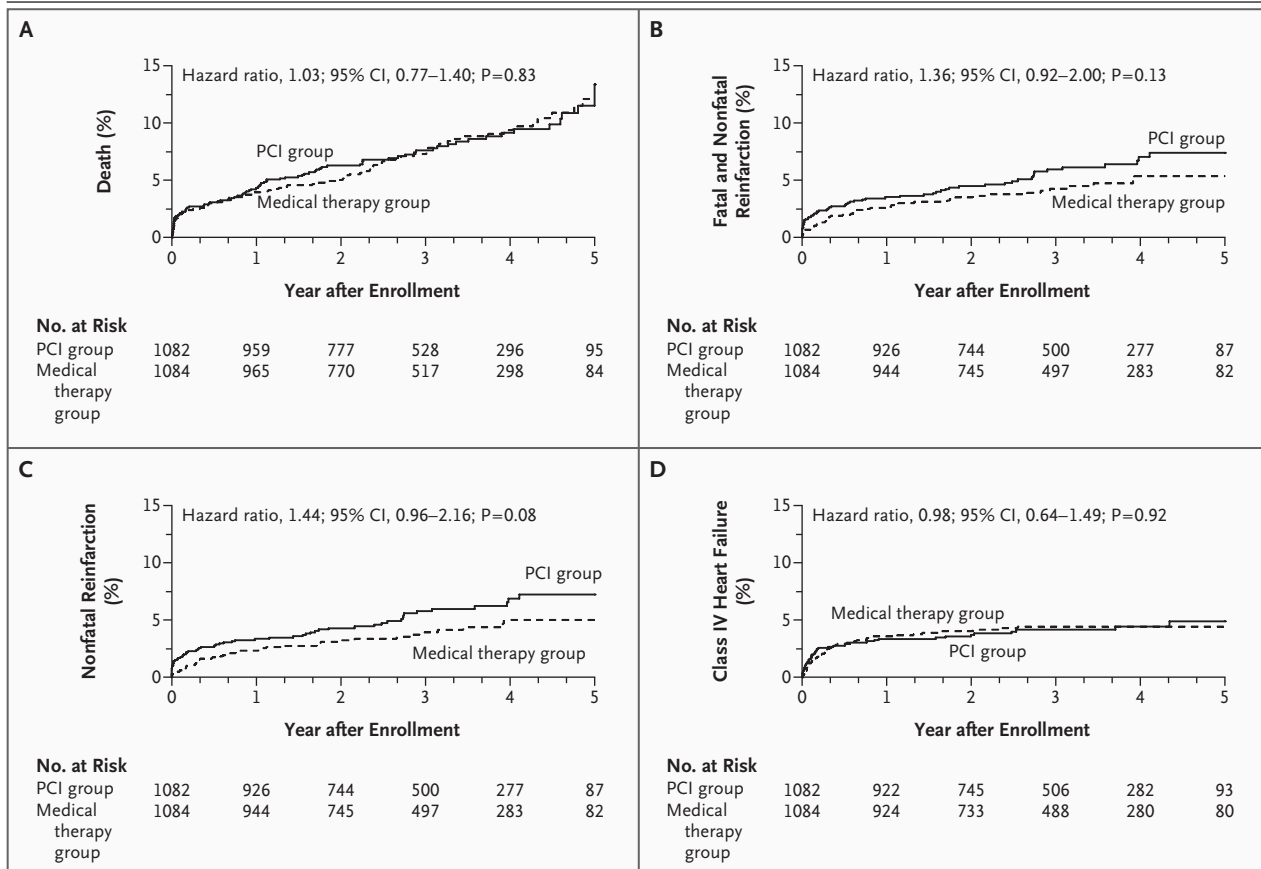


Figure 2. Kaplan–Meier Curves for the Secondary End Points, According to the Intention-to-Treat Analysis.

The secondary end points were the first adjudicated occurrences of the components of the primary end point (death from any cause, nonfatal reinfarction, or NYHA class IV heart failure requiring hospitalization or a stay in a short-stay unit). In Panel A, the estimated cumulative event rates for death from all causes in the PCI group and the medical therapy group, respectively, were 7.6% and 7.3% at 3 years, 9.1% and 9.4% at 4 years, and 13.4% and 12.1% at 5 years. In Panel B, the estimated cumulative event rates for fatal and nonfatal reinfarction in the two groups, respectively, were 5.9% and 4.3% at 3 years, 7.0% and 5.3% at 4 years, and 7.4% and 5.3% at 5 years. In Panel C, the estimated cumulative event rates for nonfatal reinfarction in the two groups, respectively, were 5.7% and 3.9% at 3 years, 6.9% and 5.0% at 4 years, and 7.2% and 5.0% at 5 years. In Panel D, the estimated cumulative event rates for NYHA class IV heart failure requiring hospitalization or admission for a stay in a short-stay unit in the two groups, respectively, were 4.2% and 4.5% at 3 years, 4.4% and 4.5% at 4 years, and 4.9% and 4.5% at 5 years. The P values for the estimated cumulative event curves at 5 years were calculated with the use of the log-rank test. The 4-year cumulative event rate for the adjudicated primary outcome in the PCI group was 16.8 for 937 patients in whom PCI was successful, 16.8 for 134 patients in whom PCI failed, and 48.6 for 11 patients who did not undergo PCI. The 4-year cumulative event rate for the adjudicated primary outcome in the medical therapy group was 18.8 for the 27 patients who crossed over to PCI within 30 days after randomization and 15.6 for the 1057 patients who did not cross over to PCI within 30 days after randomization.

after myocardial infarction has been reported in post hoc analyses, but in the largest database analysis, this association was not independent at 1 year.^{8–11} Small randomized trials of PCI versus medical therapy for total occlusion in the subacute phase of myocardial infarction have had conflicting results regarding left ventricular function and size and clinical events, ranging from benefit to harm for each end point. Data from three of four studies show a range of reinfarction rates that are 1.5 to 3.5 times higher in the PCI group than in the medical therapy group (Zagler A: personal communication).^{3,6,7} The angiographic ancillary substudy showed a similar ejection fraction in the two groups at 1 year. The assignment to PCI appeared to be predictive of a somewhat smaller increase in the left ventricular volume in a subgroup of patients for whom volume measurements were available.²⁸ A potential benefit of attenuation of left ventricular remodeling may be countered by excess nonfatal reinfarctions.

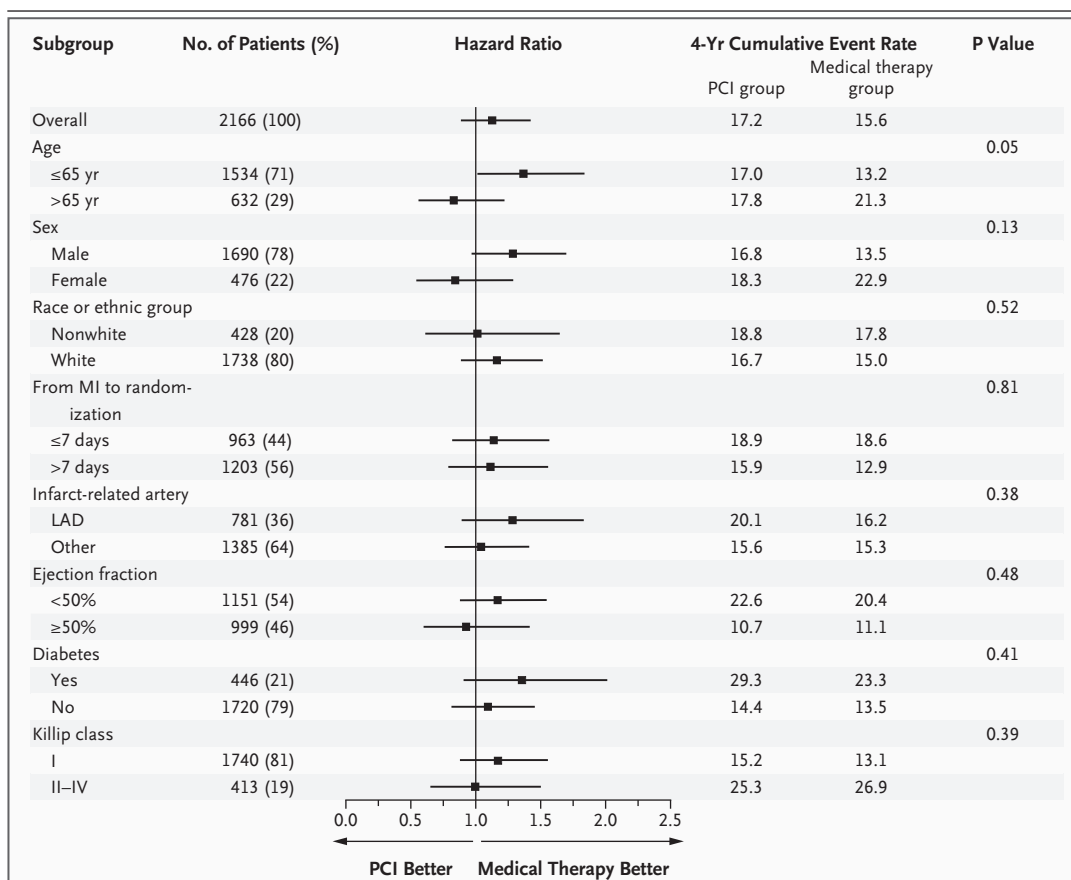


Figure 3. Subgroup Analysis.

Hazard ratios (black squares), 95% CIs (horizontal lines), P values for the interaction between the treatment effect and any subgroup variable, and cumulative estimated 4-year event rates for the primary outcome (death from any cause, nonfatal reinfarction, or NYHA class IV heart failure requiring hospitalization or a stay in a short-stay unit) for PCI versus medical therapy for the specified subgroups are shown. Age, sex, race or ethnic group, the location of the infarct-related artery, the ejection fraction, and the time from the index myocardial infarction (MI) to randomization were prespecified. Race was self-reported. Diabetes and the highest Killip class during the index MI were not prespecified for the subgroup analysis. Originally, the cutoff point for age was 70 years, but early during the trial monitoring and before any analyses were performed, it was changed to 65 years because of insufficient numbers of patients older than 70. There was no significant interaction between treatment and subgroup variable as defined according to the prespecified value for interaction ($P < 0.01$). The use of a cutoff of 40% rather than the prespecified 50% for the ejection fraction did not alter the results. There was no interaction for the presence or absence of ST-segment elevation, Q-wave loss, or R-wave loss. LAD denotes left anterior descending artery.

The results of our study should be considered in the context of the available medical and interventional therapeutics. In contrast to previous studies examining the late open-artery hypothesis, our study used high rates of glycoprotein IIb/IIIa antagonists and stents, reflecting best practices for the period of enrollment³⁴; patency rates at 1 year were high. Drug-eluting stents were approved during the later years of recruitment. Randomized trials comparing drug-eluting stents and bare-metal stents have shown no reduction in

the components of our primary end point with the use of drug-eluting stents. On the contrary, there is growing concern regarding the increased risk of late thrombosis with the use of drug-eluting stents, as compared with bare-metal stents.^{35,36} Moreover, trials of thrombectomy and distal-protection devices to prevent downstream embolization during PCI for myocardial infarction with ST-segment elevation have yielded disappointing results.^{37,38}

In summary, our study involving 2166 patients

showed no reduction in major cardiovascular events during a mean follow-up of 3 years. There was a trend toward excess nonfatal reinfarction when routine PCI was performed in stable patients who were found to have occlusion of the infarct-related artery 3 to 28 days after myocardial infarction.

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REFERENCES

- Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, López-Sendón J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet* 2002;359:373-7.
- Cohen M, Gensini GF, Maritz F, et al. Prospective evaluation of clinical outcomes after acute ST-elevation myocardial infarction in patients who are ineligible for reperfusion therapy: preliminary results from the TETAMI registry and randomized trial. *Circulation* 2003;108:Suppl III:III-14-III-21.
- Topol EJ, Califf RM, Vandormael M, et al. A randomized trial of late reperfusion therapy for acute myocardial infarction. *Circulation* 1992;85:2090-9.
- Dzavik V, Beanlands DS, Davies RF, et al. Effects of late percutaneous transluminal coronary angioplasty of an occluded infarct-related coronary artery on left ventricular function in patients with a recent (<6 weeks) Q-wave acute myocardial infarction (Total Occlusion Post-Myocardial Infarction Intervention Study [TOMIIS]—a pilot study). *Am J Cardiol* 1994;73:856-61.
- Horie H, Takahashi M, Minai K, et al. Long-term beneficial effect of late reperfusion for acute anterior myocardial infarction with percutaneous transluminal coronary angioplasty. *Circulation* 1998;98:2377-82.
- Yousef ZR, Redwood SR, Bucknall CA, Sulke AN, Marber MS. Late intervention after anterior myocardial infarction: effects on left ventricular size, function, quality of life, and exercise tolerance: results of the Open Artery Trial (TOAT Study). *J Am Coll Cardiol* 2002;40:869-76.
- Steg PG, Thuair C, Himbert D, et al. DECOPI (DEsobstruction COronaire en Post-Infarctus): a randomized multi-centre trial of occluded artery angioplasty after acute myocardial infarction. *Eur Heart J* 2004;25:2187-94.
- Cigarroa RG, Lange RA, Hillis LD. Prognosis after acute myocardial infarction in patients with and without residual anterograde coronary blood flow. *Am J Cardiol* 1989;64:155-60.
- Galvani M, Ottani F, Ferrini D, Sorbello F, Rusticali F. Patency of the infarct-related artery and left ventricular function as the major determinants of survival after Q-wave acute myocardial infarction. *Am J Cardiol* 1993;71:1-7.
- Lamas GA, Flaker GC, Mitchell G, et al. Effect of infarct artery patency on prognosis after acute myocardial infarction. *Circulation* 1995;92:1101-9.
- Puma JA, Sketch MH Jr, Thompson TD, et al. Support for the open-artery hypothesis in survivors of acute myocardial infarction: analysis of 11,228 patients treated with thrombolytic therapy. *Am J Cardiol* 1999;83:482-7.
- Berger AK, Edris DW, Breall JA, Oetgen WJ, Marciniak TA, Molinari GF. Resource use and quality of care for Medicare patients with acute myocardial infarction in Maryland and the District of Columbia: analysis of data from the Cooperative Cardiovascular Project. *Am Heart J* 1998;135:349-56.
- Guadagnoli E, Hauptman PJ, Ayanian JZ, Pashos CL, McNeil BJ, Cleary PD. Variation in the use of cardiac procedures after acute myocardial infarction. *N Engl J Med* 1995;333:573-8.
- Pilote L, Califf RM, Sapp S, et al. Regional variation across the United States in the management of acute myocardial infarction. *N Engl J Med* 1995;333:565-72.
- Fox KA, Goodman SG, Anderson FA Jr, et al. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;24:1414-24.
- Silva JC, Rochitte CE, Junior JS, et al. Late coronary artery recanalization effects on left ventricular remodelling and contractility by magnetic resonance imaging. *Eur Heart J* 2005;26:36-43.

17. White HD, Braunwald E. Applying the open artery theory: use of predictive survival markers. *Eur Heart J* 1998;19:1132-9.
18. Monteiro P, Antunes A, Goncalves LM, Providencia LA. Long-term clinical impact of coronary-collateral vessels after acute myocardial infarction. *Rev Port Cardiol* 2003;22:1051-61.
19. Porto I, Selvanayagam JB, Van Gaal WJ, et al. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, Thrombolysis in Myocardial Infarction myocardial perfusion grade analysis, and intravascular ultrasound. *Circulation* 2006;114:662-9.
20. Singh M, Rihal CS, Lennon RJ, Garratt KN, Mathew V, Holmes DR Jr. Prediction of complications following nonemergency percutaneous coronary interventions. *Am J Cardiol* 2005;96:907-12.
21. Hochman JS, Lamas GA, Knatterud GL, et al. Design and methodology of the Occluded Artery Trial (OAT). *Am Heart J* 2005;150:627-42.
22. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. [Errata, *N Engl J Med* 2001;345:1506, 1716.]
23. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20. [Erratum, *JAMA* 2003;289:987.]
24. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
25. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
26. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
27. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 2004;44(3):E1-E211.
28. Dzavik V, Buller CE, Lamas G, et al. Late revascularization of occluded infarct-related arteries to achieve long-term patency and improve ventricular function: the Total Occlusion Study of Canada (TOSCA)-2 Trial. *Circulation* (in press).
29. Myocardial infarction redefined — a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000;21:1502-13.
30. Werner GS, Emig U, Mutschke O, Schwarz G, Bahrmann P, Figulla HR. Regression of collateral function after recanalization of chronic total coronary occlusions: a serial assessment by intracoronary pressure and Doppler recordings. *Circulation* 2003;108:2877-82.
31. Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. *Circulation* 1987;75:299-306.
32. Meijer A, Verheugt FW, van Eenige MJ, Werter CJ. Left ventricular function at 3 months after successful thrombolysis: impact of reocclusion without reinfarction on ejection fraction, regional function, and remodeling. *Circulation* 1994;90:1706-14.
33. Sabia PJ, Powers ER, Ragosta M, Sarembock IJ, Burwell LR, Kaul S. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. *N Engl J Med* 1992;327:1825-31.
34. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines) — executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. *Circulation* 2001;103:3019-41.
35. Pfisterer ME, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol* (in press).
36. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* (in press).
37. Kaltoft A, Bottcher M, Nielsen SS, et al. Routine thrombectomy in percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: a randomized, controlled trial. *Circulation* 2006;114:40-7.
38. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA* 2005;293:1063-72.

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