Long-Term Effects of Percutaneous Coronary Intervention of the Totally Occluded Infarct-Related Artery in the Subacute Phase After Myocardial Infarction

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Background—Despite observations suggesting a benefit for late opening of totally occluded infarct-related arteries after myocardial infarction, the Occluded Artery Trial (OAT) demonstrated no reduction in the composite of death, reinfarction, and class IV heart failure over a 2.9-year mean follow-up. Follow-up was extended to determine whether late trends would favor either treatment group.

Methods and Results—OAT randomized 2201 stable patients with infarct-related artery total occlusion >24 hours (calendar days 3–28) after myocardial infarction. Patients with severe inducible ischemia, rest angina, class III-IV heart failure, and 3-vessel/left main disease were excluded. We conducted extended follow-up of enrolled patients for an additional 3 years for the primary end point and angina (6-year median survivor follow-up; longest, 9 years; 12 234 patient-years). Rates of the primary end point (hazard ratio, 1.06; 95% confidence interval, 0.88–1.28), fatal and nonfatal myocardial infarction (hazard ratio, 1.25; 95% confidence interval, 0.89–1.75), death, and class IV heart failure were similar for the percutaneous coronary intervention (PCI) and medical therapy alone groups. No interactions between baseline characteristics and treatment group on outcomes were observed. The vast majority of patients at each follow-up visit did not report angina. There was less angina in the PCI group through early in follow-up; by 3 years, the between group difference was consistently <4 patients per 100 treated and not significantly different, although there was a trend toward less angina in the PCI group at 3 and 5 years. The 7-year rate of PCI of the infarct-related artery during follow-up was 11.1% for the PCI group compared with 14.7% for the medical therapy alone group (hazard ratio, 0.79; 95% confidence interval, 0.61–1.01; P=0.06).

Conclusions—Extended follow-up of the OAT cohort provides robust evidence for no reduction of long-term rates of clinical events after routine PCI in stable patients with a totally occluded infarct-related artery and without severe inducible ischemia in the subacute phase after myocardial infarction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00004562. (Circulation. 2011;124:00:00-00.)

Key Words: myocardial infarction • stents • trials

Early reperfusion reduces mortality from acute myocardial infarction (MI). However, the role of late opening of the totally occluded infarct-related artery (IRA) after MI has been controversial. Despite observational data suggesting a lower event rate for those demonstrated to have an open artery after MI and experimental studies reporting a reduction in adverse left ventricular remodeling after late reperfusion, the Occluded Artery Trial (OAT) failed to confirm the hypothesis that percutaneous coronary intervention (PCI) after MI in stable patients with a totally occluded IRA who met entry criteria on calendar days 3 to 28 would reduce the occurrence of death, reinfarction, or hospitalization for class IV heart failure (HF) over a 2.9-year mean follow-up compared with optimal medical therapy alone. There was an adverse trend in

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the PCI group in the secondary end point of nonfatal reinfarctions \( (P=0.08) \).\textsuperscript{1} Angina was reduced in the PCI group through 3 years in the main trial. Rose angina and dyspnea were demonstrated in the quality-of-life substudy to have been reduced in the PCI group over 24 months, with no difference in physical functioning beyond 4 months of follow-up.\textsuperscript{2} From event rates observed over the initial study period, it was determined that power was excellent (80\%–96\%) to show superiority for medical therapy alone with extended follow-up. We therefore conducted an extended follow-up phase of OAT to examine long-term trends.

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**Clinical Perspective on p ●●●**

**Methods**

The design, methods, and primary results of OAT have been described in detail previously.\textsuperscript{1,3} In brief, 2201 patients with total occlusion of the IRA as visualized on coronary angiography performed >24 hours (calendar days 3–28) after MI were enrolled in the trial if they met the criteria for increased risk of events based on ejection fraction (EF) <50\% and/or proximal occlusion of a large vessel (supplying >25\% of the left ventricular myocardium). Major exclusion criteria were severe inducible ischemia, angina at rest, class III to IV HF, and significant left main or 3-vessel coronary artery disease. Stress testing was recommended before randomization unless there was akinesis or dyskinesis in the infarct zone and no disease remote from the IRA. The time window was based on calendar days, not hours, with day 1 defined as the date of symptom onset. The minimum time from MI to qualifying angiography was therefore just over 24 hours.\textsuperscript{4}

Patients were randomized to PCI of the occluded IRA with optimal medical therapy (PCI group) or optimal medical therapy alone (MED group). PCI of vessels other than the IRA was permitted at the discretion of the treating physician. Patients assigned to receive PCI were to undergo the procedure within 24 hours of randomization. A stent was to be used unless placement was not possible or contraindicated. If the IRA had opened spontaneously between the time of qualifying angiography and protocol-assigned PCI, the investigators proceeded with PCI if technically feasible, provided that residual stenosis was >50\%. PCI success was judged by the angiographic core laboratory, which reviewed all qualifying and procedural angiograms, as an open artery with <50\% residual stenosis and Thrombolysis in Myocardial Infarction grade 2 or 3 flow. All patients in the trial were to receive optimal medical therapy as outlined in a procedures manual, which included aspirin, anticoagulation if indicated, angiotensin-converting enzyme inhibitors, \( \beta \)-blockers, and lipid-lowering therapy unless such treatment was contraindicated. A thienopyridine was recommended before PCI and for 2 to 4 weeks for all patients undergoing stent placement. After the publication of Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO),\textsuperscript{5,6} clopidogrel was recommended as part of medical therapy in general for 1 year.

The primary end point was the composite of death, reinfarction, and class IV HF. The definition of reinfarction required at least two of the following: symptoms, electrocardiogram (ECG) changes, and at least 2-fold elevation of cardiac biomarkers. Class IV HF required admission to a hospital or a short-stay unit. Primary end-point events were confirmed by an independent Mortality and Morbidity Classification Committee; committee members were blinded to treatment assignment. Secondary end points included the components of the primary composite, stroke, HF, revascularization, and angina, among others.\textsuperscript{3}

The primary analysis of the trial included 2166 patients who had been enrolled through December 2005 with an average follow-up of 2.9 years. An additional 35 patients were enrolled through June 2006 during an extended period of enrollment in the nuclear viability ancillary study. All 2201 patients are included here. Additional support was obtained from the National Heart, Lung, and Blood Institute (NHBLI), grant U01 HL062509, to extend follow-up of enrolled patients by another 3 years and to conduct detailed analyses of reinfarctions. As patients at individual sites reached the 5-year mark (the maximum duration of follow-up specified in the original informed consent form), consent for additional follow-up or a waiver of written reconsent granted by the site Institutional Review Board or Ethics Committee was obtained.

All additional follow-up was conducted by telephone. Hospital records were obtained for events. Sites no longer able to follow patients because of staffing issues were encouraged to transfer patients to the Clinical Coordinating Center in the United States or the appropriate regional coordinating center with the approval of the local Institutional Review Board or Ethics Committee. A national or local death index was used to determine vital status (and date of death) at study completion for patients who did not agree to continued follow-up or who could not be contacted.

Among 192 of 212 sites (91\%) with patients eligible for long-term follow-up, 175 sites continued follow-up and 17 transferred follow-up to the Clinical Coordinating Center or a regional coordinating center. The remaining 20 sites did not participate (total, 51 surviving patients). Four hundred thirty-two patients did not provide consent; vital status was available for 198 of these patients and unavailable for the remaining 234 patients (12\% of survivors to 5 years), 193 of whom had not reached a primary end point (102 PCI, 91 MED). Only 1.4\% of patients in the trial (14 PCI, 16 MED) were lost to follow-up before the occurrence of a primary end-point event or 12 months.

The primary end point for long-term follow-up of the cohort remained the composite of death, reinfarction, and hospitalization for class IV HF.\textsuperscript{3} Secondary end points included the components of the composite in addition to cardiovascular death and class III or IV HF. Sites were requested to indicate whether a reinfarction event was procedure-related and to submit cardiac marker data. All potential reinfarction events submitted by sites that occurred at any time throughout the follow-up were reviewed centrally by a group of 5 investigators blinded to treatment assignment to permit classification according to the universal definition of MI.\textsuperscript{7} Sites were not queried routinely for cardiac marker results after revascularization in follow-up or for source documents when isolated postprocedural marker elevation was reported; therefore, we may not have completely captured silent PCI- or coronary artery bypass grafting-related reinfarctions defined by marker elevation as a sole criterion, or combined with ECG in the case of coronary artery bypass grafting.\textsuperscript{7}

Sensitivity analyses were performed comparing 5-year outcomes by treatment group among those surviving patients who declined consent for follow-up beyond the original study period of 5 years (n=432), and among those surviving patients who did provide consent for continued follow-up (n=1504). In addition, 5-year outcomes were compared between patients followed up at sites with better (\( \geq 80\% \)) retention of patients in the long-term follow-up phase (n=1267) and among those surviving patients followed up at sites with <80\% retention (n=669). In these analyses, death was not included in the endpoints because deaths before 5 years were excluded. Finally, we performed a second sensitivity analysis comparing long-term outcomes by treatment assignment among patients who did and did not consent to continued follow-up, counting patients who died before 5 years as having provided consent.

**Statistical Methods**

Baseline characteristics were summarized as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Comparisons by assigned treatment were performed using the \( \chi^2 \) or Fisher exact test for categorical variables and the Student \( t \)-test for continuous variables. Estimates of the cumulative event rates were calculated by the Kaplan-Meier product-limit method,\textsuperscript{8,9} and groups were compared by the log-rank test. Hazard ratios (HRs) and 95\% confidence intervals (CIs) were calculated by Cox proportional hazards regression models.\textsuperscript{10} Interaction tests of treatment by prespecified baseline characteristics were
performed by Cox proportional hazards regression models that included the following terms: treatment, baseline characteristic, and interaction. To control for the covariate-adjusted HR, we used a Cox proportional hazards regression model with 9 baseline variables for the prediction of the long-term follow-up primary outcome. These variables were chosen by backward elimination and were the only variables remaining in the final model with \( P < 0.01 \). A test of treatment interaction with a composite of the 9 baseline variables was performed by ranking patients on the Cox predictors, forming 3 groups (tertiles), and evaluating treatment HR within each risk tertile. The 7-year event rates are presented because the number of patients followed up for \( > 7 \) years was small. Data for patients lost to follow-up were censored at the time of the last contact. This last contact occurred at 5 years from randomization for patients who declined consent for extension of follow-up. Analyses were performed according to the intention-to-treat principle, except for an as-treated analysis.

To control for the type I error rate, it was prespecified in the study protocol that a value of \( P \leq 0.01 \) would be considered to show evidence of differences in secondary analysis. SAS version 9.2 (SAS Institute, Cary, NC) was used for statistical analyses.

**Power Considerations**

The power at the end of the additional follow-up, conditional on the primary outcome event rates by 148 (49%) and deaths by 132 (77%).

**Results**

The addition of the 35 patients in the OAT nuclear viability ancillary study extension phase did not affect baseline characteristics, which were previously published.\(^1\) The average age was 58.6 years. The cohort was made up of 22% women, 21% patients with diabetes mellitus, 11% with prior history of MI, and 22% with prior angina. The mean left ventricular EF was 47.7%. Q waves were noted on the index MI/ECG in 67%. The majority (83%) had single-vessel coronary artery disease. The IRA was the left anterior descending artery in 36%. The median time from MI to randomization was 8 days (interquartile range, 5–16 days); 331 (15%) were randomized ≤3 days after MI. The median time from MI to PCI of the IRA among PCI-assigned patients was 9 days (interquartile range, 5–17 days).

**Secondary Outcomes**

There were no differences between treatment groups in the individual end points of death, reinfection, class IV HF, cardiovascular death, class III to IV HF, or any of the other composite end points examined in the intent-to-treat (Table 1 and Figure 1) or as-treated analysis. Among the reinfections, there were only 7 peri-PCI reinfection events, one of which occurred in the MED group. All 7 met symptom and/or ECG criteria plus elevation of creatine kinase-MB to \( > 3 \) times the

Table 1. Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PCI (n = 1101)</th>
<th>MED (n = 1100)</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>150 (14.6%)</td>
<td>153 (16.0%)</td>
<td>0.85</td>
<td>0.98</td>
<td>0.78–1.22</td>
</tr>
<tr>
<td>CV death</td>
<td>77 (8.0%)</td>
<td>81 (8.0%)</td>
<td>0.76</td>
<td>0.95</td>
<td>0.70–1.30</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>77 (7.7%)</td>
<td>65 (7.2%)</td>
<td>0.27</td>
<td>1.20</td>
<td>0.86–1.67</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>75 (7.5%)</td>
<td>61 (6.8%)</td>
<td>0.20</td>
<td>1.25</td>
<td>0.89–1.75</td>
</tr>
<tr>
<td>Death or MI</td>
<td>212 (20.6%)</td>
<td>199 (21.3%)</td>
<td>0.44</td>
<td>1.08</td>
<td>0.89–1.31</td>
</tr>
<tr>
<td>Class IV HF</td>
<td>51 (5.2%)</td>
<td>53 (5.4%)</td>
<td>0.87</td>
<td>0.97</td>
<td>0.66–1.42</td>
</tr>
<tr>
<td>Class III–IV HF</td>
<td>76 (7.4%)</td>
<td>74 (7.5%)</td>
<td>0.86</td>
<td>1.03</td>
<td>0.75–1.42</td>
</tr>
<tr>
<td>Death, MI, class IV HF*</td>
<td>230 (22.3%)</td>
<td>219 (22.9%)</td>
<td>0.51</td>
<td>1.06</td>
<td>0.88–1.28</td>
</tr>
<tr>
<td>Death, MI, class III–IV HF</td>
<td>249 (23.8%)</td>
<td>235 (24.4%)</td>
<td>0.43</td>
<td>1.07</td>
<td>0.90–1.28</td>
</tr>
<tr>
<td>Revascularization†</td>
<td>212 (21.3%)</td>
<td>252 (25.6%)</td>
<td>0.03</td>
<td>0.81</td>
<td>0.68–0.98</td>
</tr>
<tr>
<td>Universal definition of MI</td>
<td>95 (9.4%)</td>
<td>74 (8.0%)</td>
<td>0.08</td>
<td>1.31</td>
<td>0.97–1.77</td>
</tr>
<tr>
<td>Death, universal definition of MI, class IV HF</td>
<td>236 (22.9%)</td>
<td>221 (23.1%)</td>
<td>0.37</td>
<td>1.10</td>
<td>0.91–1.31</td>
</tr>
</tbody>
</table>

PCI indicates percutaneous coronary intervention; MED, optimal medical therapy only; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HF, heart failure; and MI, myocardial infarction. Shown are the total number of events for full follow-up period (max 9 years). Life table rates for 7 years.

**Duration of Follow-Up**

Patients were followed up to 9 years; median follow-up was 5.8 years (interquartile range, 4.5 to 7.1; 61 years [interquartile range, 5.0–7.4] for survivors), with a total follow-up of 12,234 patient-years. Extended follow up increased the number of surviving patients followed up for \( \geq 5 \) years from 163 to 1388 and increased the number of primary end-point events by 148 (49%) and deaths by 132 (77%).

**Primary Outcome**

The primary outcome (the first occurrence of death from any cause, nonfatal MI, or class IV HF) occurred in 230 patients in the PCI group compared with 219 patients in the MED group with similar 7-year cumulative event rates (see Table 1 and Figure 1). In an as-treated analysis comparing the 953 group with similar 7-year cumulative event rates (see Table 1 and Figure 1). In an as-treated analysis comparing the 953 group with similar 7-year cumulative event rates (see Table 1 and Figure 1).
Angina and Functional Status

At each time point of follow-up, the vast majority of patients did not report angina (Table 2). There was less angina in the PCI group through 1 year; thereafter, the between-group difference was consistently <4 patients per 100 treated and not significantly different, although there was a trend toward less angina in the PCI group at 2, 3, and 5 years (see Table 2). The relationship over time between revascularization and angina was complex; most patients with angina did not undergo revascularization, and some patients developed angina after revascularization. There were no differences between treatment groups in the presence of HF symptoms or New York Heart Association functional class at any time during follow-up (data not shown).

Medication Use During Follow-Up

Use of cardiovascular medications did not differ between treatment groups at any follow-up visit with the exception of clopidogrel, which was used more commonly in the PCI group through the 12-month visit. After this time, use was similar between treatment groups at ~10% to 12%. Use of aspirin, β-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors was high throughout follow-up.

Subgroup Analysis

There was no interaction between any baseline patient characteristic and treatment assignment on the primary end point (Figure 4). There was also no interaction between treatment assignment and risk defined as a continuous measure (P = 0.81) or risk tertile (P = 0.71).

Sensitivity Analysis

No differences were observed in the primary outcome or any secondary outcomes between treatment groups among patients who did or did not consent to follow-up after 5 years, regardless of whether deaths before 5 years were included in the analysis. Similarly, there were no differences in the primary outcome or any secondary outcomes by treatment groups among patients followed up at sites with higher (≥80%) or lower (<80%) rates of obtaining consent from patients for continued follow-up. Women were less likely than men to consent to continued follow-up (P = 0.01), but older (>65 years of age) and younger patients were equally likely to consent. There were no differences by treatment group in outcomes when sites were divided according to number of patients enrolled. There was also no difference in treatment effect on the primary end point or any secondary end point after covariate adjustment.

Effect of Type of Stent on Outcomes

During 2003 to 2006 (after Food and Drug Administration approval of drug-eluting stents [DES] in the United States), 393 patients who were assigned to PCI received a bare metal stent to the IRA and 79 patients received a DES. There was no difference in the primary outcome in these patients on the basis of the type of stent implanted (6-year event rate, 20.4 for DES versus 18.9 for bare metal stent; HR, 1.20; 95% CI, 0.93–4.83; P = 0.53). Rates of nonfatal reinfarction (HR, 2.12 for DES versus bare metal stent; 95% CI, 0.93–4.83; P = 0.07) and death or reinfarction (HR, 1.11; 95% CI, 0.61–2.01; P = 0.74) were also similar between groups on the basis of type of stent used.
Discussion

Additional follow-up and accrual of 194 additional events in the OAT cohort with >12,000 total patient-years provide robust evidence that there was no long-term benefit to a strategy of routine PCI of the totally occluded IRA in patients who were clinically stable in the early post-MI period.

The large majority of stents placed during protocol PCI were bare metal stents, and in most patients, clopidogrel was stopped by the 4-month visit. Although we cannot exclude the possibility that a longer duration of clopidogrel use in PCI-assigned patients would have resulted in a lower rate of stent-related reinfarction events, we believe this should not have led to an advantage of assignment to PCI or MED, because the rates of non–stent-related (types 1–3) MI were similar between groups and the large majority of reinfarction events were spontaneous, as determined when OAT MI events were classified according to the universal definition of MI.12 In fact, greater use of clopidogrel in the PCI group might have been expected to lead to a lower rate of reinfarction in that group, based on the known benefit of clopidogrel after acute coronary syndromes.6,13

Additional follow-up did not unmask any effect of routine PCI on the outcomes of HF or mortality. It had been hypothesized that the apparent attenuation of remodeling associated with assignment to the PCI group in a subset of patients in the Total Occlusion Study of Canada (TOSCA-2) angiographic ancillary study over the year following randomization14 might result in diverging HF rates later in follow-up. This hypothesis is disproved by the data.

It should be noted that there was no difference by treatment assignment in 1-year change in EF, an indicator of viable myocardium at baseline, among 389 patients who had serial measurements of left ventricular function within the nuclear viability and angiographic ancillary studies to OAT14,15; EF improved from baseline to 1 year in 66% of these patients and by ≥5 points in 73% of those patients. In addition, there was no difference in 1-year change in left ventricular volume in the nuclear viability ancillary study of OAT, which was smaller than the angiographic study but had complete volume data.15 The viability study confirmed that most included patients (70%) had at least moderately retained viability in the infarct zone and that PCI did not affect EF or volume changes compared to MED among patients with viability. This finding is consistent with the results of the multicenter Surgical Treatment for Ischemic Heart Failure, which found no interaction between the effect of revascularization on death or cardiovascular hospitalization regardless of whether viability was present at baseline, in 601 patients with left ventricular EF ≤35%.16 In contrast, prior studies that reported an association between viability and improvement in EF and outcome with revascularization were observational and did not have a randomized comparator group treated with an initial strategy of medical therapy alone.17–21

Analyses of subgroups, including those at highest risk, and as-treated analyses of those with successful PCI and MED-assigned patients who did not receive PCI of the IRA,
as well as by type of stent received, yielded findings remarkably consistent with the primary analysis. The early significant benefit of assignment to PCI on the prevalence of angina was not durable at most long-term follow-up time points, although there was a trend toward less angina at 5 years with an angina-free difference between treatment groups of <4 per 100. Angina was reported in a minority of patients during follow-up. The likelihood of angina decreased over time in both groups, with only 10% to 15% reporting angina in years 3 to 7. We have previously shown that revascularization outside of the OAT protocol was not the reason for loss of the early benefit on angina in the PCI group and that there was no difference between treatment groups in the indication for nonprotocol revascularization. In addition, MED treatment was less expensive than PCI in OAT, with a marginal quality-of-life difference between groups in very early follow-up and no quality-of-life difference thereafter. Rose angina and dyspnea were reported in a minority of patients in the quality-of-life substudy of OAT; both symptoms were less common in the PCI arm through 24 months. These results suggest that revascularization should be used selectively for the management of angina in patients with persistent total occlusion of the infarct artery as were enrolled in this trial.

The results presented here apply only to patients who would be eligible for the trial, ie, patients with persistent total occlusion of the IRA >24 hours after MI who were clinically stable, without rest angina or severe inducible ischemia, class III–IV HF, or significant left main or 3-vessel coronary artery disease. The majority of patients had single-vessel coronary artery disease. This study has several limitations. Approximately 20% of patients surviving to 5 years did not consent to additional follow-up. However, vital status was available for 46% of these patients. Clopidogrel was not continued in all patients for 1 year. Outcomes in patients with recent ST-elevation MI (STEMI) treated with PCI or MED may be significantly improved with the more potent platelet receptor ADP antagonist prasugrel. The 2009 American College of Cardiology/American Heart Association (ACC/AHA) guidelines include a class I recommendation for thienopyridines for at least 1 year in patients who have undergone stenting with a DES and “for a minimum of 1 month and ideally up to 12 months” for patients who have undergone stenting with a bare metal stent. Prolonged (1-year) treatment with thienopyridines was not required in OAT and was not used in 85% of patients. Although most reinfarctions occurred after 1 year, the extent to which this affected the results of the trial cannot be determined. Routine DES use might have been more effective in reducing angina, which was uncommon in follow-up; only 8% of PCI patients in OAT received DES.

Current ACC/AHA guidelines include a recommendation against routine PCI of the totally occluded IRA “greater than 24 hours after STEMI in asymptomatic patients with one- or two-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia” based on OAT and other studies. Analysis of the ACC National Cardiovascular Data Registry database shows no meaningful reduction in the use of PCI for patients who appear to meet OAT entry criteria. A misperception regarding the literature on PCI after MI may be contributing to this. PCI for total occlusions appears to convert a stable state to a state that includes a risk of symptomatic reocclusion. We believe this is a different pathophysiological scenario from that which exists in patients with stenotic but patent IRAs for whom a

Table 2. Angina as Reported at Each Follow-Up Visit by Treatment Group

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>PCI</th>
<th>MED</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mo</td>
<td>192/1030 18.6</td>
<td>261/1042 25.0</td>
<td>0.0004</td>
</tr>
<tr>
<td>1 y</td>
<td>165/1010 16.3</td>
<td>219/1006 21.8</td>
<td>0.002</td>
</tr>
<tr>
<td>2 y</td>
<td>132/952 13.9</td>
<td>165/948 17.4</td>
<td>0.03</td>
</tr>
<tr>
<td>3 y</td>
<td>88/865 10.2</td>
<td>117/877 13.3</td>
<td>0.04</td>
</tr>
<tr>
<td>4 y</td>
<td>98/768 12.8</td>
<td>106/790 13.4</td>
<td>0.70</td>
</tr>
<tr>
<td>5 y</td>
<td>73/671 10.9</td>
<td>97/662 14.7</td>
<td>0.04</td>
</tr>
<tr>
<td>6 y</td>
<td>43/431 10.0</td>
<td>58/437 13.3</td>
<td>0.13</td>
</tr>
<tr>
<td>7 y</td>
<td>26/277 9.4</td>
<td>29/253 11.5</td>
<td>0.43</td>
</tr>
<tr>
<td>8 y</td>
<td>16/153 10.5</td>
<td>10/132 7.6</td>
<td>0.40</td>
</tr>
</tbody>
</table>

PCI indicates percutaneous coronary intervention; MED, optimal medical therapy only.

Figure 3. Kaplan-Meier curves for nonprotocol revascularization by treatment assignment. A, Nonprotocol percutaneous coronary intervention (PCI) of any vessel (infarct-related artery [IRA] or non-IRA, percutaneous or surgical). B, Nonprotocol PCI of the IRA by treatment assignment (all indications). Of 135 nonprotocol PCIs performed on the IRA over the follow-up period in the medical therapy alone (MED) group, 22 occurred after a primary end-point event. CI indicates confidence interval.
Figure 4. Subgroup analysis of 7-year primary end-point rate by treatment assignment with interaction testing. Reinfarction events are those confirmed to meet the Occluded Artery Trial (OAT) definition (see Methods). The hazard ratio (HR), (percutaneous coronary intervention [PCI] vs medical therapy alone [MED]) for the primary end point was 0.99 (95% confidence interval [CI], 0.62–1.56) for 331 patients enrolled within 3 days of myocardial infarction (MI) onset and 1.05 (95% CI, 0.86–1.30) among 1870 patients enrolled from MI onset, interaction \( P \) value 0.80. The HR (PCI vs MED) for the primary end point for the subset of patients with proximal left anterior descending coronary artery (LAD) occlusion \((n=271)\) was 1.58 (95% CI, 0.93–2.69). The HR (PCI vs MED) for the primary end point was 1.08 (95% CI, 0.86–1.30) among 1870 patients enrolled >3 days from MI onset, interaction \( P \) value 0.56 for 331 patients enrolled within 3 days of myocardial infarction (MI) onset and 1.05 (95% CI, 0.86–1.30) among 1870 patients enrolled from MI onset, interaction \( P \) value 0.80. The HR (PCI vs MED) for the primary end point for the subset of patients with proximal left anterior descending coronary artery (LAD) occlusion \((n=271)\) was 1.58 (95% CI, 0.93–2.69). The HR (PCI vs MED) for the primary end point was 1.08 (95% CI, 0.86–1.30) among 1870 patients enrolled >3 days from MI onset, interaction \( P \) value 0.56. Baseline heart failure (HF) was defined as 1 or more of the following: history of HF before randomization, rales on examination, S3 gallop on examination, highest Killip class \( \geq 1 \) during index MI before randomization, highest New York Heart Association (NYHA) class \( \geq I \) before index MI, or NYHA class II at randomization. The HR (PCI vs MED) for the primary end point was 1.08 (95% CI, 0.60–1.94) for 240 patients with ischemia on a prerandomization stress test, 1.13 (95% CI, 0.64–1.99) for 358 patients with no ischemia, and 1.04 (95% CI, 0.85–1.29) for 1603 patients who did not have a prerandomization stress test. Stress testing was required unless there was akinesis or dyskinesis of the infarct zone. IRA indicates infarct-related artery.

<table>
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<tr>
<th>Subgroup</th>
<th>PCI</th>
<th>MED</th>
<th>HR</th>
<th>95% CI</th>
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<td>22.3</td>
<td>22.9</td>
<td>1.04</td>
<td>0.86-1.26</td>
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<td>Minority</td>
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<td>37.9</td>
<td>37.3</td>
<td>1.16</td>
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risk of symptomatic reocclusion exists independent of PCI. These 2 very different types of patients have been inappropriately combined in a meta-analysis.\textsuperscript{28} The results of this meta-analysis may have blunted the expected effect of new guideline recommendations on clinical practice. The present publication presents more robust data with far longer follow-up and confirms no improvement in clinical outcomes with routine PCI for total occlusions in stable post-MI patients. As noted, these results apply to patients with at least moderately preserved viability.\textsuperscript{15} In light of the excess cost in patients assigned to routine PCI in OAT,\textsuperscript{2} these findings should now influence this practice pattern.

Conclusion

Robust long-term data confirm that there is no benefit on cardiovascular events associated with a routine strategy of PCI in stable patients with persistent total occlusion of the IRA, 1- or 2-vessel coronary artery disease, and the absence of severe inducible ischemia in the subacute phase after MI.

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Disclosures

None.

References


A substantial proportion of patients with myocardial infarction do not receive early reperfusion, for example, because of late presentation. Persistent total occlusion of the infarct-related artery is a marker of subsequent risk. Despite observational data suggesting a benefit for late opening of occluded infarct-related arteries after myocardial infarction, the Occluded Artery Trial (OAT) demonstrated no reduction in the composite of death, reinfarction, and class IV heart failure over an ≈3-year mean follow-up. OAT randomized 2201 stable patients with total infarct-related artery occlusion >24 hours (calendar days 3–28) after myocardial infarction. Patients with severe inducible ischemia, rest angina, class III to IV heart failure, and 3-vessel/left main disease were excluded. Follow-up was extended to determine whether late trends would favor either treatment group for the primary end point and angina (6-year median survivor follow-up; longest, 9 years). Rates of the primary end point, reinfarction, death, and class IV heart failure were similar for the percutaneous coronary intervention and medical therapy only groups. No interaction between baseline characteristics and treatment group on outcomes was observed, including for those at highest risk. The vast majority of patients at each follow-up visit did not report angina. There was less angina in the PCI group through early follow-up; by 3 years, the between-group difference was <4 per 100 and did not reach statistical significance. Additional follow-up of the OAT cohort with >12 000 total patient-years provides robust evidence for no long-term reduction in clinical events with a strategy of routine percutaneous coronary intervention of the totally occluded infarct-related artery in clinically stable patients in the subacute phase after myocardial infarction.
Long-Term Effects of Percutaneous Coronary Intervention of the Totally Occluded Infarct-Related Artery in the Subacute Phase After Myocardial Infarction
Judith S. Hochman, Harmony R. Reynolds, Vladimír Dzavík, Christopher E. Buller, Witold Ruzyllo, Zygmunt P. Sadowski, Aldo P. Maggioni, Antonio C. Carvalho, James M. Rankin, Harvey D. White, Suzanne Goldberg, Sandra A. Forman, Daniel B. Mark, Gervasio A. Lamas and for the Occluded Artery Trial Investigators

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막힌 혈관, 나중에 여는 것은 소용없다

조 상호 교수 한림대학교 성심병원 순환기내과

Summary

배경
심근경색에서 완전 폐색된 경색 관련 관상동맥을 개통하여 주는 것이 이득이 있을 수 있다는 가능성이 제기되어 왔으나, OAT(the Occluded Artery Trial) 연구에서 평균 2.9년 추적 관찰하였을 때 사망, 재경색과 class IV의 심부전을 합친 임상 사건을 감소시키지 못하였다. 추적 기간을 늘려서 재개통 군에서 장기 예후가 좋아지지 않아 보였다.

방법 및 결과
OAT 연구는 경색 관련 혈관이 24시간 이상(달력으로는 3-28일간) 완전히 막히고 안정적인 2,201명의 안정형 환자를 무작위 배정하였다. 유발 가능한 심한 협심증, 안정형 협심증, Class III-IV의 심부전, 3-혈관에 또는 좌주간 지에 병이 있는 경우는 제외하였다. 일차 목표점과 협심증에 대해서 환자를 추가로 3년간 더 연장하여 추적 관찰 하였다(중간값 6년간, 최장 9년간 추적 관찰, 12,234 환자-년). 일차 목표점의 발생 비율(HR, 1.06; 95% CI, 0.88-1.28), 치명적, 비치명적 심근경색증(HR, 1.25; 95% CI, 0.89-1.75), 사망, Class IV의 심부전은 percutaneous coronary intervention(PCI) 시행군과 약물치료 단독군에서 유사하였다. 기저 환자의 특성과 각 환자군의 상호 간섭(interaction)이 임상 사건에 영향을 미치지 않았다. 거의 대부분의 환자는 추적 관찰기간의 각 방문시에 협심증을 호소하지 않았다. PCI 시행군에서 초기 관찰 기간 동안에 적은 협심증 증상을 호소하였다; 초기 3년까지 양군 간의 차이는 지속적으로 100명 치료당 4명 미만이었고, 3-5년 사이에는 PCI 시행군에서 증상이 적은 경향을 보였으나, 통계적인 차이는 없었다. 7년 관찰 기간 동안 경색 관련 관상동맥에 PCI를 시행하게 되는 비율은 11.1%였고, 약물치료 단독군에서는 14.7%로 차이가 없었다(HR, 0.79; 95% CI, 0.61–1.01; P=0.06).

결론
OAT 연구를 연장해서 추적 관찰하였을 때, 안정적이며 심한 협심증이 유발되지 않는 아급성 상태의 심근경색 환자에서 완전히 막힌 경색 관련 혈관에 일괄적으로 모두 PCI를 시행하는 것이 장기간의 임상 사건을 감소시키지 못하였다.
OAT 연구는 1,082명의 심근경색 후 안정적인 환자를, 경색 3-28일 경과한 후 관상동맥중재술 시행과 약물치료를 병행한 군과 약물치료 단독군으로 나누어 4년간 사망, 재경색, 혹은 심부전을 살펴본 연구인데, 양군 간에 차이가 없었다. 단지 PCI 시행군에서 4개월, 1개월째 협심증 증상이 의미있게 적었으나, 이것도 3년째에는 차이가 없었다.

또한, 이후에 출간된 이러한 환자에서 협심증을 포함한 생활의 질(quality-of-life) 측면에서도 PCI를 시행한 군에서 이득이 없었고 비용은 많이 소요되었다. 단지 심의 질을 반영한 생명 연장에서 PCI 시행군에서 약간의 이득이 있을 뿐이었다. 1

이번 연구는 이러한 OAT 연구를 연장하여, 평균 6년(최장 9년)이라는 비교적 장기간 관찰한 결과이다. 결론은 PCI와 약물치료를 병행한 군과 약물치료 단독군에서 사망, 재경색, 재관류 등의 hard endpoint는 물론 협심증을 비롯한 증상도 양군 간에 차이가 없다는 결과를 보여 주어 다시 한번 OAT 연구의 결과를 재확인시켜 주었다.

이러한 초기 OAT 연구 결과는 2007년에 개정된 American College of Cardiology(ACC)/American Heart Association(AHA)의 ST-segment elevation myocardial infarction(STEMI) 치료 가이드라인에 반영되었다. 즉, 증상이 없고 안정적인 급성 심근경색 환자에서는 24시간 이상 경과한 후에 막힌 관상동맥을 열어주지 않을 것을 권하고 권유하고 있다(class III).

그러나 OAT 연구의 대상 환자와 유사한 환자 28,780명을 대상으로 미국에서 시행된 최근의 분석에 따르면 OAT와 상기 가이드라인이 발표된 이후에도 유사 환자들에서 PCI를 시행하는 비율이 감소하지 않았다. 2 즉, 미국의 많은 의사들이 이러한 가이드라인이 OAT의 연구 결과를 따르지 않고, 심근경색 후 시간이 경과한 막힌 혈관을 돌고 있다는 것이다. 그 이유로는 의사들의 새로운 연구 결과 및 개정된 가이드라인에 대한 인지 부족, 연구에 대한 신뢰 결여, 그동안의 치료 관행(inertia)을 들 수 있었다. 객관적 데이터와는 무관하게 막힌 혈관을 재개통시키는 것이 이로울 것이라는 막연한 생각이 큰 부분을 차지할 것이다.

이러한 현상은 비단 미국에만 국한된 이야기가 아닐 것이다. 국내에서도 1일 이상 경과, 더욱 느슨하게 적용하여, 3일 이상 경과한 소위 recent MI(myocardial infarction) 환자에서 증상이 없고 안정적인 경우에도 경색 관련 혈관에 PCI를 시행하는 경우가 많으리라 생각된다.

Long-Term Effects of Percutaneous Coronary Intervention of the Totally Occluded Infarct-Related Artery in the Subacute Phase After Myocardial Infarction

Judith S. Hochman, MD; Harmony R. Reynolds, MD; Vladimír Džavík, MD; Christopher E. Buller, MD; Witold Ruzlylo, MD; Zygmun P. Sadowski, MD; Aldo P. Maggioni, MD; Antonio C. Carvalho, MD; James M. Rankin, MD; Harvey D. White, MD; Suzanne Goldberg, RN, M SN; Sandra A. Forman, MA; Daniel B. Mark, MD, MPH; Gervasio A. Lamas, MD; for the Occluded Artery Trial Investigators

Background—Despite observations suggesting a benefit for late opening of totally occluded infarct-related arteries after myocardial infarction, the Occluded Artery Trial (OAT) demonstrated no reduction in the composite of death, reinfarction, and class IV heart failure over a 2.9-year mean follow-up. Follow-up was extended to determine whether late trends would favor either treatment group.

Methods and Results—OAT randomized 2201 stable patients with infarct-related artery total occlusion ≥24 hours (calendar days 3–28) after myocardial infarction. Patients with severe inducible ischemia, rest angina, class III-IV heart failure, and 3-vessel/left main disease were excluded. We conducted extended follow-up of enrolled patients for an additional 3 years for the primary end point and angina (6-year median survivor follow-up; longest, 9 years; 12234 patient-years). Rates of the primary end point (hazard ratio, 1.06; 95% confidence interval, 0.88–1.28), fatal and nonfatal myocardial infarction (hazard ratio, 1.25; 95% confidence interval, 0.89–1.75), death, and class IV heart failure were similar for the percutaneous coronary intervention (PCI) and medical therapy alone groups. No interactions between baseline characteristics and treatment group on outcomes were observed. The vast majority of patients at each follow-up visit did not report angina. There was less angina in the PCI group through early in follow-up; by 3 years, the between group difference was consistently <4 patients per 100 treated and not significantly different, although there was a trend toward less angina in the PCI group at 3 and 5 years. The 7-year rate of PCI of the infarct-related artery during follow-up was 11.1% for the PCI group compared with 14.7% for the medical therapy alone group (hazard ratio, 0.79; 95% confidence interval, 0.61–1.01; P = 0.06).

Conclusions—Extended follow-up of the OAT cohort provides robust evidence for no reduction of long-term rates of clinical events after routine PCI in stable patients with a totally occluded infarct-related artery and without severe inducible ischemia in the subacute phase after myocardial infarction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00004562.

Key Words: myocardial infarction • stents • trials

Early reperfusion reduces mortality from acute myocardial infarction (MI). However, the role of late opening of the totally occluded infarct-related artery (IRA) after MI has been controversial. Despite observational data suggesting a lower event rate for those demonstrated to have an open artery after MI and experimental studies reporting a reduction in adverse left ventricular remodeling after late reperfusion, the Occluded Artery Trial (OAT) failed to confirm the hypothesis that percutaneous coronary intervention (PCI) after MI in stable patients with a totally occluded IRA who met entry criteria on calendar days 3 to 28 would reduce the occurrence of death, reinfarction, or hospitalization for class IV heart
failure (HF) over a 2.9-year mean follow-up compared with optimal medical therapy alone. There was an adverse trend in the PCI group in the secondary end point of nonfatal reinfarctions (P = 0.08). Angina was reduced in the PCI group through 3 years in the main trial. Rose angina and dyspnea were demonstrated in the quality-of-life substudy to have been reduced in the PCI group over 24 months, with no difference in physical functioning beyond 4 months of follow-up. From event rates observed over the initial study period, it was determined that power was excellent (80-96%) to show superiority for medical therapy alone with extended follow-up. We therefore conducted an extended follow-up phase of OAT to examine long-term trends.

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**Methods**

The design, methods, and primary results of OAT have been described in detail previously. In brief, 2201 patients with total occlusion of the IRA as visualized on coronary angiography performed >24 hours (calendar days 3–28) after MI were enrolled in the trial if they met the criteria for increased risk of events based on ejection fraction (EF) <50% and/or proximal occlusion of a large vessel (supplying >25% of the left ventricular myocardium). Major exclusion criteria were severe inducible ischemia, angina at rest, class III to IV HF, and significant left main or 3-vessel coronary artery disease. Stress testing was recommended before randomization unless there was akinesis or dyskinesia in the infarct zone and no disease remote from the IRA. The time window was based on calendar days, not hours, with day 1 defined as the day of symptom onset. The minimum time from MI to qualifying angiography was therefore just over 24 hours.

Patients were randomized to PCI of the occluded IRA with optimal medical therapy (PCI group) or optimal medical therapy alone (MED group). PCI of vessels other than the IRA was permitted at the discretion of the treating physician. Patients assigned to receive PCI were to undergo the procedure within 24 hours of randomization. A stent was to be used unless placement was not possible or contraindicated. If the IRA had opened spontaneously between the time of qualifying angiography and protocol-defined PCI, the investigators proceeded with PCI if technically feasible, provided that residual stenosis was >50%. PCI success was judged by the angiographic core laboratory, which reviewed all qualifying and procedural angiograms, as an open artery with <50% residual stenosis and Thrombolysis in Myocardial Infarction grade 2 or 3 flow. All patients in the trial were to receive optimal medical therapy as outlined in a procedures manual, which included aspirin, anticoagulation if indicated, angiotensin-converting enzyme inhibitors, β-blockers, and lipid-lowering therapy unless such treatment was contraindicated. A thienopyridine was recommended before PCI and for 2 to 4 weeks for all patients undergoing stent placement. A letter the publication of Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO), clopidogrel was recommended as part of medical therapy in general for 1 year.

The primary end point was the composite of death, reinfarction, and class IV HF. The definition of reinfarction required at least two of the following: symptoms, electrocardiogram (ECG) changes, and at least 2-fold elevation of cardiac biomarkers. Class IV HF required admission to a hospital or a short-term visit. Primary end-point events were confirmed by an independent Mortality and Morbidity Classification Committee; committee members were blinded to treatment assignment. Secondary end points included the components of the primary composite, stroke, HF, revascularization, and angina, among others.

The primary analysis of the trial included 2166 patients who had been enrolled through December 2005 with an average follow-up of 2.9 years. An additional 35 patients were enrolled through June 2006 during an extended period of enrollment in the nuclear viability ancillary study. All 2201 patients are included here. Additional support was obtained from the National Heart, Lung, and Blood Institute (NHLBI), grant U01 HL062509, to extend follow-up of enrolled patients by another 3 years and to conduct detailed analyses of reinfarctions. As patients at individual sites reached the 5-year mark (the maximum duration of follow-up specified in the original informed consent form), consent for additional follow-up or a waiver of written reconsent granted by the site Institutional Review Board or Ethics Committee was obtained.

All additional follow-up was conducted by telephone. Hospital records were obtained for events. Sites no longer able to follow patients because of staffing issues were encouraged to transfer patients to the Clinical Coordinating Center in the United States or the appropriate regional coordinating center with the approval of the local Institutional Review Board or Ethics Committee. A national or local death index was used to determine vital status (and date of death) at study completion for patients who did not agree to continued follow-up or who could not be contacted.

Among 192 of 211 sites (91%) with patients eligible for long-term follow-up, 175 sites continued follow-up and 17 transferred follow-up to the Clinical Coordinating Center or a regional coordinating center. The remaining 20 sites did not participate (total, 51 surviving patients). Four hundred thirty-two patients did not provide consent; vital status was available for 198 of these patients and unavailable for the remaining 234 patients (12% of survivors to 5 years), 193 of whom had not reached a primary end point (102 PCI, 91 MED). Only 1.4% of patients in the trial (14 PCI, 16 MED) were lost to follow-up before the occurrence of a primary end-point event or 12 months.

The primary end point for long-term follow-up of the cohort remained the composite of death, reinfarction, and hospitalization for class IV HF. Secondary end points included the components of the composite in addition to cardiovascular death and class III or IV HF. Sites were requested to indicate whether a reinfarction event was procedure-related and to submit cardiac marker data. All potential reinfarction events submitted by sites that occurred at any time throughout the follow-up were reviewed centrally by a group of 5 investigators blinded to treatment assignment to permit classification according to the universal definition of MI. Sites were not queried routinely for cardiac marker results after revascularization in follow-up or for source documents when isolated postprocedural marker elevation was reported; therefore, we may not have completely captured silent PCI- or coronary artery bypass grafting-related reinfarctions defined by marker elevation as a sole criterion, or combined with ECG in the case of coronary artery bypass grafting.

Sensitivity analyses were performed comparing 5-year outcomes by treatment group among those surviving patients who declined consent for follow-up beyond the original study period of 5 years (n = 432) and among those surviving patients who did provide consent for continued follow-up (n = 1504). In addition, 5-year outcomes were compared between patients followed up at sites with better (≥80%) retention of patients in the long-term follow-up phase (n = 1267) and among those surviving patients followed up at sites with <80% retention (n = 669). In these analyses, death was not included in the endpoints because deaths before 5 years were excluded. Finally, we performed a second sensitivity analysis comparing long-term outcomes by treatment assignment among patients who did and did not consent to continued follow-up, counting patients who died before 5 years as having provided consent.

**Statistical Methods**

Baseline characteristics were summarized as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Comparisons by assigned treatment were performed using the χ² or Fisher exact test for categorical variables and the Student t-test for continuous variables. Estimates of the cumulative event rates were calculated by the Kaplan-Meier product-limit method, and groups were compared by the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were
calculated by Cox proportional hazards regression models.10 Interaction tests of treatment by prespecified baseline characteristics were performed by Cox proportional hazards regression models that included the following terms: treatment, baseline characteristic, and interaction. To generate the covariate-adjusted HR, we used a Cox proportional hazards regression model with 9 baseline variables for the prediction of the long-term follow-up primary outcome. These variables were chosen by backward elimination and were the only variables remaining in the final model with $P<0.01$. A test of treatment interaction with a composite of the 9 baseline variables was performed by ranking patients on the Cox predictors, forming 3 tertiles, and evaluating treatment HR within each risk tertile. The 7-year event rates are presented because the number of patients followed up for $>7$ years was small. Data for patients lost to follow-up were censored at the time of the last contact. This last contact occurred at 5 years from randomization for patients who declined consent for extension of follow-up. Analyses were performed according to the intention-to-treat principle, except for an as-treated analysis.

To control for the type I error rate, it was prespecified in the study protocol that a value of $P \leq 0.01$ would be considered to show evidence of differences in secondary analysis. SAS version 9.2 (SAS Institute, Cary, NC) was used for statistical analyses.

### Power Considerations

The power at the end of the additional follow-up, conditional on the observed event rates, was projected to be 80% to 96% based on average event rates over years 4–5 or 3–5, respectively to detect a significant difference between groups at the end of year 8 with a log-rank test (2 tailed) at $\alpha=0.05$.

### Results

The addition of the 35 patients in the OAT nuclear viability ancillary study extension phase did not affect baseline characteristics, which were previously published.1 The average age was 58.6 years. The cohort was made up of 22% women, 21% patients with diabetes mellitus, 11% with prior history of MI, and 22% with prior angina. The mean left ventricular EF was 47.7%. Q waves were noted on the index MI/ECG in 67%. The majority (83%) had single-vessel coronary artery disease. The IRA was the left anterior descending artery in 36%. The median time from MI to randomization was 8 days (interquartile range, 5–16 days); 331 (15%) were randomized $\leq 3$ days after MI. The median time from MI to PCI of the IRA among PCI-assigned patients was 9 days (interquartile range, 5–17 days).

### Duration of Follow-Up

Patients were followed up to 9 years; median follow-up was 5.8 years (interquartile range, 4.5 to 7.1; 6.1 years [interquartile range, 5.0–7.4] for survivors), with a total follow-up of 12,234 patient-years. Extended follow-up increased the number of surviving patients followed up for $>5$ years from 163 to 1388 and increased the number of primary end-point events by 148 (49%) and deaths by 132 (77%).

### Primary Outcome

The primary outcome (the first occurrence of death from any cause, nonfatal MI, or class IV HF) occurred in 230 patients in the PCI group compared with 219 patients in the MED group with similar 7-year cumulative event rates (see Table 1 and Figure 1). In an as-treated analysis comparing the 953 patients in the PCI group in whom PCI was adjudicated to be successful with the 1070 patients in the MED group who did not cross over to PCI within 30 days after randomization, there was no difference between groups for the primary end point (HR, 1.04; 95% CI, 0.86–1.27; $P=0.68$).

### Secondary Outcomes

There were no differences between treatment groups in the individual end points of death, reinfarction, class IV HF, cardiovascular death, class III to IV HF, or any of the other composite end points examined in the intent-to-treat (Table 1 and Figure 2) or as-treated analysis. Among the reinfarctions, there were only 7 peri-PCI reinfarction events, one of which

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**Table 1. Primary and Secondary Outcomes**

<table>
<thead>
<tr>
<th>Event</th>
<th>PCI (n = 1101)</th>
<th>MED (n = 1100)</th>
<th>$P$</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>150</td>
<td>153</td>
<td>0.85</td>
<td>0.98</td>
<td>0.78–1.22</td>
</tr>
<tr>
<td>CV death</td>
<td>77</td>
<td>81</td>
<td>0.76</td>
<td>0.95</td>
<td>0.70–1.30</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>77</td>
<td>65</td>
<td>0.27</td>
<td>1.20</td>
<td>0.86–1.67</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>75</td>
<td>61</td>
<td>0.20</td>
<td>1.25</td>
<td>0.89–1.75</td>
</tr>
<tr>
<td>Death or MI</td>
<td>212</td>
<td>199</td>
<td>0.44</td>
<td>1.08</td>
<td>0.89–1.31</td>
</tr>
<tr>
<td>Class IV HF</td>
<td>51</td>
<td>53</td>
<td>0.87</td>
<td>0.97</td>
<td>0.66–1.42</td>
</tr>
<tr>
<td>Class III–IV HF</td>
<td>76</td>
<td>74</td>
<td>0.86</td>
<td>1.03</td>
<td>0.75–1.42</td>
</tr>
<tr>
<td>Death, MI, class IV HF*</td>
<td>230</td>
<td>219</td>
<td>0.51</td>
<td>1.06</td>
<td>0.88–1.28</td>
</tr>
<tr>
<td>Death, MI, class III–IV HF</td>
<td>249</td>
<td>235</td>
<td>0.43</td>
<td>1.07</td>
<td>0.90–1.28</td>
</tr>
<tr>
<td>Revascularization†</td>
<td>212</td>
<td>252</td>
<td>0.03</td>
<td>0.81</td>
<td>0.68–0.98</td>
</tr>
<tr>
<td>Universal definition of MI</td>
<td>95</td>
<td>74</td>
<td>0.08</td>
<td>1.31</td>
<td>0.97–1.77</td>
</tr>
<tr>
<td>Death, universal definition of MI, class IV HF</td>
<td>236</td>
<td>221</td>
<td>0.37</td>
<td>1.09</td>
<td>0.91–1.31</td>
</tr>
</tbody>
</table>

*Primary outcome.†Excluding protocol PCI.

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1. The power at the end of the additional follow-up, conditional on the observed event rates, was projected to be 80% to 96% (based on average event rates over years 4–5 or 3–5, respectively) to detect a significant difference between groups at the end of year 8 with a log-rank test (2 tailed) at $\alpha=0.05$.

2. Cox proportional hazards regression models were used for statistical analyses.

3. The primary outcome (the first occurrence of death from any cause, nonfatal MI, or class IV HF) occurred in 230 patients in the PCI group compared with 219 patients in the MED group with similar 7-year cumulative event rates (see Table 1 and Figure 1). In an as-treated analysis comparing the 953 patients in the PCI group in whom PCI was adjudicated to be successful with the 1070 patients in the MED group who did not cross over to PCI within 30 days after randomization, there was no difference between groups for the primary end point (HR, 1.04; 95% CI, 0.86–1.27; $P=0.68$).

4. There were no differences between treatment groups in the individual end points of death, reinfarction, class IV HF, cardiovascular death, class III to IV HF, or any of the other composite end points examined in the intent-to-treat (Table 1 and Figure 2) or as-treated analysis. Among the reinfarctions, there were only 7 peri-PCI reinfarction events, one of which
occurred in the MED group. All 7 met symptom and/or ECG criteria plus elevation of creatine kinase-MB to >3 times the upper limit of normal. When the universal definition of MI was used, a total of 169 site-determined MI events were confirmed compared with 142 that met OAT criteria. The reinfarction rates according to the universal definition of MI were similar for PCI compared with MED (HR, 1.31; 95% CI, 1.06–1.65), indicating that lesion location may be a factor in the pathogenesis of reinfarction. In the PCI group, 179 patients underwent follow-up in the PCI group, but this differed significantly from that in the PCI group (Figure 3B). Among 135 nonprotocol PCIs, 152 (38%) did not undergo revascularization and some patients developed angina after revascularization.11 There were no differences between treatment groups in the presence of HF symptoms or New York Heart Association functional class at any time during follow-up (data not shown).

Angina and Functional Status
At each time point of follow-up, the vast majority of patients did not report angina (Table 2). There was less angina in the PCI group through 1 year; thereafter, the between-group difference was consistently <4 patients per 100 treated and not significantly different, although there was a trend toward less angina in the PCI group at 2, 3, and 5 years (see Table 2). The relationship over time between revascularization and angina was complex; most patients with angina did not undergo revascularization, and some patients developed angina after revascularization.11 There were no differences between treatment groups in the presence of HF symptoms or New York Heart Association functional class at any time during follow-up (data not shown).

Medication Use During Follow-Up
Use of cardiovascular medications did not differ between treatment groups at any follow-up visit with the exception of aspirin, β-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors was high throughout follow-up.

Subgroup Analysis
There was no interaction between any baseline patient characteristic and treatment assignment on the primary end point (Figure 4). There was also no interaction between treatment assignment and risk defined as a continuous measure (P = 0.81) or risk tertile (P = 0.71).

Sensitivity Analysis
No differences were observed in the primary outcome or any secondary outcomes between treatment groups among patients who did or did not consent to follow-up after 5 years, regardless of whether deaths before 5 years were included in the analysis. Similarly, there were no differences in the primary outcome or any secondary outcomes by treatment groups among patients followed up at sites with higher (≥80%) or lower (<80%) rates of obtaining consent from patients for continued follow-up. Women were less likely than men to consent to continued follow-up (P = 0.01), but older (>65 years of age) and younger patients were equally likely to consent. There were no differences by treatment group in outcomes when sites were divided according to number of patients enrolled. There was also no difference in treatment effect on the primary end point or any secondary end point after covariate adjustment.

Effect of Type of Stent on Outcomes
During 2003 to 2006 (after Food and Drug Administration approval of drug-eluting stents [DES] in the United States), 393 patients who were assigned to PCI received a bare metal stent to the IRA and 79 patients received a DES. There was no difference in the primary outcome in these patients on the basis of the type of stent implanted (6-year event rate, 20.4 for DES versus 18.9 for bare metal stent; HR, 1.20; 95% CI, 0.68–2.1; P = 0.53). Rates of nonfatal reinfarction (HR, 2.12 for DES versus bare metal stent; 95% CI, 0.93–4.83;
P=0.07) and death or reinfarction (HR, 1.11; 95% CI, 0.61–2.01; P=0.74) were also similar between groups on the basis of type of stent used.

Discussion

Additional follow-up and accrual of 194 additional events in the OAT cohort with >12 000 total patient-years provide robust evidence that there was no long-term benefit to a strategy of routine PCI of the totally occluded IRA in patients who were clinically stable in the early post-MI period.

The large majority of stents placed during protocol PCI were bare metal stents, and in most patients, clopidogrel was stopped by the 4-month visit. Although we cannot exclude the possibility that a longer duration of clopidogrel use in PCI-assigned patients would have resulted in a lower rate of stent-related reinfarction events, we believe this should not have led to an advantage of assignment to PCI or MED, because the rates of non–stent-related (types 1–3) MI were similar between groups and the large majority of reinfarction events were spontaneous, as determined when OAT MI events were classified according to the universal definition of MI.12 In fact, greater use of clopidogrel in the PCI group might have been expected to lead to a lower rate of reinfarction in that group, based on the known benefit of clopidogrel after acute coronary syndromes.6,13

Additional follow-up did not unmask any effect of routine PCI on the outcomes of HF or mortality. It had been hypothesized that the apparent attenuation of remodeling associated with assignment to the PCI group in a subset of patients in the Total Occlusion Study of Canada (TOSCA-2) angiographic ancillary study over the year following randomization14 might result in diverging HF rates later in follow-up. This hypothesis is disproved by the data.

It should be noted that there was no difference by treatment assignment in 1-year change in EF, an indicator of viable myocardium at baseline, among 389 patients who had serial measurements of left ventricular function within the nuclear viability and angiographic ancillary studies to OAT14,15; EF improved from baseline to 1 year in 66% of these patients and by ≥5 points in 73% of those patients. In addition, there was no difference in 1-year change in left ventricular volume in the nuclear viability ancillary study of OAT, which was smaller than the angiographic study but had complete volume data.15 The viability study confirmed that most included patients (70%) had at least moderately retained viability in the infarct zone and that PCI did not affect EF or volume changes compared to MED among patients with viability. This finding is consistent with the results of the multicenter Surgical Treatment for Ischemic Heart Failure, which found no interaction between the effect of revascularization on death or cardiovascular hospitalization regardless of whether viability was present at baseline, in 601 patients with left ventricular EF ≤35%.16 In contrast, prior studies that reported an association between viability and improvement in EF and outcome with revascularization were observational and did

Figure 2. Kaplan-Meier curves for the secondary end points according to the intention-to-treat analysis. A, Death (%). B, Fatal and nonfatal reinfarction (ReMI; %). C, Nonfatal reinfarction (%). Reinfarction events are those confirmed to meet the OAT definition (see Methods). D, Class IV heart failure (%). CHF indicates congestive heart failure; MED, medical therapy alone; PCI, percutaneous coronary intervention; and CI, confidence interval.
not have a randomized comparator group treated with an initial strategy of medical therapy alone.17–21 Analyses of subgroups, including those at highest risk, and as-treated analyses of those with successful PCI and MED-assigned patients who did not receive PCI of the IRA, as well as by type of stent received, yielded findings remarkably consistent with the primary analysis.

The early significant benefit of assignment to PCI on the prevalence of angina was not durable at most long-term follow-up time points, although there was a trend toward less angina at 5 years with an angina-free difference between treatment groups of <4 per 100. Angina was reported in a minority of patients during follow-up. The likelihood of angina decreased over time in both groups, with only 10% to 15% reporting angina in years 3 to 7. We have previously shown that revascularization outside of the OAT protocol was not the reason for loss of the early benefit on angina in the PCI group and that there was no difference between treatment groups in the indication for nonprotocol revascularization.21 In addition, MED treatment was less expensive than PCI in OAT, with a marginal quality-of-life difference between groups in very early follow-up and no quality-of-life difference thereafter.2 Rose angina and dyspnea were reported in a minority of patients in the quality-of-life substudy of OAT; both symptoms were less common in the PCI arm through 24 months.2 These results suggest that revascularization should be used selectively for the management of angina in patients with persistent total occlusion of the infarct artery as were enrolled in this trial.

The results presented here apply only to patients who would be eligible for the trial, ie, patients with persistent total occlusion of the IRA >24 hours after MI who were clinically stable, without rest angina or severe inducible ischemia, class III-IV HF, or significant left main or 3-vessel coronary artery disease. The majority of patients had single-vessel coronary artery disease. This study has several limitations. Approximately 20% of patients surviving to 5 years did not consent to additional follow-up. However, vital status was available for 46% of these patients. Clopidogrel was not continued in all patients for 1 year. Outcomes in patients with recent ST-elevation MI (STEMI) treated with PCI or MED may be significantly improved with the more potent platelet receptor ADP antagonist prasugrel.22 The 2009 American College of Cardiology/American Heart Association (ACC/AHA) guidelines include a class I recommendation for thienopyridines for at least 1 year in patients who have undergone stenting with a DES and “for a minimum or 1 month and ideally up to 12 months” for patients who have undergone stenting with a bare metal stent.23 Prolonged (1-year) treatment with thienopyridines was not required in OAT and was not used in 85% of patients. Although most reinfarctions occurred after 1 year, the extent to which this affected the results of the trial cannot be determined. Routine DES use might have been more effective in reducing angina, which was uncommon in follow-up; only 8% of PCI patients in OAT received DES.24 Current ACC/AHA guidelines include a recommendation against routine PCI of the totally occluded IRA “greater than 24 hours after STEMI in asymptomatic patients with one- or two-vessel disease if they are hemodynamically and electrically stable and do not have evidence of severe ischemia” based on OAT and other studies.26 Analysis of the ACC National Cardiovascular Data Registry database27 shows no meaningful reduction in the use of PCI for patients who appear to meet OAT entry criteria. A misperception regarding

![Figure 3. Kaplan-Meier curves for nonprotocol revascularization by treatment assignment. A, Nonprotocol percutaneous coronary intervention (PCI) of any vessel (infarct-related artery [IRA] or non-IRA, percutaneous or surgical). B, Nonprotocol PCI of the IRA by treatment assignment (all indications). Of 135 nonprotocol PCIs performed on the IRA over the follow-up period in the medical therapy alone (MED) group, 22 occurred after a primary end-point event. CI indicates confidence interval.](http://circ1ahajournals1org/Downloaded from)

| Table 2. Angina as Reported at Each Follow-Up Visit by Treatment Group |
|------------------|------------------|
| Follow-Up       | PCI              | MED              | P     |
|                 | n    | %    | n    | %    |
| 4 mo            | 192/1030 | 18.6 | 261/1042 | 25.0 | 0.0004 |
| 1 y             | 165/1010 | 16.3 | 219/1006 | 21.8 | 0.002 |
| 2 y             | 132/952  | 13.9 | 165/948  | 17.4 | 0.03  |
| 3 y             | 88/865   | 10.2 | 117/877  | 13.3 | 0.04  |
| 4 y             | 98/768   | 12.8 | 106/790  | 13.4 | 0.70  |
| 5 y             | 73/671   | 10.9 | 97/862   | 14.7 | 0.04  |
| 6 y             | 43/431   | 10.0 | 58/437   | 13.3 | 0.13  |
| 7 y             | 26/277   | 9.4  | 29/253   | 11.5 | 0.43  |
| 8 y             | 16/153   | 10.5 | 10/132   | 7.6  | 0.40  |

PCI indicates percutaneous coronary intervention; MED, optimal medical therapy only.
Figure 4. Subgroup analysis of 7-year primary end-point rate by treatment assignment with interaction testing. Reinfarction events are those confirmed to meet the Occluded Artery Trial (OAT) definition (see Methods). The hazard ratio (HR), (percutaneous coronary intervention [PCI] vs medical therapy alone [MED]) for the primary end point was 0.99 (95% confidence interval [CI], 0.62–1.56) for 331 patients enrolled within 3 days of myocardial infarction (MI) onset and 1.05 (95% CI, 0.86–1.30) among 1870 patients enrolled >3 days from MI onset, interaction \( P \) [int-p] = 0.80. The HR (PCI vs MED) for the primary end point for the subset of patients with proximal left anterior descending coronary artery (LAD) occlusion (n=271) was 1.58 (95% CI, 0.93–2.69). The HR (PCI vs MED) for the primary end point was 1.08 (95% CI, 0.60–1.94) for 240 patients with ischemia on a prerandomization stress test, 1.13 (95% CI, 0.64–1.99) for 358 patients with no ischemia, and 1.04 (95% CI, 0.85–1.29) for 1603 patients who did not have a prerandomization stress test. Stress testing was required unless there was akinesis or dyskinesis of the infarct zone. IRA indicates infarct-related artery.
the literature on PCI after MI may be contributing to this. PCI for total occlusions appears to convert a stable state to a state that includes a risk of symptomatic reocclusion. We believe this is a different pathophysiological scenario from that which exists in patients with stenotic but patent IRA's for whom a risk of symptomatic reocclusion exists independent of PCI. These 2 very different types of patients have been inappropriately combined in a meta-analysis. The results of this meta-analysis may have blunted the expected effect of new guideline recommendations on clinical practice. The present publication presents more robust data with far longer follow-up and confirms no improvement in clinical outcomes following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;288:2411–2420.


He ZX, Yang MF, Liu XJ, Shi RF, Gao RL, Hu SS, Wu QY, Yan YJ, Chen JL. Association of myocardial viability on nitrate-augmented technetium-99m hexakis-2-methoxyisobutyl isonitri lemyocardial...


CLINICAL PERSPECTIVE

A substantial proportion of patients with myocardial infarction do not receive early reperfusion, for example, because of late presentation. Persistent total occlusion of the infarct-related artery is a marker of subsequent risk. Despite observational data suggesting a benefit for late opening of occluded infarct-related arteries after myocardial infarction, the Occluded Artery Trial (OAT) demonstrated no reduction in the composite of death, reinfarction, and class IV heart failure over an ~3-year mean follow-up. OAT randomized 2201 stable patients with total infarct-related artery occlusion >24 hours (calendar days 3–28) after myocardial infarction. Patients with severe inducible ischemia, rest angina, class III to IV heart failure, and 3-vessel/left main disease were excluded. Follow-up was extended to determine whether late trends would favor either treatment group for the primary end point and angina (6-year median survivor follow-up; longest, 9 years). Rates of the primary end point, reinfarction, death, and class IV heart failure were similar for the percutaneous coronary intervention and medical therapy only groups. No interaction between baseline characteristics and treatment group on outcomes was observed, including for those at highest risk. The vast majority of patients at each follow-up visit did not report angina. There was less angina in the PCI group through early follow-up; by 3 years, the between-group difference was <4 per 100 and did not reach statistical significance. Additional follow-up of the OAT cohort with >12 000 total patient-years provides robust evidence for no long-term reduction in clinical events with a strategy of routine percutaneous coronary intervention of the totally occluded infarct-related artery in clinically stable patients in the subacute phase after myocardial infarction.