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Loss of Short Term Symptomatic Benefit in Patients with an Occluded Infarct Artery is Unrelated to Non-Protocol Revascularization: Results from the Occluded Artery Trial (OAT)

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Abstract

Background—The Occluded Artery Trial found that routine late (3–28d post-MI) percutaneous coronary intervention (PCI) of an occluded infarct-related artery (IRA) did not reduce death, re-infarction or heart failure relative to medical treatment (MED). Angina rates were lower in PCI early, but the advantage over MED was lost by 3 years.

Methods—Angina and revascularization status were collected at 4 months, then annually. We assessed whether non-protocol revascularization procedures in MED accounted for loss of the early symptomatic advantage of PCI.

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Results—Seven per 100 more PCI patients were angina-free at 4 months ($p<0.001$) and 5 per 100 at 12 months ($p=.005$) with the difference narrowing to 1 per 100 at 3 years ($p=.34$). Non-protocol revascularization was more frequent in MED (5-yr rate 22% vs. 19% PCI, $p=.05$). Indications for revascularization included acute coronary syndromes (39% PCI vs. 38% MED), stable angina/inducible ischemia (39% in each group), and physician preference (17% PCI vs. 15% MED). Revascularization rates among patients with angina at any time during follow up (35% of cohort) did not differ by treatment group (5-year rates 26% PCI vs. 28% MED). Most symptomatic patients were treated without revascularization during follow-up (77%).

Conclusions—In a large randomized clinical trial of stable post-MI patients, the modest benefit on angina from PCI of an occluded IRA was lost by 3 years. Revascularization was slightly more common in MED during follow up but was not driven by acute ischemia, and almost one in five procedures were attributed to physician preference alone.

INTRODUCTION

In patients presenting with acute myocardial infarction (MI), early reperfusion, achieved either pharmacologically or mechanically, significantly reduces mortality and morbidity. Unfortunately, a significant subset of patients do not receive early reperfusion therapy because of late presentation. 1-2 Management of these patients has been unclear but recently better defined by the Occluded Artery Trial (OAT), which tested the hypothesis that a strategy of routine percutaneous coronary intervention (PCI) for total occlusion of the infarct-related artery in stable patients without rest angina or severe inducible ischemia would be beneficial in the subacute phase after acute MI. The results showed no reduction in the primary end point, a composite of death, myocardial reinfarction, or hospitalization for New York Heart Association (NYHA) class IV heart failure for such a strategy relative to medical therapy alone (MED) during a mean follow-up of 3 years. 3 PCI is, however, very effective at reducing symptoms in patients with chronic angina. 4-8 It is unknown if a similar benefit exists when PCI is performed routinely post MI to the occluded culprit vessel, in the absence of ongoing symptoms or severe inducible ischemia. A major secondary end point of OAT was, thus, to assess if routine PCI of the occluded infarct-related vessel in the stable patient after MI resulted in less subsequent angina. Non-protocol revascularization, a possible reflection of the development of angina, was an additional secondary end point.

METHODS

The methods used in OAT have been described in detail previously. 9 Specific to this analysis, telephone interviews were conducted at 4 months, 1 year, and then annually for 5 years by study coordinators to ascertain anginal symptom status (using the Canadian Cardiovascular Society (CCS) Classification) and the occurrence of revascularization procedures during the interval since the prior assessment. Patients hospitalized with angina or in whom angina was the indication for non-protocol revascularization were also included in the symptomatic group.

Sponsorship and oversight of the OAT trial were provided by the National Heart, Lung, and Blood Institute of the National Institutes of Health (USA). In the preparation of this report, data management and 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 this manuscript for publication.

OAT Trial Methods and Primary Clinical Results

Patients were eligible for enrolment in OAT if coronary angiography, performed 3 to 28 calendar days after MI (minimum 24 hours), 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. Exclusion criteria included NYHA class III or IV heart failure, shock, a serum creatinine concentration higher than 2.5 mg per decilitre (221 μ mol per litre), angiographically significant left main or three-vessel coronary artery disease, angina at rest, and severe ischemia on stress testing.⁹ Stress testing was required only for patients with preserved wall motion or hypokinesis within the infarct region. Although exertional angina was not an exclusion criterion per se, investigators were instructed to minimize crossovers to PCI. Therefore the OAT cohort would not be expected to include patients with low threshold effort angina due to an occluded IRA post MI despite medical therapy.

Patients were randomly assigned to PCI with stent placement and optimal medical therapy [PCI group] or optimal medical therapy alone [MED group]. Optimal medical therapy included 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,^{10, 11} a thienopyridine was recommended in the two study groups for one year after MI. By protocol, revascularization of the IRA was by random allocation. Between February 2000 and December 2005, 2166 patients were enrolled in the trial. In 2006, an additional 35 patients were enrolled in the extension phase of the OAT-NUC substudy to bring the total number of OAT patients to 2201. Of these, 1101 were randomly assigned to routine PCI plus optimal medical therapy, and 1100 to optimal medical therapy alone. The analyses for this manuscript were all performed on patients with at least one follow-up visit (N=2116). Classes of medications taken by participants, but not doses, were collected.

PCI of non-IRA vessels was permitted either at the time of OAT-assigned PCI or as a separate procedure, as determined by the treating physician. PCI of the non-IRA, repeat PCI of the IRA in PCI assigned patients, and PCI of the IRA in optimal medical therapy only assigned patients in the absence of a primary endpoint event are referred to as non-protocol PCI. The indication for revascularization was assigned to physician preference in the absence of any of the following indications: symptomatic ischemic heart disease, silent ischemia on stress testing, ventricular arrhythmias, new onset heart failure or patient preference.

Statistical Analysis

Baseline characteristics were summarized as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Comparisons by angina status (angina during follow-up vs. none) and by non-protocol revascularization status (non-protocol revascularization performed vs. not performed) were performed using Chi square/Fisher's exact test for categorical variables and Student t-test for continuous variables. Estimates of the cumulative revascularization rates were calculated by the Kaplan-Meier product-limit method¹² and groups were compared by the log-rank test of the 5-year curves.¹³ Hazard ratios and 99% confidence intervals were calculated by Cox proportional hazards regression models.¹⁴ Multivariable Cox regression models were developed to evaluate the relation between 37 baseline characteristics and the occurrence of angina.

Backward elimination was used with $p \leq .01$ for variables remaining in the final model. To examine the relationships of visit and treatment to presence or absence of angina, longitudinal logistic regression models were fitted using the generalized estimating equation (GEE) method. This method takes into account within-individual correlations in repeated measurements of the dependent variable. To reduce the Type I error rate, we prespecified that a p-value of less than 0.01 would be considered as showing evidence of differences in secondary analysis. SAS version 9.1.3 (SAS Institute, Cary, NC) was used for statistical analyses

RESULTS

As previously reported³, one in five patients in both groups had a prior history of angina. Few patients at presentation had undergone revascularization with 5% (104/2166) treated previously with PCI and less than 1% (9/2166) with CABG. Stress testing prior to randomization was performed in 27% (589/2166) overall with no ischemia demonstrated in the majority of these patients [60% (351/589)] and mild to moderate ischemia in 43% (125/290) of those undergoing stress testing among the PCI group and 37% (112/299) of the medical therapy group ($p=NS$). Multivessel disease was documented at angiography in 18% (383/2166) of patients in both groups. PCI of the qualifying occlusion was attempted in 99% of the PCI group and was successful in 87%. At least one stent was placed in 87% in the PCI group, of whom 8% (77) received drug-eluting stents. 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 near the time of study entry. Among the 1084 patients in the medical therapy group, 27 (3%) crossed over to PCI within 30 days after randomization, and an additional 63 patients (6%) crossed over after 30 days. Four patients (0.4%) in each of the two groups underwent CABG within 30 days after randomization. At discharge, the rates of use of medications recommended in contemporaneous guidelines¹⁶ were high. Baseline characteristics of the patients in the two arms of OAT were similar except for a higher prevalence of diabetes in the group assigned to medical therapy (23% MED vs. 18% PCI $p=0.02$).³ With respect to antianginal therapy, the use of nitrates was higher in the medically-treated group (26% MED vs. 19% PCI, $p < 0.001$) but no difference was noted in beta-blocker (89% MED vs. 86% PCI, $p=0.05$) or calcium channel antagonist use (6% MED vs. 6% PCI, $p=0.69$) at discharge.

Overall, 39% of patients in OAT reported angina at the time of at least one visit during follow-up (830/2116). This includes 20.4% of patients who reported angina between 20–40% of visits, 11.8% of patients who reported angina between 50–80% of visits and 6.6% of patients who reported angina at all visits. Angina patterns were complex. For example, 535/821 (65%) of patients who reported angina at a follow up visit were angina-free at some subsequent visit, including 389/821 (47%) who were angina-free at the very next visit. Angina reports were far from stable over time – 395/821 (48%) of patients reported angina after being angina-free. Analysis of angina patterns excludes 9 patients, who reported angina for the first time at the 60 month visit. The number of permutations of reports of angina during follow up is too large to permit meaningful reporting in this analysis.

As seen in Figure 1, seven per 100 more PCI patients were angina-free at 4 months ($p < 0.001$) and 5 per 100 at 12 months ($p = .005$) with the difference narrowing to 1 per 100 at 3 years ($p = .34$). Baseline characteristics of patients with and without follow-up angina are shown in Table 1. Multivariate analysis identified six predictors of angina during follow up. Of note, angina was more likely in patients with a past history of angina (HR 1.42 99% CI 1.16–1.74), initial randomization to medical therapy (HR 1.28 99% CI 1.07–1.53), no ST-segment elevation, Q wave or R loss event on the electrocardiogram (HR 1.42 99% CI 1.12–

1.81) and Killip class II or greater heart failure at 24 hours (HR 1.36, 99% CI 1.09–1.70). (Figure 2)

No significant difference was noted in the use of beta-blockers or calcium antagonists during follow-up. Severe angina was uncommon. CCS class III or IV symptoms were reported in only 3.8% of the PCI group and 4.5% of medically-assigned patients at 4 months ($p=ns$) and in 2% or less of patients in both groups at all time points from 12 months on. In patients with angina ($n=830$), only the use of chronic nitrate therapy was more frequent in the MED group (30% vs. 17% PCI, $p<0.001$). The presence of multivessel disease did not influence symptoms. No difference was noted in the rate of reported angina between US and non-US centers.

From 2003 onwards, drug-eluting stents were implanted in 77 PCI-assigned patients and bare metal stents in 386 pts. Although not significant at individual time points, utilizing longitudinal unadjusted analysis, angina of any severity occurred less frequently with drug-eluting vs. bare metal stent use ($p=0.01$).¹⁷

Non-protocol follow-up revascularization was performed in 18% (378/2116) of the study population overall. This was more frequent, in both groups, with symptomatic angina (5 year event rate 27% v 11% $p<0.0001$) or when there was a history of pre-existing angina (5 year event rate 26% previous angina vs. 19% no previous angina, $p=0.001$) or multivessel disease (5 year event rate 26% multivessel vs. 19% single vessel disease, $p<0.001$). Despite similar symptomatic status for patients enrolled in US centers, they were more likely to undergo non-protocol revascularization (5 year event rate 26% USA vs. 19% non-USA, $p=0.002$).

Timing of non-protocol follow-up revascularization was within 12 months of randomization in 3 of 4 patients who underwent these procedures. Early revascularization, within 4 months, was more common in MED patients (Figure 3). Overall, non-protocol revascularization was more frequently reported in medically treated patients (5 year event rate 22% MED vs. 19% PCI, $p=.05$). Most revascularization consisted of PCI, with coronary artery bypass grafting performed in only 5% of patients in each treatment group. Non-protocol PCI in both groups was performed most frequently in the IRA (63% MED vs. 61% PCI, $p=0.72$).

There were no differences noted between treatment groups in the indications for non-protocol revascularization. These included acute coronary syndromes (39% PCI vs. 38% MED), stable angina or inducible ischemia (39% PCI vs. 39% MED), physician preference (17% PCI vs. 15% MED), and patient preference (4% PCI vs. 4% MED) (Figure 4).

Patients with angina (175/751=23%) were more likely to undergo revascularization than patients without angina (124/1286=10%) ($p<0.0001$; excludes 79 patients who underwent revascularization prior to symptom onset). However, most patients with angina (77%) did not undergo a revascularization procedure. Five year revascularization rates were similar in both treatment groups for symptomatic patients (26% PCI vs. 28% MED, $p=0.25$) (Figure 5).

DISCUSSION

The primary results of OAT did not support a strategy of routine PCI to reduce major cardiac events in stable patients with an occluded infarct-related artery post MI³. The primary results of OAT, however, do not address a potential important consequence of the totally occluded infarct artery – chronic angina.

For these post MI patients with persistent total occlusion of the IRA and absence of rest angina or severe inducible ischemia, our results suggest only a modest early benefit of PCI on symptoms with 6 and 1 fewer symptomatic patients per 100 treated with PCI at 1 and 3 years, respectively. Extinction of angina over time, as was seen in both randomization groups in OAT, has been noted often in other studies and the reason for reduction in angina over time is not fully understood. A small, early, but non-sustained benefit of PCI has also been reported by the COURAGE investigators in a population with stable coronary disease¹⁸. This study reported 7 and 3 fewer symptomatic patients per 100 treated with PCI at 1 and 3 years, respectively. Although the populations treated in COURAGE and OAT are different, the pattern and magnitude of angina differences between the PCI and MED arms is remarkably similar^{19, 20}.

Why this early but non-sustained difference in symptom status exists is difficult to ascertain due to small numbers. Although treadmill testing was only performed in 25% of the study population, the presence of mild to moderate ischemia did not appear to predict benefit from PCI on angina. Severe ischemia was an exclusion criterion for the trial. This finding is consistent with the recently published results from the INSPIRE investigators, who concluded that a strategy of intensive medical therapy is comparable to coronary revascularization for suppressing ischemia in stable patients after acute infarction.²¹ Patients in INSPIRE, however, had preserved LV function, in contrast to OAT where ejection fraction was reduced in over half. One interesting and previously unreported observation was the apparently more durable symptom relief with drug eluting stents in comparison to bare metal stents in the TOSCA-2 DES substudy, although the very small cohort precludes definitive conclusions¹⁷. Freedom from angina appeared not to be influenced by the presence or absence of multivessel disease.

The prevalence of post-MI angina and factors associated with it are poorly documented. One in three patients in OAT reported symptoms during follow-up. The PREMIER investigators recently reported a slightly lower prevalence of angina of 19.9% one year post MI in a registry of approximately 2,500 MI patients. Patients with angina in this registry were more likely to undergo revascularization at 12 months than those without angina (12.9% vs. 7.1%, $p < 0.001$)²². Comparison of these rates may suggest that persistent total occlusion is associated with chronic angina after MI, albeit in a minority of patients. We found, however, that 61% of OAT patients were angina-free at outset, and for the duration of follow up analyzed here, regardless of whether PCI was performed or not.

The reasons for complex patterns of angina observed during follow-up, such as when angina was reported at one visit, not the next visit and then again at the following visit, are not clear. This could reflect medication dose titration, which was not captured in this clinical trial, or changes in collateral flow over time or fluctuations in patient recall. Alternatively, this may reflect the nature of the disease process.

In addition to higher rates of angina during early follow up, medically-assigned patients also underwent more non-protocol revascularization. Overall, 3 more non-protocol revascularizations were performed in the medically-assigned cohort per 100 patients treated. This difference was essentially due to more non-protocol PCI in patients with single vessel disease. The majority of these occurred within the first year and as such it is tempting to conclude cause and effect, namely that improved symptomatic status in medically-assigned patients resulting in similar proportions of individuals free from angina at 3 years is due to increased non-protocol revascularization. Limited patient numbers with symptomatic angina and some uncertainty about the timing of revascularization relative to onset of angina during the interval follow up periods prohibit us from definitively confirming or refuting this hypothesis. However, the available evidence suggests this is unlikely, with similar

proportions in each group being referred for revascularization for symptoms in the first 2 years when the difference in symptomatic status is evident. In addition, only one in five patients with angina in both groups had non-protocol revascularization during follow-up. An important finding, in almost one-fifth of patients, was the influence of physician bias on referral for revascularization. In this regard, the difference between US and non-US centers is of note with more non-protocol revascularization performed in the US, particularly in medically-randomized patients despite a similar prevalence of symptoms.

Conclusions

In a large randomized clinical trial of stable post-MI patients without rest or low threshold angina or severe inducible ischemia, PCI of an occluded infarct-related artery produced a modest early benefit on angina status that was lost by 3 years. The majority of patients were angina-free at one year in both treatment groups. Revascularization was more common in medically-assigned patients and in patients (in both groups) with a past history of angina and multivessel disease. While symptomatic patients were more likely to undergo revascularization, this difference was modest and most patients with angina did not undergo revascularization. The greater rate of revascularization in the medical group did not appear to be driven by symptoms or ischemia with almost one in five procedures related to physician preference alone. These results do not support a routine practice of intervention to the infarct-related vessel in stable patients to reduce the frequency of late symptom onset.

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Figure 1. Freedom from Angina (%). The proportion of patients in each randomized group who did not have angina is depicted for each follow up contact.

Figure 2. Ratio for Angina during Follow-up. The hazard ratio for angina during follow up is shown with bars indicating 99% confidence intervals for each predictor.

Revascularization during Follow up N=2116

Figure 3.
Timing of Non-Protocol Revascularization. Kaplan Meier analysis of time to revascularization (non-protocol PCI or CABG), among 2,116 patients who completed at least one follow up visit.

Figure 4. Indications for Non-Protocol Revascularization. Among those patients undergoing a non-protocol-assigned revascularization procedure, the proportion in each randomization group with each indication. Note that there are no differences in these proportions between PCI and MED groups.

Figure 5. Non-Protocol Revascularization in Symptomatic Patients. Kaplan Meier analysis of time to revascularization by treatment group among patients who had angina prior to revascularization. This analysis excludes 79 patients who underwent revascularization before the development of angina and 1286 patients who did not have angina at any time during follow up.

Table 1

Baseline Characteristics by Angina Status during Follow Up Characteristic

	Angina (n=830)	No Angina (n=1286)	P value
Mean age	57.5 years	59.1 years	0.0005
Male	78%	78%	0.68
History:			
Angina	28%	19%	0.0001
Myocardial infarction	14%	9%	0.0002
Cerebrovascular Disease	3%	4%	0.80
Peripheral vascular disease	4%	3%	0.22
Past History PCI	7%	3%	0.0007
Past History CABG	0.4	0.4	1.00
Hypercholesterolemia	56%	50%	0.01
Hypertension	49%	48%	0.68
Diabetes Mellitus	20%	21%	0.61
Smoking	41%	38%	0.19
History Renal failure	1%	1%	0.81
History Heart Failure	3.3%	1.6%	0.009
Killip Class II-IV (24 hrs)	22%	16%	0.0001
New Q Wave or STEMI or R wave loss	83%	89%	0.0003
Infarct related Artery			
LAD	36%	35%	0.97 for 2*3chisq
Cx	15%	15%	
RCA	48%	49%	
Ejection Fraction < 50%	53.3	52.7	0.78
Multivessel Disease	17%	17%	0.66
Collaterals, any grade	89%	88%	0.54