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Comparison of Late Results of Percutaneous Coronary Intervention Among Stable Patients ≤ 65 vs. >65 Years of Age With An Occluded Infarct Related Artery (From The Occluded Artery Trial)

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Abstract

While opening an occluded infarct-related artery (IRA) > 24 hours post myocardial infarction in stable patients in the Occluded Artery Trial (OAT) did not reduce events over 7 years, there was a suggestion that effect of treatment may differ by patient age. Baseline characteristics and outcomes by treatment with percutaneous coronary intervention (PCI) vs. optimal medical therapy (MED) alone were compared by pre-specified stratification at age 65. $P < 0.01$ was pre-specified as significant for OAT secondary analyses. The primary outcome was death, myocardial infarction or Class IV heart failure. Patients > 65 years of age ($n=641$) were more likely to be female, non-smokers, and to have hypertension, lower estimated glomerular filtration rate and multivessel disease compared to younger patients (age ≤ 65 , $n=1560$), $p < 0.001$. There was no significant observed interaction between treatment assignment and age for the primary outcome after adjustment ($p=0.1$) and there was no difference between PCI and MED observed in either age group. At 7 year follow-up, younger patients tended to have angina more often compared to the older group (H.R. 1.21, 99% CI: 1.00–1.46, $p=0.01$). The 7-year composite primary outcome was more common in older patients ($p < 0.001$), and age remained significant after co-variate adjustment (H.R. 1.42, 99% CI: 1.09–1.84). The rate of early PCI complications was low in both age groups. The trend toward a differential effect of PCI in the young vs. the old for the primary outcome was likely driven by measured and unmeasured confounders, and by chance. PCI reduces

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angina to a similar degree in the young and old. There is no indication for routine PCI to open a persistently occluded IRA in stable patients post-MI regardless of age.

Keywords

Elderly; PCI; Age; occlusion

Introduction

The Occluded Artery Trial (OAT) randomized stable patients with a persistent occlusion of the infarct-related artery (IRA) >24 hours post MI to optimal medical therapy with percutaneous coronary intervention (PCI) vs. optimal medical therapy alone (MED). While in the overall OAT population, there was no clinical benefit of PCI on a composite outcome of death, MI or Class IV heart failure at a mean follow-up of 3 years, PCI reduced angina early in follow-up, and in a pre-specified substudy, modestly reduced adverse remodeling at 1 year.^{1,2} There was also a trend observed ($p=0.03$) toward an interaction between treatment and age >65 years on the primary outcome measure at 5 years, raising the possibility of a differential effect of PCI in older patients.² We therefore set out to compare treatment and outcomes in detail in the two prespecified age groups.

Methods

The study design of OAT has been described previously.³ Patients with MI who underwent coronary angiography with persistent IRA occlusion >24 hours (3 to 28 calendar days, with symptom onset on day 1) were eligible if they had a left ventricular ejection fraction of $\leq 50\%$ or a proximal occlusion of a major epicardial vessel. Exclusion criteria were New York Heart Association (NYHA) class III or IV heart failure, shock, a serum creatinine level >2.5 mg/dl, left main or three-vessel coronary artery disease in need of surgical revascularization, rest angina, and high-grade ischemia on stress testing, which was required if the infarct zone was not akinetic or dyskinetic. Patients were randomly assigned to PCI with stent deployment and optimal medical therapy or optimal medical therapy alone. Follow-up during extended follow up was conducted for up to 9 years by the participating sites or centrally for some patients. Event rates were presented at 7 years because of few events and unstable event rates in subsequent years. Mean follow up duration for this analysis was 6.0 years.⁴

The primary endpoint was a composite of death, reinfarction, or New York Heart Association class IV heart failure requiring hospitalization or treatment in a short stay unit. Secondary endpoints included the separate components of the primary end point as well as symptoms and other clinical events. All study end-point events were adjudicated by an independent events committee blinded to treatment assignment. The age stratification point, originally prespecified at 70 years, was changed to 65 years prior to completion of enrollment due to lower than anticipated number of participants older than 70. Based upon the revised pre-specified stratification, older patients >65 years enrolled in OAT were compared with younger patients ≤ 65 years with respect to baseline characteristics and outcomes by treatment assignment. Angina was assessed at baseline, 4 months and at yearly follow-up contacts.

Estimates of the cumulative event rates were calculated by the Kaplan–Meier product-limit method and treatments were compared with the use of log-rank tests of the 7-year curves.^{5,6} Hazard ratios and 99% confidence intervals were calculated by Cox proportional hazards regression models. Adjusted analyses incorporated variables from the risk model for the

primary outcome.⁴ Data for patients lost to follow-up were censored as of the time of the last contact. Categorical variables were compared with the use of the chi-square test, and continuous variables were compared with the use of the Student's t-test. To control for Type I error, a p-value of ≤ 0.01 was pre-specified by the study protocol as showing evidence of differences in secondary analyses. Analyses were performed according to the intention-to-treat principle. Statistical analyses were performed using SAS Version 9.1.3 for Windows (SAS Institute Inc, Cary, North Carolina).

Results

Of the 2201 randomized OAT subjects, 641 were older than 65 years, a prespecified subgroup, and 1560 were ≤ 65 years, with a range of 24 to 89 years old. There were 37 patients over the age of 80 years. When comparing the OAT Trial with the OAT Registry, there was no difference in mean age (58 ± 10 years). Among older randomized patients, 309 were assigned to PCI and 332 were assigned to MED. Older patients were more likely to be female (35.3 vs. 16.5%), to have prior cerebrovascular disease (6.7 vs. 2.5%), baseline heart failure (39.2 vs. 28.6%), multivessel disease (22.1 vs. 15.4%) and lower estimated glomerular filtration rate (70.4 vs. 84.8 ml/min/1.73m²), all $p < 0.001$ (Table 1). They were also less likely to have a family history of CAD (30.1 vs. 44.2%; $p < 0.001$) or to be a current smoker (18.1 vs. 47.6%; $p < 0.001$). The distribution of prior MI, prior coronary revascularization and time from qualifying MI was similar between older and younger patients.

Presenting features, ST-segment elevation electrocardiogram findings and prior MI, as well as rates of prior PCI and coronary artery bypass grafting surgery were similar by patient age (Table 1). Similar to the overall OAT population, among older patients the right coronary artery was the most common IRA (45.6 %), followed by the left anterior descending (40.6 %) and then the left circumflex (13.9 %). The left anterior descending artery was more often the infarct-related artery in older than younger patients (40.6 vs. 34.2%, $p = 0.005$). Older patients in both treatment groups had lower likelihood of angiographically visible collaterals and Q-waves and more likely to have multi-vessel disease; however there were no significant differences in these characteristics between treatment groups *within* each age group. Left ventricular dysfunction was slightly more common among the elderly.

Compliance with guideline recommended medical treatment was excellent in the overall trial and in the elderly cohort (Table 2). When compared to younger trial participants, the elderly group, however, had lower rates of aspirin and beta blocker use, $p < 0.001$. Only 75% of patients > 65 years of age were treated with lipid-lowering agents. Older patients were more likely to be taking diuretics and antiarrhythmic agents, $p < 0.001$ compared with the younger cohort (Table 2).

Observed event rates were significantly higher amongst those > 65 years of age for the overall primary outcome ($p < 0.001$) when compared to younger trial participants irrespective of treatment assignment (Figure 1). The previously observed trend toward an age-treatment interaction on the primary outcome ($p = 0.03$) at 4-year follow-up was weaker after adjustment at 5-year ($p = 0.06$) and 7-year ($p = 0.1$) follow-up, and no significant age-treatment interactions were observed for any of the components of the primary outcome (Table 3).

Comparing outcomes by treatment *within* each age group, there was no difference in the primary outcome over 7 years among older adults. All components of the primary endpoint occurred with similar frequency in those assigned to PCI or MED within both age groups.

Older age was associated with occurrence of the primary outcome (H.R. 1.77 (99% CI 1.39–2.27) in unadjusted models ($p<0.001$). When adjusted for 8 baseline variables, including estimated glomerular filtration rate, older age remained significant. Older age was also associated with death in both adjusted and unadjusted models, and with Class IV heart failure in unadjusted models only (Table 4).

Primary outcomes were also similar in analyses stratified by baseline global risk. Among older patients in the highest risk tertile, the 7-year primary outcome rate was 39.8% in PCI (N=160) vs. 40.9% in MED (N=184), $p=0.89$, HR 1.03, 99% CI 0.63–1.61. In the 194 PCI and 196 MED younger patients in highest risk tertile, the 7-year primary outcome rate was 35.7% vs. 33.7%, $p=0.09$, HR 1.37, 99% CI 0.85–2.18.

By life table estimates for time to first angina ever, 7-year angina event rate was 48.9% in younger patients, 43.0% in older patients, $p=0.01$. H.R. (older vs. younger) 1.21, 99% CI: 1.00–1.46, $p=0.01$. Interaction between age and treatment was not significant ($p=0.98$). At 4 months, older MED patients were more likely to have angina than older PCI assigned patients (23.5% vs. 15.2%, $p=0.011$). Similarly at the 4-month time point younger MED patients had angina more often than younger PCI patients (28.6% vs. 21.2%, $p<0.001$). The difference in angina was no longer significant at 1 year of follow-up. No significant age-treatment interaction for angina was observed at any timepoint (Figure 2).

When attempted, PCI was successfully performed in 86% of both older and younger patients. Thrombolysis in Myocardial Infarction 3 flow was achieved in 81.9% of younger patients and 83.3% of older patients ($p=0.85$). Bare metal and drug-eluting stents were used in 82.6% and 17.4% in older patients and 83.6% and 16.4% of younger patients, respectively.

Complications have been previously described and were assessed as site-reported as well as adjudicated events, both for treatment assigned as well as treatment received.⁷ Among older patients randomized to PCI, the rate of site-reported complications was low and similar to that of younger patients. The most common complication was major hemorrhage and non-fatal MI within 48 hours of protocol-mandated PCI. While major hemorrhage occurred in 0.5% of younger PCI patients compared with 1.3% of older PCI patients, this difference did not reach statistical significance due to the low number of events. There were 7 non-fatal myocardial infarctions (0.9%) among younger PCI patients compared with 1 non-fatal MI (0.3%) among older PCI patients. Remarkably, among 309 older patients randomized to PCI 96.8% were free of any early complications.

With respect to repeat myocardial infarctions among PCI-treated patients over the 9-year follow-up period, there was no significant difference in type 4a (PCI-related) myocardial infarctions (4 (1.29%) among older patient and 5 (0.63%) among younger patients, $p=0.28$). Among younger PCI patients, there was a strong trend towards more type 4b (stent thromboses) myocardial infarctions (25 (3.16%) among younger vs. 2 (0.65%) among older patients, $p=0.015$).

Discussion

Data to guide the management of stable older adults with coronary artery disease are sparse due to low numbers of older patients included in most randomized trials. One of the few trials adequately powered to assess outcomes among stable older patients with coronary artery disease was the Trial of Invasive versus Medical Therapy in the Elderly (TIME) in stable angina. TIME randomized patients >75 years with stable angina refractory to medical therapy to either invasive management or improved medical therapy alone.⁸ While it might be assumed that the risk profile of this stable anginal population was lower than our post-MI

population, the mortality in TIME at 4 years was 28%, significantly higher than the 5 year mortality in our patient population (9.4%), likely due to the inclusion of many more octogenarians and nonagenarians (mean age of 80 years), and more extensive coronary artery disease (60% with 3-vessel disease). In TIME, at 1-year follow-up there was no significant difference in overall mortality, cardiac death, or non-fatal MI between the invasive and the optimal medical therapy group. Late revascularizations, however, were more frequent in the optimal medical therapy alone group (45% vs. 12%, $P<0.0001$).⁹ If these crossovers were included in an *as-treated* analysis, revascularization was associated with a significant survival benefit at 1-year ($p = 0.0027$). Most of these crossovers were due to refractory angina, an important consideration, as rest angina or other unstable features were exclusion criteria for OAT.¹⁰

TIME assessed several quality of life outcomes, including angina. Similar to our findings, elderly patients treated with PCI derived significant benefit in terms of angina in the first few months. In that trial, however, the improvement in angina remained significant at 1 year, irrespective of treatment group, although patients on optimal medical therapy were taking more anti-anginal medications. In our study, the early reduction in angina observed at 4 months, disappeared by 1 year, and the age-treatment interaction p-value was not significant at any timepoint.

This difference between TIME and OAT in the durability of relief of angina with PCI may be due to several factors. In the former study, all patients were highly symptomatic prior to randomization while in our study, many patients were asymptomatic prior to their index MI, and patients with severe symptoms post-MI were excluded from participation. Few patients in TIME had an occluded IRA, while OAT patients by definition had occluded culprit vessels, which are more prone to high rates of restenosis and reocclusion after successful stenting even outside of the thrombotic setting of a recent infarct. In the Total Occlusion Study of Canada (TOSCA)-2, the angiographic substudy of OAT, 83% of patients randomized to PCI had an open artery at 1 year and binary restenosis was observed in almost half of PCI patients.¹¹ In addition, overall in OAT there was a benefit of PCI on angina at the 1-year timepoint and power is reduced for analysis in the elderly subgroup, as for all subgroups.

Most patients in OAT assigned to PCI were treated with bare metal stents. During the later stages of enrollment some patients received drug-eluting stents, and in a substudy of TOSCA-2 (TOSCA-2 DES), there was a significantly lower rate of binary restenosis in patients treated with drug-eluting stents vs. bare metal stents (13.0% vs. 44.3%, $p=0.005$), a reduction paralleled by a reduced occurrence of angina during follow-up as analyzed by time to first event ($p=0.01$).¹² It is reasonable to consider that with more frequent use of drug-eluting stents in the occluded IRA, OAT PCI patients might have had a more durable improvement in angina compared to those randomized to MED.

The relatively small number of older adults in our study limits the statistical power to detect small differences in outcomes. While age 65 years was a pre-specified cutpoint for analysis, the randomization process did not stratify by age. Thus there may have been undetected confounders present in the older adults in the MED or PCI arms that affect the ability to measure the effects of age group alone.

The suggestion of an interaction between older age and treatment with PCI in OAT was likely a chance finding, as the interaction was not significant after co-variate adjustment. We observed neither benefit nor harm of PCI on clinical outcomes among older patients enrolled in OAT, including those at higher risk of events.

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Figure 1.

Over 7 years of follow-up, cumulative rates of death, MI or Class IV heart failure are significantly higher among those >65 for both PCI and MED.

Figure 2.

Bar graph demonstrating the reporting of Angina at 4 months and yearly follow-up among younger and older PCI and MED patients.

Table 1

Baseline Characteristics by Age Group

Clinical Characteristic	Age (Years)		p-value
	≤65 (n=1560)	>65 (n=641)	
Mean Age (years)	53.1 ± 7.6	72.0 ± 4.6	<0.001
Male	83.5%	64.7%	<0.001
White	79.2%	82.4%	0.09
Mean Body Mass Index (kg/m ²)	28.8 ± 5.2	27.8 ± 4.5	<0.001
Diabetes Mellitus	20.3%	21.5%	0.50
Prior Angina Pectoris	21.3%	25.4%	0.03
Prior Myocardial Infarction	10.9%	12.0%	0.45
Prior Cerebrovascular Disease	2.5%	6.7%	<0.001
Prior Peripheral Vascular Disease	3.3%	5.0%	0.05
Prior Hypertension	44.7%	58.3%	<0.001
Prior Hypercholesterolemia	53.9%	47.0%	0.003
Family History of Coronary Heart Disease	44.2%	30.1%	<0.001
Prior Heart Failure	1.9%	3.6%	0.02
Heart Failure at Baseline	28.6%	39.2%	<0.001
Rales	4.7%	10.0%	<0.001
New Q-waves	69.2%	61.8	<0.001
Current smoker	47.6%	18.1%	<0.001
Prior Percutaneous Coronary Intervention	5.0%	4.2%	0.43
Prior Coronary Bypass Surgery	0.4%	0.3%	0.65
Mean Left Ventricular Ejection Fraction	48.0+/-10.8%	47.0+/-11.8%	0.05
Left Ventricular Ejection Fraction <40%	19.1%	24.1%	0.009
Mean estimated Glomerular Filtration Rate (ml/min/1.73m ²)	84.8 ± 20.6	70.4 ± 20.2	<0.001
ST-segment Elevation	66.3%	66.2%	0.97
Coronary Collaterals	89.8%	85.1%	0.002
Multivessel Disease	15.4%	22.1%	<0.001
Mean Systolic Blood Pressure (mm Hg)	119 ± 17	124 ± 19	<0.001

Table 2

Discharge Medications By Age Group

Medication	Age (Years)		p-value
	Age ≤ 65 years (n=1560)	Age>65 years (N=641)	
Aspirin	96.7%	93.0%	<0.001
Thienopyridine	60.4%	60.4%	0.99
Beta Blocker	89.0%	84.9%	0.008
Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker	79.6%	82.7%	0.09
Lipid-lowering agent	83.7%	75.2%	<0.001
Long-acting nitrates	20.3%	28.2%	<0.001
Calcium Channel Blocker	5.3%	7.2%	0.09
Warfarin	8.7%	12.3%	0.01
Oral hypoglycemic	13.1%	14.7%	0.32
Insulin	6.7%	5.0%	0.13
Diuretic	12.6%	27.1%	<0.001
Antiarrhythmic	2.4%	7.3%	<0.001

Table 3

Seven-year Adjudicated Outcomes by Age and Treatment Group

Variable	Primary Outcome	Death	Fatal and NonFatal Myocardial Infarction	Class IV Heart Failure
<i>Younger MED</i> (N= 768)	18.1%	11.1%	7.3%	3.6%
<i>Younger PCI</i> (N= 792)	19.2%	10.8%	8.3%	3.7%
<i>Older MED</i> (N= 332)	33.5%	26.8%	7.0%	9.4%
<i>Older PCI</i> (N= 309)	29.6%	23.8%	6.2%	9.0%
Younger: PCI vs. MED H.R. (99% CI)	1.23 (0.89–1.69) p=0.10	1.07 (0.71–1.63) p=0.67	1.38 (0.83–2.30) p=0.10	0.98 (0.49–1.98) p=0.95
Older: PCI vs. MED H.R. (99% CI)	0.87 (0.60–1.28) p=0.36	0.91 (0.60–1.39) p=0.58	0.81 (0.35–1.91) p=0.53	0.99 (0.48–2.04) p=0.96
Unadjusted Age-Treatment Interaction P-value	0.08	0.50	0.16	0.99
Adjusted* Age-Treatment Interaction P-value	0.10	0.47	0.17	0.88

* Adjusted for history of diabetes, cerebrovascular disease, PCI and peripheral vascular disease before study entry, lower eGFR, lower EF and heart failure at baseline, shorter time from OAT qualifying MI to randomization.

Table 4

Unadjusted and Adjusted* Hazard Ratios By Age Group

Outcome	Older vs. Younger <i>Unadjusted</i> H.R. (99% CI)	p-value	Older vs. Younger <i>Adjusted</i> H.R. (99% CI)	p-value
Primary Outcome	1.77 (1.39–2.27)	<0.001	1.42 (1.09–1.84)	<0.001
Death	2.46 (1.83–3.30)	<0.001	1.91 (1.39–2.62)	<0.001
Fatal and Non-Fatal MI	0.88 (0.53–1.43)	0.49	0.80 (0.48–1.34)	0.27
Class IV Heart Failure	2.34 (1.41–3.88)	<0.001	1.58 (0.92–2.71)	0.03

* Adjusted for history of diabetes, cerebrovascular disease, PCI and peripheral vascular disease before study entry, lower eGFR, lower EF and heart failure at baseline, shorter time from OAT qualifying MI to randomization.