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Infarct Artery Distribution and Clinical Outcomes in Occluded Artery Trial Subjects Presenting with Non ST elevation Myocardial Infarction (From the Long Term Follow-up of the Occluded Artery Trial)

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Abstract

We hypothesized that the insensitivity of the electrocardiogram (ECG) in identifying acute circumflex occlusion would result in differences in the distribution of the infarct related artery (IRA) between patients with non ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) enrolled in the Occluded Artery Trial. We also sought to evaluate the impact of percutaneous intervention to the IRA on clinical outcomes for patients with NSTEMI. Overall NSTEMI subjects comprised 13% (n=283) of the trial population. The circumflex IRA was overrepresented in the NSTEMI group compared to patients enrolled with STEMI (42.5 vs. 11.2%; p<0.0001). The 7 year clinical outcomes for NSTEMI patients randomized to percutaneous intervention and optimal medical therapy versus optimal medical therapy alone were similar for the primary composite of Death, MI and Class IV Congestive Heart Failure (CHF) (22.3 vs. 20.23%, p=0.51, HR 1.20; 0.59-2.43); as well as the individual endpoints of Death (13.8 vs. 17.0%, p=0.51, HR 0.81; 0.36-1.85); MI (6.1 vs. 5.1%, p=0.84, HR=1.11; 0.28-4.41); Class IV CHF (6.7 vs. 6.0%, p=0.45, HR 1.50; 0.37-6.02). There was no interaction between MI type by ECG and treatment effect (p= NS). In conclusion the occluded circumflex IRA is overrepresented in the NSTEMI population. Consistent with the overall trial results, stable patients with NSTEMI and a totally occluded IRA did not benefit from randomization to PCI.

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Keywords

Coronary artery disease; Myocardial Infarction; Percutaneous coronary intervention; Prognosis

Introduction

The insensitivity of the surface electrocardiogram (ECG) to identify acute Circumflex occlusion is well established. Failure or delay to recognize acute Circumflex occlusion often results in delayed or missed acute reperfusion and has been associated with worsened outcome.¹⁻³ We hypothesized that this insensitivity of the surface would result in an over representation of culprit occluded left Circumflex infarct related artery in patients with non ST elevation myocardial infarction (NSTEMI) enrolled in the Occluded Artery Trial (OAT). We also sought to evaluate the outcomes of sub acute infarct related artery percutaneous intervention (PCI) compared to medical therapy alone in the subgroup of patients with an ECG-defined NSTEMI enrolled in OAT.

Methods

The design, methodology, and results of OAT have been previously reported.^{4,5} In brief, the trial randomized 2201 stable patients with TIMI 0/1 flow in the IRA, at least 24 hours (calendar days 3–28) following MI onset either to a strategy of PCI of the IRA with optimal medical therapy (PCI) or to a strategy of optimal medical therapy alone (MED). The current analysis includes 35 patients recruited in 2006 as part of nuclear sub study in addition to the 2166 patients presented in the original report. The trial excluded subjects with cardiogenic shock, NYHA class III/IV congestive heart failure (CHF), rest angina or severe ischemia on stress testing, significant left main or three-vessel coronary artery disease. By design, all patients in the study were required to either have an ejection fraction (EF) <50% and/or a culprit occlusion in a proximal coronary vessel. We compared infarct related artery (IRA), baseline characteristics and outcomes for 283 subjects in OAT with NSTEMI (absence of ST elevation/Q waves /loss of R wave voltage or new LBBB) to 1918 patients with diagnostic ECG for a recent STEMI. We also report the results of 9 year extended follow up (mean duration of 6 years) with a combined primary end point of centrally adjudicated death, recurrent myocardial infarction (MI), and development of new onset New York Heart Association (NYHA) class IV CHF.

A chi-square test was utilized to compare discrete variables and a Student's *t*-test for continuous variables. Outcomes of death, MI, or occurrence of class IV CHF are reported as estimates of 7 year (84 month) event rates due to the smaller number of events thereafter. These estimates were calculated using the Kaplan–Meier (KM) product-limit method. Patients lost to follow-up were censored at the time of last available contact. A covariate-adjusted hazard ratio was then quantified utilizing a Cox proportional hazards regression model utilizing a risk model that included demographic, clinical, and angiographic variables. We performed formal testing for interaction between ECG type (NSTEMI vs. STEMI) and treatment effect utilizing a Cox regression model with ECG type, treatment, and interaction terms all in the model. To control for the type I error rate, it was prespecified by the study protocol that a *p* value < 0.01 would be considered as showing evidence of difference in secondary analyses in OAT. SAS version 9.2 (SAS Institute, Cary, NC) was used for statistical analyses.

Results

Overall 283 (12.9%) subjects with NSTEMI findings were enrolled in the OAT trial. Amongst them, 136 were randomized to percutaneous intervention (PCI) and 147 were assigned to optimal medical therapy (MED). Similarly, amongst the 1918 OAT patients with STEMI findings; 965 were randomized to PCI and 953 to MED. Subjects with NSTEMI enrolled in OAT differed significantly from patients with ECG evidence of a typical ST elevation myocardial infarction (Table 1). By trial design, regardless of ECG presentation, angiography revealed TIMI 0/1 universally in both groups.

The distribution of the infarct related artery (IRA) amongst OAT patients based on presentation ECG differed significantly ($p < 0.0001$). For patients with diagnostic ECG findings consistent with STEMI, the right coronary artery (49.6%) was the most common IRA. The prevalence of left anterior descending (LAD) IRA was 39.2% and only a minority of patients had a culprit occluded Circumflex (11.2%). In contrast the nature of the IRA differed significantly in the NSTEMI group. The LAD was seldom the culprit (14.4%) and the predominant infarct related vessels were the Right coronary artery (43.2%) and Circumflex (42.5%) respectively. Identification of visible collaterals to the IRA on the qualifying coronary angiogram were similar for patients with non diagnostic as well as diagnostic ECG (88.9 vs. 88.4%; $p = 0.79$). The median time to randomization was two calendar days earlier for patients with non diagnostic ECG (7 days (inter quartile range (IQR) 4-15) vs. 9 days (IQR 5-17) $p = 0.015$).

Amongst the 283 patients with NSTEMI enrolled in OAT, 136 (48.1%) were assigned to PCI with 135 (99.3%) receiving protocol mandated treatment. Similarly, amongst the 1918 patients with diagnostic STEMI, 965 (50.3%) were assigned to PCI with 955 (99%) receiving intervention. Overall rates of procedural PCI success were similar for both groups (87.5 vs. 86.4%; $p = 0.91$). The time from index MI to protocol assigned PCI was similar for NSTEMI and STEMI subjects (8 days (interquartile range 5-15) vs. 9 days (interquartile range 5-17) $p = 0.22$). Time from randomization to protocol assigned PCI was also similar for both groups (0-1 day, $p = 0.14$).

The unadjusted and adjusted 7 year (84 month) event rates and hazard ratios (HR) for the combined and individual study endpoints of death, MI and new onset Class IV CHF for patients with NSTEMI and STEMI enrolled in OAT as well as the KM event curves are presented in Table 2 and Figure 1 respectively. Overall clinical outcomes for patients with NSTEMI and STEMI were similar (all $p = \text{NS}$). There was no interaction between ECG type and treatment effect on the combined outcome of death, non fatal MI and Class IV CHF (interaction $p = 0.63$), or on the individual endpoints of death (interaction $p = 0.56$), fatal and non fatal MI (interaction $p = 0.88$) or Class IV CHF (interaction $p = 0.37$).

Similarly the unadjusted and adjusted 7 year (84 month) event rates and HR for the combined and individual study endpoints of death, MI and new onset Class IV CHF for patients with NSTEMI and STEMI, stratified by treatment assignment are presented in Table 3. The related KM curves for NSTEMI are presented in Figure 2. Within the NSTEMI group, event rates for the 136 subjects assigned to PCI were similar to the 147 subjects assigned to MED.

Discussion

Early reperfusion of the acutely occluded infarct related artery aborts ongoing myocardial necrosis, salvages myocardium in jeopardy, preserves left ventricular function, and translates into a mortality benefit that persists into the next decade.^{6,7} While primary reperfusion guided by findings on the surface ECG is the current standard of care, the

magnitude of missed reperfusion opportunities due to ECG insensitivity has not been adequately quantified. This knowledge gap largely arises because of exclusive datasets that deal independently with the management of STEMI and NSTEMI subjects respectively. Our observations from OAT suggest that the magnitude of this phenomenon may not be inconsequential. While circumflex vessels accounted for a minority of occluded IRA in patients with STEMI ECG findings; they accounted for nearly half of the culprit IRA in patients presenting with a NSTEMI. It is well recognized that there are missed reperfusion opportunities amongst the elderly, women, diabetics and minorities who often present late (>12 hours following index MI) due to atypical symptoms or delayed medical activation. Our current observation suggests that there should be a similar emphasis on highlighting strategies to identify acutely occluded Circumflex IRA in patients with NSTEMI ECG findings. These interventions may include a heightened emphasis on early angiography in patients with persistent symptoms, performing emergent angiography in patients with non diagnostic ECG findings suspicious for posterior circulation infarction, increasing ECG sensitivity by using additional leads and/or novel ECG strategies that increase yield for acute posterior circulation ischemia or utilizing adjunctive echo imaging strategies to identify new wall motion abnormalities in a more protocol driven manner in this setting.⁸⁻¹⁶ Further, the elderly and women appear over represented in the NSTEMI group and these findings may also be contributing to the mechanism of missed reperfusion opportunities in these vital patient subsets.

The natural history of the untreated totally occluded infarct related artery is well recognized. A significant proportion of acutely occluded infarct vessels following STEMI will spontaneously recanalize over time.¹⁷ The OAT time window was specifically chosen to minimize spontaneous biologic “crossover” as the recanalization rate following STEMI is highest in the early hours following acute coronary occlusion but then diminishes and stabilizes within and following the time period evaluated in OAT (> 24 hours; calendar days 3-28 days post acute occlusion). In the angiographic ancillary study of the OAT trial only 20% of medically treated patients were noted to undergo spontaneous recanalization between the baseline and 1 year follow up angiogram.¹⁸

In the setting of randomized clinical trials evaluating non ST elevation acute coronary syndromes, a significant proportion of subjects undergoing coronary angiography have also been noted to have TIMI 0/1 flow in the IRA on their angiogram.¹⁹ Consistent with the natural history noted above, the incidence of early TIMI 0/1 flow in these trials also appears to be time dependent and ranges from 19% in ISAR REACT 2²⁰ in which mean angiography was performed at 6.1 hours following presentation to 13 % in the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial in which mean time to angiography was 19.5 hours.²¹ When angiography was performed at a mean of 65 hours in the Platelet receptor inhibition for ischemic syndrome management in patients limited by unstable signs and symptoms (PRISM) Plus trial, the incidence of TIMI 0/1 flow was only 10%.²² These findings suggest that a significant proportion of subjects, perhaps greater than 20% with NSTEMI, have an occluded artery in the early infarct setting.

Our observations suggest a missed opportunity to perform prompt reperfusion in a subset of patients with acute occlusion that is not manifested on ECG. The disparity in distribution of the IRA suggests that this phenomenon is pronounced in the Circumflex distribution. In the absence of a valid denominator, the magnitude is unclear but ranges from 10-20% in randomized clinical trials of NSTEMI.²⁰⁻²² Consequently, given the over 1 million NSTEMI admissions in the US each year,²³ current under recognition of the occluded IRA in the reperfusion time window is significant.

In the absence of symptoms, hemodynamic instability or significant spontaneous ischemia, our observations from OAT demonstrate no benefit to be had from routine percutaneous revascularization of the occluded TIMI 0/1 IRA in this time window.^{4,24} This mirrors the findings of the overall OAT trial and is likely due to the fact that despite differing ECG on presentation, NSTEMI subjects had similar IRA status. Delayed identification of the occluded IRA with a NSTEMI presentation also appears to carry adverse clinical consequences. Bahrmann and colleagues evaluated 448 consecutive patients who underwent early coronary angiography within 72 hours of symptom onset.²⁵ In their study 130/448 (29%) had an occluded coronary artery mainly in vessels supplying the posterolateral myocardium. These subjects had larger enzymatic infarctions than their counterparts and had higher risk-adjusted 6 month clinical events.

Our observations are limited by the retrospective nature of the analysis. By design, the trial is underpowered to detect differences in subsets. However, there is consistency of treatment effect across the NSTEMI and STEMI subsets with no suggestion of heterogeneity. Although supported by observational data, our comments about missed acute reperfusion opportunities in patients with NSTEMI remain largely speculative. However multiple clinical observations and large angiographic datasets from randomized clinical trials mirror our findings.

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Figure 1.

Kaplan-Meier curves on the composite end point of death, non fatal myocardial infarction and new onset Class IV congestive heart failure (CHF), as well as individual endpoints for all patients (ST elevation myocardial infarction versus non ST elevation myocardial infarction) enrolled in the Occluded Artery Trial over long term follow up.

Figure 2.

Kaplan-Meier curves on the composite end point of death, non fatal myocardial infarction and new onset Class IV congestive heart failure (CHF), as well as individual endpoints for patients with non ST elevation myocardial infarction randomized to percutaneous intervention and medical therapy versus medical therapy alone in the Occluded Artery Trial over long term follow up.

Table 1

Baseline characteristics in patient with non ST elevation myocardial infarction (NSTEMI) electrocardiogram compared to typical ST elevation myocardial infarction (STEMI) ECG in the Occluded Artery Trial.

Parameter	NSTEMI (N=283)	STEMI (N=1918)	p-value
Age (years)	60.4 ± 11.7	58.3 ± 10.8	0.003
Heart Rate (beats/minute)	70.1 ± 11.5	72.0 ± 12.0	0.013
Systolic Blood Pressure (mm Hg)	123.8 ± 18.1	120.4 ± 17.9	0.002
Diastolic Blood Pressure (mm Hg)	72.2 ± 11.7	72.3 ± 11.3	0.88
Body Mass Index (Kg/m ²)	28.8 ± 5.3	28.4 ± 5.0	0.21
Estimated GFR (ml/min/1.73m ²)	79.5 ± 22.4	80.8 ± 21.4	0.38
Male	72.1%	78.9%	0.01
White	81.3%	79.9%	0.60
Current Smokers	33.6%	39.8%	0.04
Diabetes Mellitus	25.1%	20.0%	0.05
Prior MI	20.8%	9.8%	<0.0001
Prior angina pectoris	31.8%	21.1%	<0.0001
Hypertension	50.5%	48.4%	0.50
Cerebrovascular disease	6.0%	3.4%	0.03
Peripheral Vascular Disease	4.9%	3.6%	0.27
Renal insufficiency	0.7%	1.5%	0.42
Percutaneous Intervention	8.1%	4.3%	0.005
Elevated cholesterol	56.8%	51.2%	0.07
Baseline Heart Failure factors *	30.4%	31.9%	0.62
Ejection Fraction < 40%	10.7%	22%	<0.0001
Ejection Fraction (mean ± SD)	51.6±10.7%	47.1±11.0%	<0.0001

* Baseline heart failure factors was defined as 1 or more of the following: history of heart failure before randomization, rales on examination, S3 gallop on examination, highest Killip class >1 during index myocardial infarction (MI) before randomization, highest New York Heart Association (NYHA) class>I before index MI, or NYHA class II at randomization.

Table 2

Overall 7-year event rate (%) of the combined primary endpoint, death, myocardial infarction (MI) and new onset class IV congestive heart failure (CHF) in the Occluded Artery Trial for patients with non ST elevation myocardial infarction (NSTEMI) electrocardiogram (ECG) and ST elevation myocardial infarction (STEMI) ECG

Outcome	Non STEMI EKG (N=283)	Typical STEMI EKG (N=1918)	Unadjusted (STEMI vs. NSTEMI)		Adjusted* (STEMI vs. NSTEMI)		Interaction** p-value (EKGxTRT)	
	% (n)	% (n)	Hazard ratio	99% CI	Hazard ratio	99% CI	p-value	p-value
Death/MI/Class IV CHF	21.2 % (55)	22.8% (394)	1.06	0.73-1.54	1.07	0.73-1.56	0.64	0.63
Death	15.5% (42)	15.3% (261)	0.92	0.60-1.41	0.95	0.61-1.47	0.75	0.56
Fatal / Non Fatal MI	5.5 % (14)	7.7% (128)	1.37	0.66-2.82	1.45	0.70-3.04	0.19	0.88
Class IV CHF	6.4 % (14)	5.1% (90)	0.94	0.45-1.98	0.97	0.45-2.07	0.91	0.37

*The baseline risk factors for the outcomes included in the multi-variable analysis are age (per 10-years older), history of diabetes mellitus at study entry, lower estimated glomerular filtration rate (per 10 unit decrease), lower ejection fraction at baseline (per 10 percentage lower), history of cerebrovascular disease, history of percutaneous coronary intervention (PCI) before study entry, shorter time from qualifying myocardial infarction (MI) to randomization (per day decrease), history of peripheral vascular disease, and heart failure at baseline.

**The interaction is between type of ECG (STEMI, Non-STEMI) and treatment (PCI, MED)

Table 3

Overall 7-year event rate (%) of the combined primary endpoint, death, myocardial infarction (MI) and new onset class IV Congestive Heart Failure (CHF) in the Occluded Artery Trial for patients with non ST (NSTEMI) and ST elevation (STEMI) myocardial infarction electrocardiogram (ECG)

Outcome	PCI % (n)	MED % (n)	Unadjusted (PCI vs. MED)			Adjusted* (PCI vs. MED)		
			Hazard ratio	99% CI	p-value	Hazard ratio	99% CI	p-value
Non STEMI ECG								
	N=136	N=147						
Death/MI/Class IV CHF	22.3% (28)	20.2% (27)	1.20	0.60-2.40	0.51	1.03	0.49-2.20	0.91
Death	13.8% (18)	17.0% (24)	0.82	0.37-1.84	0.53	0.64	0.26-1.55	0.19
Fatal / Non Fatal MI	6.1% (7)	5.1% (7)	1.11	0.28-4.41	0.84	1.03	0.24-4.44	0.96
Class IV CHF	6.7% (8)	6.0% (6)	1.50	0.37-6.02	0.45	1.51	0.34-6.75	0.47
Typical STEMI ECG								
	N=965	N=953						
Death/MI/Class IV CHF	22.3% (202)	23.3 % (192)	1.04	0.81-1.35	0.67	1.04	0.80-1.35	0.73
Death	14.7% (132)	15.9% (129)	1.00	0.73-1.38	0.97	0.97	0.71-1.34	0.83
Fatal / Non Fatal MI	7.9% (70)	7.5% (58)	1.21	0.76-1.91	0.29	1.26	0.79-1.99	0.20
Class IV CHF	5.0% (43)	5.2% (46)	0.90	0.53-1.56	0.63	0.91	0.53-1.58	0.67

* The baseline risk factors for the outcomes included in the multi-variable analysis are same as ones for the models presented in Table 2.