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Effects of timing, location and definition of reinfarction on mortality in patients with totally occluded infarct related arteries late after myocardial infarction

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ABSTRACT

Background: The Occluded Artery Trial (OAT) randomized stable patients (n = 2201) >24 h (calendar days 3–28) after myocardial infarction (MI) with totally occluded infarct-related arteries (IRA), to percutaneous coronary intervention (PCI) with optimal medical therapy, or optimal medical therapy alone (MED). PCI had no impact on the composite of death, reinfarction, or class IV heart failure over extended follow-up of up to 9 years. We evaluated the impact of early and late reinfarction and definition of MI on subsequent mortality.

Methods and results: Reinfarction was adjudicated according to an adaptation of the 2007 universal definition of MI and the OAT definition (≥2 of the following — symptoms, EKG and biomarkers). Cox regression models were used to analyze the effect of post-randomization reinfarction and baseline variables on time to death.

After adjustment for baseline characteristics the 169 (PCI: n = 95; MED: n = 74) patients who developed reinfarction by the universal definition had a 4.15-fold (95% CI 3.03–5.69, p < 0.001) increased risk of death compared to patients without reinfarction. This risk was similar for both treatment groups (interaction p = 0.26) and when MI was defined by the stricter OAT criteria. Reinfarctions occurring within 6 months of randomization had similar impact on mortality as reinfarctions occurring later, and the impact of reinfarction due to the same IRA and a different epicardial vessel was similar.

Conclusions: For stable post-MI patients with totally occluded infarct arteries, reinfarction significantly independently increased the risk of death regardless of the initial management strategy (PCI vs. MED), reinfarction definition, location and early or late occurrence.

1. Introduction

The Occluded Artery Trial (OAT) [1] compared the clinical outcome of stable patients with totally occluded infarct-related arteries (IRA) after myocardial infarction (MI) re-canalized by percutaneous coronary intervention (PCI) versus conservative treatment with optimal medical therapy (MED) alone. PCI of occluded arteries had no impact on the composite of death, reinfarction and class IV heart failure (HF) over the initial or extended follow-up periods [2,3], or on quality of life [4].

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Most reinfarctions were spontaneous (type 1) and occurred at a statistically similar frequency in both treatment groups [5]. There was a higher rate of reinfarction due to stent thrombosis in the PCI group (2.7% PCI vs 0.6% MED, $p < 0.001$).

Reinfarction following fibrinolysis has been shown to be associated with a marked increase in mortality [6]. The impact of reinfarction based on the definition (i.e., universal vs OAT definition) and based on timing of early vs. late reinfarction and reocclusion of the infarct vs. another artery in patients with prior total occlusion is unknown. Therefore, we analyzed long-term follow-up data on OAT patients to study the consequences of reinfarction in stable patients initially randomized to late percutaneous IRA revascularization of total occlusions with optimal medical therapy or conservative initial optimal medical therapy alone in the subacute phase after an index MI.

2. Methods

This analysis of the 2201 patient OAT cohort [2] was prospectively predefined as an aim in conjunction with the NHLBI/NIH supported long-term follow-up phase.

2.1. OAT study protocol and definition of reinfarction

The OAT protocol has previously been published [1]. Briefly, stable patients who had total occlusion of the IRA >24 h (on calendar days 3–28) after MI were randomly assigned to receive optimal medical therapy alone ($n = 1100$) or with PCI ($n = 1101$). Patients were followed via bi-annual telephone calls for up to 9 years (mean of 6 years). The combined primary endpoint was death, MI or hospitalization for New York Heart Association (NYHA) class IV HF. The OAT definition of reinfarction required 2 of the following 3 criteria: Ischemic symptoms for at least 30 min, electrocardiographic changes, and elevation of cardiac serum markers, with different threshold levels for MI peri-PCI [1]. The OAT definition of elevation of markers required a creatine kinase (CK)-MB fraction that was greater than the upper limit of the normal (ULN) range at the local laboratory or, if unavailable, troponin I or T ≥2 times ULN or CK >2 times ULN for spontaneous reinfarction. For peri-procedural reinfarction, marker elevation was defined as ≥3 times ULN after PCI and ≥5 times ULN after coronary artery bypass grafting. Troponin levels were not used to diagnose reinfarction within 10 days after the index MI.

An independent Morbidity and Mortality Classification Committee (MMCC) reviewed patient data on reinfarctions according to the original protocol definition of MI [1]. In conjunction with the long term follow-up phase of OAT, reinfarctions during the entire follow-up period were also reviewed centrally by a group of 5 investigators to permit classification according to the universal definition of MI [3,5,7]. This definition is an adapted, practical application of the universal definition of MI. This is necessary because most institutions use a local upper limit of normal for troponin and do not use the universal definition of MI recommended 99 percentile for troponin, as we have previously reported [8].

Two reviewers, blinded to treatment assignment, reviewed hospital records and case report forms for each event; the group adjudicated disagreements. The universal definition of reinfarction required symptoms, EKG changes and an elevation of biomarkers (troponin preferred) to any level above the ULN for spontaneous or type 2 infarction (supply–demand), or ≥3× ULN after PCI, or ≥5× ULN after CABG. We used laboratory reported upper reference limit values according to the individual study site laboratories. This review also designated the IRA associated with the reinfarction.

Study report forms collected information on whether cardiac markers were designated by sites to be re-elevated within 48 h of the initial randomization in OAT to ascertain PCI-related marker release and comparable rates in the MED group. Laboratory data for these cases of asymptomatic marker re-elevation were not centrally confirmed and this information alone did not constitute MI by either the OAT or universal MI definition.

Study sites submitted clinical records of HF-related hospitalizations for review. Whether HF was the primary cause for these hospitalizations was centrally confirmed according to pre-specified criteria. The impact of reinfarction on the subsequent risk of NYHA class III or IV HF was a secondary aim of this analysis.

2.2. Statistical methods

Statistical analysis was performed on baseline variables using the *t*-test, Wilcoxon, chi-square or Fisher exact test as appropriate. Kaplan–Meier product-limit estimates were used to show survival curves for patients with and without reinfarction [9,10]. Cox regression models were used to analyze the effect of post-randomization reinfarction on time to death adjusting for baseline variables and interactions with the study treatment [11]. Reinfarction was fit as a time-dependent variable in the Cox regression models. Results are presented as hazard ratio (HR) for mortality compared to patients with no post-randomization reinfarction and 95% confidence interval (CI). Two different cutoff times (30 days, 6 months) for early or late reinfarction were examined. Patients experiencing a fatal reinfarction were included in all analyses.

The 7-year event rates are presented because the number of patients followed for more than 7 years was small. Data for the patients lost to follow-up were censored as of the last contact. This last contact occurred at 5 years from randomization for patients who declined consent for extension of follow-up. Only 1.4% of patients (14 in PCI and 16 in MED group) were lost to follow-up before the occurrence of a primary end-point event or 12 months of follow-up. Average follow-up time for survivors was 6 years and was similar in the two treatment groups.

Analyses were performed according to the intention-to-treat principle. To control for the Type I error rate, it was pre-specified in the study protocol that a p-value of ≤0.01 would be considered as showing evidence of differences in secondary analysis. Therefore, a variable with p-value ≤0.01 in the final multivariate model would be presented as having independent impact on death. In this analysis a variable with p-value between 0.05 and 0.01 in the final multivariate model would be considered as showing trend toward the impact on death.

All analyses were performed using SAS V9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Mean age of the 2201 randomized patients was 58.6 ± 11 years, 78% were male, ejection fraction was 47.7 ± 11.1% and prevalence of Killip Class 2–4 during index MI was 18.9%. The time interval between MI and randomization was a median of 8 days (IQR 5–16). Among 2201 total patients, 303 patients died (PCI vs. MED HR = 0.98, 95% CI 0.78–1.22), and 142 and 169 had reinfarction according to the OAT and universal definition, respectively, over a 6 year mean follow-up. 29 events were identified by the universal definition but not by the OAT study definition. The 7-year reinfarction event rate by the OAT definition was 7.4% (PCI vs. MED HR = 1.20, 95% CI 0.86–1.67, $p = 0.27$) and by the universal definition was 8.7% (PCI vs. MED HR = 1.31, 95% CI 0.97–1.77, $p = 0.08$) [3,5]. Details of baseline and angiographic characteristics of patients with and without reinfarction are presented in Table 1a for patients who died and in Table 1b for patients who survived the follow-up period, respectively. Medical therapy in hospital and at discharge is presented in Table 2. Statins, beta blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers were used at high rates during follow-up, with no difference between patients with or without reinfarction, or by treatment group.

3.2. Impact of reinfarction on mortality

Patients who developed reinfarction by the universal definition had a significantly higher mortality compared to the patients without reinfarction (31.5% vs. 13.9%, Fig. 1) with an unadjusted risk of death that was 4.8-fold increased (95% CI 3.52–6.53, $p < 0.001$). After adjustment for baseline characteristics, occurrence of reinfarction fit as a time-dependent variable was an independent predictor of death (HR 4.15; 95% CI 3.03–5.69, $p < 0.001$) (Table 3). The risk of death following reinfarction was similar in the two treatment groups (PCI: 3.64; 95% CI 2.35–5.64, $p < 0.001$; MED: 4.90; 95% CI 3.09–7.75, $p < 0.001$; PCI vs MED HR = 0.91, 95% CI 0.73–1.14, $p = 0.42$; reinfarction and treatment interaction $p = 0.26$). 29 events were identified by the universal definition but not by the OAT study definition. Of these 29 subjects with events, 16 died during the follow-up period. The risk of death was similar and independent predictors of death were unchanged when the original OAT definition of reinfarction was assessed (HR = 3.22 95% CI 2.24–4.65, $p < 0.001$, reinfarction and treatment interaction $p = 0.28$).

The infarct-related artery (IRA) could be identified based on angiography, wall motion studies and/or ECG in 135 of 169 patients with reinfarction by the universal definition. Sixty-seven of these 135 patients (49.6%) had reinfarction due to the initial OAT IRA. Reinfarctions due to the qualifying IRA fit as a time-dependent variable independently increased mortality (HR 2.94, 95% CI 1.76–4.93, $p < 0.001$). Reinfarctions occurring in an epicardial coronary artery different from the initial IRA also increased mortality (HR 3.77, 95% CI 2.22–6.44, $p < 0.001$). The impact of reinfarction on death was similar when reinfarction was due to the OAT index IRA or a different epicardial vessel (HR 1.11, 95% CI 0.55–2.25, $p = 0.77$).