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Does marital status contribute to the explanation of the hypercholesterolemia paradox in relation to long term mortality in myocardial infarction? Findings from the MONICA/KORA Myocardial Infarction Registry

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ABSTRACT

Objective. A recent study found long-term mortality after first acute myocardial infarction (AMI) to be particularly reduced among married individuals with hypercholesterolemia. This study explores, whether statin treatments during the last week prior to AMI offer an explanation to this phenomenon.

Methods. Data were retrieved 2000–2008 from the population-based KORA myocardial infarction registry, located in Bavaria, Germany. The sample included 3162 individuals, alive 28 days after first AMI, who received statins both in hospital and at discharge. Associations with long-term mortality were examined via multivariable Cox regression. Among patients with hypercholesterolemia, individuals with and without prior statin treatment were each tested against the reference group "neither (hypercholesterolemia nor statin)" and tested for interaction with "marital status".

Results. Among patients with and without prior statins, hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.46–0.93 and HR 0.72, 95% CI 0.55–0.94, were observed, respectively. Mortality reductions diminished after introduction of the following interaction terms with marital status: HR 0.49, p 0.042 for patients with and HR 0.77, p 0.370, for patients without prior statins.

Conclusions. Prior statin treatments appear to be an underlying factor for long-term mortality reduction in married AMI-survivors with hypercholesterolemia. Confirmation of our results in further studies is warranted.

Introduction

Hypercholesterolemia is one of the main risk-factors for coronary heart disease (CHD), coronary death and other cardiovascular diseases in general populations (De Backer et al., 2003; Pekkanen et al., 1990). The reduction of adverse outcomes in patients with hypercholesterolemia, observed in populations with acute coronary syndrome (ACS), chronic heart failure (CHF), chronic kidney disease (CKD), etc. has become known as the "hypercholesterolemia paradox" (HP) (Kalantar-Zadeh et al., 2007; Wan et al., 2007; Wang et al., 2009). Various different theories explaining the HP include: time differentials between two competing risk factors such as over-nutrition (long-term killer but short-term protective) versus under-nutrition (short-term killer), endotoxin–lipoprotein interaction, reverse causation and others (Kalantar-Zadeh et al., 2007).

While protective effects of lipid-lowering via HMG-CoA reductase inhibitor (statin)-therapy on long-term mortality outcomes have been confirmed as both primary and secondary pharmaceutical interventions across various populations (Wilt et al., 2004; Cholesterol Treatment Trialists' (CTT) Collaboration et al., 2010; Mills et al., 2011; Taylor et al., 2013), controversy over the adequacy of statin treatments within populations, in which the HP is observable, continues (Kalantar-Zadeh

Abbreviations: ACE-I, angiotensin-converting-enzyme-inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; Beta-blocker, beta adrenergic blocking agent; CHD, coronary heart disease; CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; ECG, electrocardiography; HP, hypercholesterolemia paradox; HR, hazard ratio; IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg; MONICA, Monitoring trends and determinants on cardiovascular diseases; OR, odds ratio.

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et al., 2007; Wan et al., 2007; Wang et al., 2009). Adjustment for statin treatment, co-morbidities and other risk-factors could not explain in-hospital mortality reductions in ACS patients with history of hypercholesterolemia (Wang et al., 2009). However, studies examining prior statin treatment as an underlying effect of the HP for long-term mortality outcomes are lacking. Furthermore, the role of psychosocial factors in underlying mechanisms of the HP has only been sparsely examined to date. A recent study examining long-term all-cause mortality among first acute myocardial infarction (AMI) — survivors within our study region, discovered substantial mortality reductions to be particular to married individuals with a history of hypercholesterolemia (Quinones et al., 2014).

The objective of this study was to compare whether the mortality reductions, observed for married men and women with a history of hypercholesterolemia, are also observable in married individuals, who were treated with statins in the last week prior to their first AMI.

Methods

The population-based Augsburg Myocardial Infarction Registry began continuously registering all cases of coronary deaths and non-fatal AMI in 1984 within the framework of the MONICA (Monitoring trends and determinants on cardiovascular diseases)-project. The registry has been part of the KORA (Cooperative Health Research in the Region of Augsburg) framework since 1995. The data covers the 25–74 year old population in the city of Augsburg and two adjacent districts located in southern Bavaria, Germany (totalling 600,000 inhabitants). Patients hospitalized in eight hospitals within the study region and two hospitals in the surrounding areas are included. The study was approved by the Ethics Committee of the Bavarian Medical Association. All participants submitted written informed consent before being enrolled in the study. Methods of case identification, diagnostic classification of AMI, and data quality control have been described elsewhere (Kuch et al., 2008; Meisinger et al., 2006).

Sample

The sample was based on data from all patients registered between January 1, 2000, and December 31, 2008. A total of 3391 men and women who were hospitalized after their first AMI, received statin treatments both in-hospital and at discharge, and survived the first 28 days after AMI was included. Due to missing data in covariates 229 persons were excluded leaving a total sample of 3162 individuals. The follow-up was continued until August 26th 2010.

Data collection and endpoint

Study participants were interviewed by trained study nurses with a standardized questionnaire during their hospital stay after being transferred from the intensive care unit. Prior treatments, co-morbidities, socio-demographic data and other risk factors were assessed. Information on diagnosis, in-hospital procedures, complications, in-hospital and discharge medications were obtained from chart review. Pharmaceutical treatments during the last week prior to AMI (defined as prior treatments) were computed by combination of information from interviews and chart reviews. Among these, statins, angiotensin-converting-enzyme-inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs), beta-blockers, antiplatelet drugs, and diuretics were included. Patients not receiving beta-blockers, antiplatelet drugs, and ACE-Is or ARBs at discharge, were too infrequent for stable multivariable analyses. Consequently, a combined variable assessing whether the patient was receiving all three discharge medications at once was computed. The study end-point was long-term all-cause mortality. Mortality was assessed by checking the vital status of all registered persons in the KORA AMI registry through the population registries, inside and outside the study area in 2010. This procedure guaranteed that the vital status of cohort members who had moved outside of the study area could also be assessed.

Statistical analyses

Observation time was computed as the number of consecutive days between infarction date and date of death or end of study on August 26th 2010. Relevant explanatory variables listed in Table 1 were determined through literature review (Antman et al., 2004; Atzema et al., 2011; Bata et al., 2006; Bogale et al., 2007; Braunwald et al., 2000; Chandra et al., 1983; Consuegra-Sánchez et al., 2014; De Backer et al., 2003; Ekberg-Aronsson et al., 2007; Fagard, 2010; Fox et al., 2006; García-García et al., 2011; Gustafsson et al., 1998, 2004; Gutierrez et al., 2012; Marcinkiewicz et al., 2013; McManus et al., 2012; Meisinger et al., 2010; Pekkanen et al., 1990; Strand and Tverdal, 2004) and expert knowledge. Among these, smoking status was omitted as it had failed to show effects on long-term survival in multi- and bi-variable analyses of a previous study examining the same study population (Quinones et al., 2014). Hypertension was omitted to avoid multicollinearity with pharmaceutical treatment variables.

A composite variable was created out of "history of hypercholesterolemia" and "statin treatment during the last week prior to AMI". It contained the categories "hypercholesterolemia and statin", "hypercholesterolemia no statin" and the reference category "neither". The fourth category "statin no hypercholesterolemia" contained only 34 observations and 11 events. It was added to the category "hypercholesterolemia and statin" since prior statin treatment may imply undocumented history of hypercholesterolemia.

In the crude model the composite variable was the explanatory variable for long-term survival. The minimally adjusted model included marital status, sex, and age-group. Furthermore, "recruitment day" was included to adjust for variation in the time of study entry. Recruitment day was defined as the number of consecutive days between December 31, 1999 and the recruitment date. The fully adjusted model included marital status, sex, age-group, history of diabetes, history of stroke, history of angina pectoris, treatments with ACE-Is or ARBs, diuretics, beta-blockers, or antiplatelet drugs during the last week prior to AMI, time between symptom onset and hospital admission in minutes, bundle branch block, ST-segment elevation MI, complications in hospital (pulmonary oedema, ventricular fibrillation, re-infarction, or cardiac arrest), reperfusion therapy (coronary artery bypass graft, percutaneous coronary intervention, or fibrinolysis), diuretics at discharge, three discharge medications combined (ACE-Is or ARBs, beta-blockers, and antiplatelet drugs), and recruitment day. The proportional hazards assumption was examined in the fully adjusted model by correlation of Schönfeld-residuals against observation-time and squared observation-time for each explanatory variable, respectively. A violation of the proportional hazards assumption was observed for reperfusion therapy. Time-dependency was incorporated into the model by introducing an interaction-term with observation time, with a p-value < 0.0001. Multicollinearity presented no major concern as variance inflation factors were well below 2.5 for all explanatory variables. All models were rerun after introduction of interaction terms with marital status for both categories of the composite variable. Fully adjusted, analyses with interaction terms were run for different survival cut-offs from one to 10 years. All analyses were rerun after omission of 34 observations from the fourth category "statin no hypercholesterolemia", as sensitivity analyses. All tests within the multivariable models were conducted at an alpha level of 0.05. All statistical analyses were performed using SAS software, release 9.2 (SAS Institute, Cary, NC).

Results

Sample characteristics

A total of 350 (11.1%) deaths were recorded within 17,062.3 person-years. During a median follow-up of 5.2 years with an IQR of 3.3 to 7.4 years, observation times ranged from 33 to 3889 days (10.6 years).

Among 3162 men and women, 75.7% ($n = 2395$) were married and 24.3% ($n = 767$) were unmarried. Married individuals were admitted to a hospital in a shorter median time period (165 min, IQR 80–610 min) compared with the unmarried (median 198 min, IQR 96–633 min). Among married individuals 10.4% ($n = 248$) died while 13.3% ($n = 102$) of unmarried persons died. Other characteristics are similarly frequent among married and unmarried individuals. Distributions of population characteristics by composite variable categories are presented in Table 1. Individuals with prior statin treatments were older (median 65 years, IQR 59–69 years) than those not treated (median 60 years IQR 52–67 years). Furthermore, co-morbidities and pharmaceutical treatments are more frequent in Individuals with prior statin treatments.

Results of multivariable analyses of long-term survival

The associations between prior statin treatment and long-term all-cause mortality within the full sample are presented in Table 2. While prior statin treatment shows a crude, statistically insignificant