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Original Article

Peripheral arterial disease is associated with higher mortality in patients with incident acute myocardial infarction

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ABSTRACT

Background: Little data is available on short- and long-term survival in patients with peripheral arterial disease (PAD) after acute myocardial infarction (AMI). We aimed to examine the association of PAD and 28-day case fatality as well as long-term mortality in a population-based sample of patients with incident AMI.

Methods: In this secondary analysis of data from the German MONICA/KORA Myocardial Infarction Registry 4307 patients aged 28–74 years with incident AMI with and without history of PAD (information derived from medical chart) were included. Data were collected between 2000 and 2008. Patients were followed-up until December 2011. Associations between PAD and 28-day case fatality were examined via multivariable logistic regression models, between PAD and long-term mortality with Cox proportional hazards regression models, respectively.

Results: From 303 (8.9%) patients with PAD, 22 (7.3%) died within 28-days post-AMI in contrast to 96 (2.9%) of patients without PAD. However, the fully adjusted model (OR 1.55, 95% CI 0.89–2.70) revealed no significant association. Long-term follow-up (median 5.7 years) yielded 100 (32.4%) versus 483 (14.4%) cases of deaths among patients with and without PAD, respectively. This association was significant (fully adjusted model: HR 1.70, 95% CI 1.35–2.13), persisted up to 11 years after AMI and was present in all subgroups according to age, sex and history of diabetes. The highest long-term mortality risk was found for patients younger than 63 years with PAD (HR 2.19; 95% CI 1.41–3.39).

Conclusion: AMI patients with PAD differ considerably from their counterparts without PAD in terms of long-term survival.

1. Introduction

Lower extremity peripheral arterial disease (PAD) is a systemic manifestation of atherosclerosis and a powerful predictor of future cerebrovascular and cardiovascular events as well as of increased mortality [1–3]. PAD is classified as a coronary heart disease equivalent in various treatment guidelines and is linked to acute myocardial infarction (AMI) [3–5]. Reported prevalences of PAD among patients with acute coronary syndrome (ACS) range between 8 and 13% [6–11].

Results from several studies indicate that PAD is independently associated with increased mortality in patients with AMI [6,7,11–17]. However, the findings regarding the relation of PAD with short-term survival are conflicting: some studies have found an adverse association of PAD [11,13–18] whereas other studies found no significant association between PAD and short-term mortality [6,12]. In terms of long-term mortality, only a few studies are available so far, all indicating an adverse association between PAD and long-term survival [6,7,12]. However, those studies are lacking comparability since one of these studies included only AMI patients with left ventricular systolic dysfunction and/or heart failure [7] and two studies did not adjust their analyses for possible relevant confounders such as AMI characteristics or — treatment and discharge medication [7,12]. In addition, mean

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observation time of these studies did not exceed 2.8 years. Moreover, only Spencer et al. [6] have examined the association of PAD and both short- and long-term mortality in a community-wide patient population with AMI.

Therefore, the objective of this study was to evaluate the association between PAD and short-term case fatality as well as long-term mortality using data on incident AMI recorded in the population-based MONICA/KORA AMI registry located in Augsburg, Germany.

2. Material and methods

The population-based Myocardial Infarction Registry in Augsburg was implemented within the World Health Organization MONICA (Monitoring of trends and determinants in cardiovascular disease) project in 1984. MONICA was terminated in 1995, and the registry became part of the KORA (Cooperative Health Research in the Region of Augsburg) framework. Since 1984, the registry continuously registers all cases of coronary death and non-fatal AMI of the 25–74-year old study population in the city of Augsburg and the counties Aichach-Friedberg and Augsburg (in total about 600,000 inhabitants). Patients hospitalized in one of the eight hospitals within the study region and in two hospitals in the adjacent areas are included. Methods of case finding, diagnostic classification of AMI as well as data quality control were detailed elsewhere [19,20]. Since January 1, 2000, the diagnostic criteria of AMI according to the European Society of Cardiology and American College of Cardiology were applied throughout the study region. Using a list of specific admission diagnoses, the admission books of the hospitals are screened for patients with suspected AMI or ischemic events by study nurses on a daily basis. Subsequently, ward physicians are questioned via telephone to determine whether there is clinical evidence of AMI in patients meeting the screening diagnosis. The final criterion for inclusion in the registry is a discharge diagnosis of AMI or of myocardial ischemia fulfilling the above-mentioned criteria.

The study has been approved by the ethics committee of the Bavarian Medical Association. All participants gave written informed consent before being enrolled in the study.

2.1. Data collection

Demographic, clinical and medication data were obtained by interview and/or chart review. Trained study nurses interviewed the study participants during their hospital stay using a standardized questionnaire after they were transferred from the intensive care unit and collected information from the patients' medical charts after discharge.

Study endpoints were 28-day case fatality and all-cause long-term mortality. To determine long-term mortality, the vital status of all patients registered in the KORA Myocardial Registry through the population registries in- and outside the study region until December, 31, 2011 was monitored. As a result, the vital status of patients who had moved outside of the study area could also be registered and follow-up data was almost complete (five missing cases).

2.2. Study groups

Patients were assigned to the study group “PAD”, if a history of PAD was documented in the medical chart. The group “without PAD” consisted of patients without history of PAD as indicated by medical chart, even if the patient reported to have a history of PAD in the interview.

2.3. Data analysis

Categorical variables were expressed as percentages, continuous variables as mean values with standard deviations. For comparison of quantitative variables, Student's *t*-test was used. To compare categorical variables, we used Chi^2 or Fisher's exact test, if appropriate. The level of significance was set to $p < 0.05$ for all analyses. Statistical analyses were performed using SAS software, version 9.2 (SAS institute).

2.3.1. Regression modeling

Three regression models were computed for each outcome (short-term case fatality, long-term mortality): first, a crude model, second, a minimally adjusted model including the covariables age and sex, and finally, a full model including all potential covariables was calculated. Patients with missing data concerning any covariables that should be part of the final model were excluded. Multicollinearity among the covariables was evaluated by examining variance inflation factors (VIF) in the full model.

2.3.1.1. Short-term case fatality. Logistic regression models were performed to examine the association of PAD and 28-day case fatality. Potential covariables were selected by cross-tabulation with survival and testing of frequencies using Chi^2 test. The full regression model included all variables with a p-value < 0.05. Hence, the covariables school education, angina pectoris and medication prior AMI (including all 4 EBMs prior AMI) were excluded. Sex (p-value = 0.0521) was forced to stay in the model. The covariable medication at discharge (including all 4 EBMs at discharge) was not considered in the analysis of short-term case fatality, because this information was not available for most of the patients who died within 28 days after AMI, since they have died in hospital.

2.3.1.2. Long-term mortality. Cox proportional hazards models were performed to examine the association of PAD and long-term mortality. Kaplan-Meier plots were created combined with log-rank test to compare the covariate's survival distributions and to test for statistical significance. Covariables with p-values ≥ 0.05 were not included in the full model. Furthermore, the proportional hazards assumption was tested graphically for each variable. After carrying out log-rank test and proportional hazards assumption, the variables school education, living alone, angina pectoris, hypertension, smoking and AMI type were not included in the full model. Regarding information on prescribed medication only the covariable discharge medication was considered. To control for potential cohort effects, it was tested whether the year of AMI had an influence on the association between PAD and long-term mortality, but no associations were found.

Finally, models including the same covariables as the full model were computed for follow-up periods of one to eleven years in two-year intervals.

2.3.2. Sensitivity analysis

To check the robustness of our results, several sensitivity analyses were performed additionally. First, stratified analyses by diabetes (yes/no), sex and age group (≤ 62 years vs. > 62 years) were performed. Median age was used as a cut-point to define age groups. Second, the age- and sex-distribution of the patients included and excluded from analyses were compared. Furthermore, short-term case fatality and long-term mortality were calculated for all patients that were excluded from main analyses due to missing values in any relevant covariable. Finally, we additionally included all patients who reported to have PAD but no corresponding diagnosis was documented in their medical chart and repeated all calculations analogously to the main analyses.

3. Results

In this analysis, all patients with an incident AMI registered between January 1, 2000 and December 31, 2008 AMI ($n = 7121$) were included. Patients were followed until December 31, 2011. All patients who died within 24 h after AMI ($n = 1690$) were excluded, as well as patients with reinfarction ($n = 711$), patients with missing data on PAD ($n = 408$) or long-term mortality ($n = 5$). Thus, the final data set