Association of peripheral arterial disease with short-term case fatality and long-term mortality in patients with incident acute myocardial infarction. Results from the MONICA/KORA Myocardial Infarction Registry.

Lisa Dinser[1,2,3], Christa Meisinger[1,2], Ute Amann[1,2], Margit Heier[1,2], Christian Thilo[4], Bernhard Kuch[4,5], Annette Peters[2], Inge Kirchberger[1,2]

[1] Central Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Stenglinstraße 2, 86156 Augsburg, Germany

[2] Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute of Epidemiology II, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany

[3] Institute for Medical Information Processing, Biometrics and Epidemiology, Ludwig-Maximilians-Universität München, Marchioninistraße 15, 81377 München

[4] Central Hospital of Augsburg, Department of Internal Medicine I – Cardiology, Stenglinstraße 2, 86156 Augsburg, Germany

[5] Hospital of Nördlingen, Department of Internal Medicine/Cardiology, Stoffelsberg 4, 86720 Nördlingen, Germany

Corresponding author:

Lisa Dinser

MONICA/KORA Myocardial Infarction Registry

Central Hospital of Augsburg

Stenglinstraße 2

86156 Augsburg

Phone: +49-821-400 4176

Fax: +49-821-400 2838

Email: lisa-dinser@hotmail.de

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

Results: In the study sample, 385 (8.9%) patients had a history of PAD. Compared with patients without PAD, they had a significantly higher 28-day case fatality risk (Odds ratio (OR) 3.58, 95% confidence interval (CI) 1.92-6.50) in the unadjusted model, but not in the fully adjusted model (OR 1.89, 95% CI 0.94-3.80, p= 0.0733). A significant effect of PAD on long-term mortality was found (fully adjusted model: HR 1.70, 95% CI 1.35-2.13) which 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: Patients with PAD and AMI are a high-risk group which requires particular attention by health care providers.

KEYWORDS: Peripheral arterial disease, acute myocardial infarction, long-term mortality, short-term case fatality

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 effect of PAD on short-term survival are conflicting: some studies have found an adverse effect 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 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.

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 two adjacent districts (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 have already been described elsewhere [19,20] (Meisinger, Kuch). 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.

Sample

In this analysis, all patients with an incident AMI registered between January 1, 2000 and December 31, 2008 who survived at least 24 hours after AMI (n=5426) were included. Patients were followed until December 31, 2011. Patients with missing data on PAD (n=408) were excluded, resulting in a final data set of 4307 patients.

Data Collection

Trained study nurses interviewed the study participants during their hospital stay using a standardized questionnaire after they were transferred from the intensive care unit. At the beginning of the interview patients were questioned for socio-demographic data. Whether patients had PAD (yes/no) was determined by the interview but only considered if confirmed by chart review. Information on co-morbidities such as diabetes, hypertension, and hyperlipidemia (yes/no) were collected in the same way. Since 2004 a combination of four evidence-based medications (EBM) is considered the standard of care after AMI: anti-platelet agents, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or rather angiotensin-receptor blockers (ARB), and statins [21]. Data on these four medications received prior AMI were determined both from interviews and chart reviews. Information on medication prescribed at discharge, type of AMI, reduced left ventricular ejection fraction (LVEF < 30%; yes/no) as well as any reperfusion therapy during hospital stay were collected from chart review.

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.

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).

Short-term case fatality

To determine the association between PAD and 28-day case fatality, three logistic regression models were computed: 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. 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 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. Patients with missing data concerning any covariables that should be part of the final model were excluded. As a result, the final data set for logistic regression comprised 3370 cases.

Long-term mortality

Cox proportional hazards models were performed to examine the association of PAD and long-term mortality. Besides a crude Cox regression model, a model adjusted for age and sex and a full model including all relevant covariables was calculated. 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. The covariable medication prior AMI was not considered in the analysis of long-term mortality. Patients with missing data on any of the covariables were excluded from the analysis. On this account, the final data set for the Cox proportional hazards models included 3659 patients.

Furthermore, stratified analyses by diabetes (yes/no), sex and age group (≤62 years vs. >62 years) were performed. 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.

Multicollinearity among the covariables was evaluated by examining variance inflation factors (VIF) in the full model. 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 effects were found.

Sensitivity analysis

To check the robustness of our results, several sensitivity analyses were performed additionally. First, the age and sex distribution of the patients included and excluded from analyses were compared. Second, 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. Two models were computed in each case, one unadjusted and one model adjusted for age and sex. Third, 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.

RESULTS

Descriptive Analysis

The study sample consisted of 385 (8.9%) patients with PAD and 3922 (91.1%) without PAD. Baseline socio-demographic characteristics, risk factors and co-morbidities, AMI- and treatment characteristics of the patients with and without PAD are presented in Table 1. Patients with PAD were older, and significantly more likely to have a history of angina pectoris, diabetes, hypertension, and stroke, and to be ex-smokers. Patients with PAD were prescribed antiplatelet agents, beta-blockers, ACEIs or ARBs, and statins more frequently than patients without PAD prior AMI. However, at discharge patients with PAD received these 4 medications significantly less often than patients without PAD. Furthermore, patients with PAD obtained reperfusion treatment significantly less often than patients without PAD.

Table 1: Sample characteristics and differences between patients with and without peripheral arterial disease (PAD)

	PAD (n=385)	No PAD (n=3922)	p-value
Socio-demographic characteristics			
Female	84 (21.8)	1003 (25.6)	0.1055
Age [years], ± SD	63.8±8.0	60.4±9.8	<0.0001
Living alone	62 (16.1)	557 (14.2)	0.0612
School education > 9 years	40 (10.39)	846 (21.6)	<0.0001
Employed	58 (15.1)	1398 (35.7)	<0.0001
Risk factors and co-morbidities			
Angina Pectoris	76 (19.7)	524 (13.4)	0.0018
Diabetes	186 (48.3)	1129 (28.8)	<0.0001
Hypertension	320 (83.2)	2918 (74.4)	<0.0001
Hyperlipidemia	258 (67.0)	2608 (66.5)	0.8773
Stroke	63 (16.4)	217 (5.5)	<0.0001
Smoking			
Current smoker	126 (32.7)	1366 (34.8)	<0.0001
Ex-smoker	140 (36.4)	1039 (26.5)	
Never-smoker	67 (17.4)	1040 (26.5)	
AMI characteristics			
AMI type			
ST-segment elevation MI	97 (25.2)	1505 (38.4)	<0.0001
Non-ST-segment elevation MI	242 (62.9)	2135 (54.4)	
Bundle branch block	31 (8.1)	202 (5.2)	
LVEF <30%	32 (14.4)	309 (11.9)	0.2595
Treatment			
Any reperfusion treatment	262 (68.1)	3212 (81.9)	<0.0001
Medication prior AMI			
Antiplatelet agents	184 (47.8)	785 (20.0)	<0.0001
ACEIs/ARBs	157 (40.8)	953 (24.3)	<0.0001
Beta-Blockers	140 (36.4)	1024 (26.1)	<0.0001
Statins	91 (23.6)	490 (12.5)	<0.0001
All of these four medications	36 (9.6)	132 (3.4)	<0.0001
Medication at discharge			
Antiplatelet agents	328 (85.2)	3545 (90.4)	0.0028
ACEIs/ARBs	277 (72.0)	3020 (77.0)	0.0255
Beta-Blockers	322 (83.6)	3517 (89.7)	0.0013
Statins	285 (74.0)	3211 (81.8)	0.0005
All of these four medications	220 (57.14)	2538 (64.7)	<0.0001

PAD = peripheral arterial disease, AMI=acute myocardial infarction, ARB= Angiotensin receptor blocker, ACE=Angiotensin-converting enzyme inhibitor, LVEF = Left ventricular ejection fraction

Short-term case fatality

Among the patients without PAD, X% died within 28-days after the AMI event, compared with Y% of the patients with PAD. Odds ratios (OR) and corresponding confidence intervals (CI) of the 28-day case fatality are presented in Table 2. The unadjusted model indicated an increased short-term mortality risk for AMI patients with PAD (OR 3.58, 95% CI 1.92-6.50). Adjustment for age and sex resulted in a reduced OR, but the effect was still significant. After adjusting for all covariables, patients with PAD had a 1.89-fold mortality risk compared with patients without PAD, but the effect was no longer significant (p=0.0733). VIF Scores were below 2.00 indicating no multicollinearity among the covariables.

Table 2: Logistic regression models on the association of history of peripheral arterial disease and 28-day case fatality.

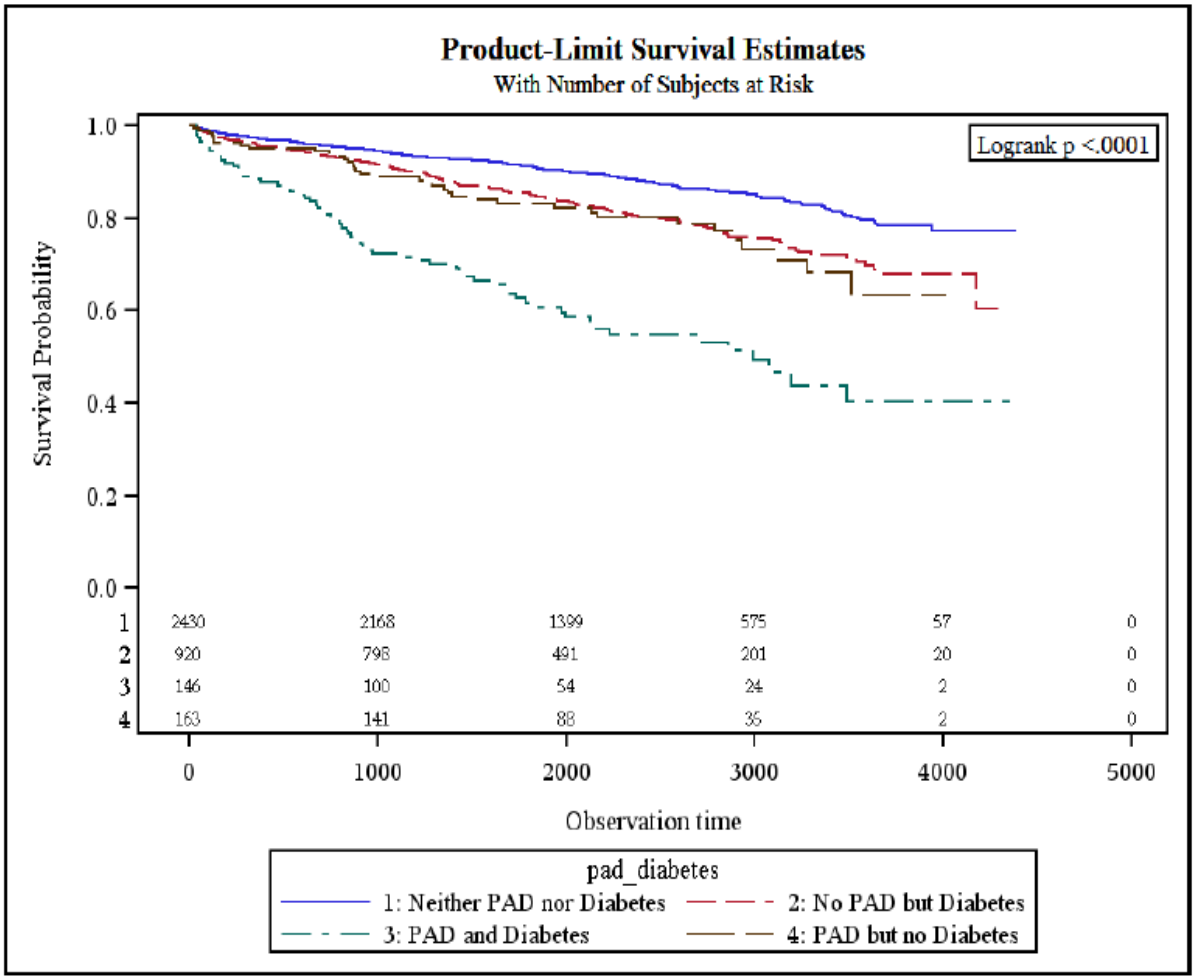
	Odds Ratio [95% confidence interval]	p-value
Crude model	3.58 [1.92-6.50]	<0.0001
Model 1[a]	2.94 [1.59-5.46]	0.0006
Model 2[b]	1.89 [0.94-3.80]	0.0733

[a] Adjusted for age and sex
[b] Adjusted for age, sex, living alone, hypertension, hyperlipidemia, stroke, diabetes, smoking, type of AMI, any reperfusion treatment and left ventricular ejection fraction (<30% vs. ≥30%)

Long-term mortality

Kaplan-Meier survival curves and log rank tests demonstrated significant differences in long-term survival between AMI patients with or without PAD and/or diabetes (see Figure 1). Survival was best for the group without PAD and diabetes and worst for those patients with both PAD and diabetes. Survival curves were quite similar for the patients who had either PAD or diabetes.

Figure 1: Kaplan-Meier curves and log-rank p-values of 12-year survival for patients with and without PAD stratified by diabetes.



The unadjusted model for the total sample demonstrated a significant greater long-term mortality risk for patients with PAD compared with those without PAD (Hazard ratio (HR) 2.45, 95% CI 2.03-3.19) (see Table 3). After adjusting for age and sex, PAD was still predictive for long-term mortality (HR 2.10, 95% CI 1.70-2.60). By adjusting for different covariables (see Table 3), HR decreased to 1.70 (95% CI 1.35-2.13) but was still significant. VIF scores were below 1.08, showing no multicollinearity among the covariables

Furthermore, crude, minimally adjusted and fully adjusted models stratified by sex, age and diabetes were calculated (see Table 3). In all models and both sexes, patients with PAD had a significantly higher long-term mortality risk. Men and women had only slightly different HRs.

Stratification by age showed that HRs of patients younger than 63 years were higher than those of the patients older than 62. In the model adjusted for all covariables, the HRof the younger age group (HR 2.19, 95% CI 1.41-3.39) was one and a half times larger than the one of patients older than 62 years (HR 1.54, 95% CI 1.18-2.01).

In the models stratified by diabetes, patients with PAD had a significantly higher long-term mortality risk than patients without PAD. In the unadjusted model, the HR for patients with PAD was significantly higher in the diabetes group (HR: 2.70, 95% CI 2.03-3.59) compared to the group without diabetes (HR: 1.84, 95% CI 1.31-1.61). However, with increasing adjustment for covariables this difference decreased. In the model including all covariables, the HR for patients with diabetes was 1.81 (95% CI 1.33-2.46) but 1.59 (95% CI 1.12-2.26) in patients without diabetes.

Table 3: Cox proportional hazards models on the association of history of peripheral arterial disease and long-term mortality.

	Hazard ratio [95% confidence interval]	p-value
Total sample		
Crude	2.45 [2.03-3.19]	<0.0001
Model 1[a]	2.10 [1.69-2.60]	<0.0001
Model 2[b]	1.70 [1.35-2.13]	<0.0001
Men		
Crude	2.50 [1.94-3.22]	<0.0001
Model 1[c]	2.09 [1.62-2.70]	<0.0001
Model 2[d]	1.70 [1.30-2.22]	<0.0001
Women		
Crude	2.63 [1.75-3.94]	<0.0001
Model 1[c]	2.07 [1.38-3.16]	<0.0001
Model 2[d]	1.85 [1.21-2.83]	0.0047
Patients ≤ 62		
Crude	3.09 [2.05-4.67]	<0.0001
Model 1[e]	2.78 [1.84-4.20]	<0.0001
Model 2[f]	2.19 [1.41-3.39]	0.0005
Patients > 62		
Crude	1.93 [1.50-2.49]	<0.0001
Model 1[e]	1.90 [1.48-2.45]	<0.0001
Model 2[f]	1.54 [1.18-2.01]	0.0013
Patients with diabetes		
Crude	2.70 [2.03-3.59]	<0.0001
Model 1[a]	2.40 [1.80-3.20]	<0.0096
Model 2[g]	1.81 [1.33-2.46]	0.0001
Patients without diabetes		
Crude	1.84 [1.31-1.61]	<0.0001

Model 1[a]	1.58 [1.12-2.24]	<0.0001
Model 2[g]	1.59 [1.12-2.26]	0.0091

[a] Adjusted for age and sex
[b] Adjusted for age, sex, hyperlipidemia, stroke, diabetes, any reperfusion therapy and 4 medications at discharge (antiplatelet therapy, ACEIs/ARBs, beta-blockers, statins)
[c] Adjusted for age
[d] Adjusted for age, hyperlipidemia, stroke, diabetes, any reperfusion therapy and 4 medications at discharge (antiplatelet therapy, ACEIs/ARBs, beta-blockers, statins)
[e] Adjusted for sex
[f] Adjusted for sex, hyperlipidemia, stroke, diabetes, any reperfusion therapy and 4 medications at discharge (antiplatelet therapy, ACEIs/ARBs, beta-blockers, statins)
[g] Adjusted for age, sex, hyperlipidemia, stroke, any reperfusion therapy and 4 medications at discharge (antiplatelet therapy, ACEIs/ARBs, beta-blockers, statins)

Table 4 displays fully-adjusted Cox models for different observation times (one to eleven years, in two-year intervals). All HRs were statistically significant, and only small changes could be seen throughout the years (at 1 year: HR 1.68, 95% CI 1.06-2.66; at 11 years: HR 1.70, 95% CI 1.36-2.13).

Table 4: Cox proportional hazards models on the association of history of peripheral arterial disease and long-term mortality in different follow-up periods

Years of follow-up	Deaths		Hazard ratio [95% confidence interval]	p-value
	PAD n (%)	No PAD n (%)		
1	25 (8.1)	107 (3.2)	1.681 [1.06-2.66]	0.0269
3	58 (18.8)	231 (6.9)	1.943 [1.44-2.63]	<0.0001
5	79 (25.6)	331 (9.9)	1.878 [1.45-2.43]	<0.0001
7	87 (28.2)	412 (12.3)	1.725 [1.36-2.19]	<0.0001
9	98 (31.7)	462 (13.8)	1.738 [1.38-2.18]	<0.0001
11	100 (32.4)	483 (14.4)	1.701 [1.36-2.13]	<0.0001

All models adjusted for age, sex, hyperlipidemia, stroke, diabetes, any reperfusion therapy and 4 medications at discharge (antiplatelet therapy, ACEIs/ARBs, beta-blockers, statins)

Sensitivity analyses

Sensitivity analyses showed that the age- and sex distribution of the patients who were excluded from the main analyses was not significantly different (data not shown). Furthermore, we found a very high short-term case fatality risk in patients with missing data in any of the included covariables. After adjusting for age and sex, the OR was 13.49 (95% CI 9.98-18.25) (see Supplement). In contrast, in the sensitivity analysis on long-term mortality the HR was 1.78 (95% CI 1.47-2.16). After considering self-reported PAD without confirmation by medical chart information, men had a slightly higher long-term mortality risk than in the main analysis (see Supplement). Besides that, the results did not change very much when also including patients with solely self-reported PAD.

DISCUSSION

The present study investigated both the association of PAD and short-term case fatality as well as long-term mortality in patients with incident AMI. The initial significant association between PAD and 28-day case fatality in the unadjusted regression model attenuated with increasing adjustment for covariables and was not significant in the fully adjusted model. In contrast, we found a significant association of PAD and long-term mortality during the entire observation period up to 11 years in the total sample as well as in subgroups according to sex, age and diabetes.

To our knowledge, our study was the first which had a follow-up time up to 12 years and provided survival analyses adjusted for AMI treatment as well as discharge medication. In accordance with other studies [7-11], 8.9% of all AMI survivors had a history of PAD and patients with PAD were older and more likely to have hypertension, diabetes and stroke than patients without PAD [7,13,14,22].

Contrary to findings from other studies [8,12,23], in our study patients with PAD were not prescribed beta-blockers, ACEIs/ARBs, antiplatelet agents and statins less frequently than patients without PAD prior to AMI. In accordance with the results reported by Spencer et al. [6], the utilization rates in patients with PAD were even significantly higher than in patients without PAD, indicating improvements in previously reported treatment disparities in primary care [24]. However, the use of lipid-lowering, antihypertensive, and antiplatelet therapy remains low with less than 50% of the patients in our study being treated according to the guideline recommendations [25].

Our study confirms previous reports that AMI patients with PAD were less likely to receive appropriate secondary prevention medication and interventional cardiac procedures despite their

higher risk profile and incidence of comorbidities [6,15,26,27]. Although it cannot be concluded from our study results that treatment disparities are responsible for the adverse survival outcomes, studies have demonstrated that guideline-recommended medication and procedures affect clinical outcomes positively irrespective of the specific subgroup of AMI. Januzzi et al [28] found that an early invasive treatment in PAD patients with non-ST-segment elevation ACS was accompanied by significant reduction in mortality. These findings highlight the need to further evaluate treatment decisions in AMI patients with PAD.

Short-term mortality

In our study, we found a significant association of PAD and 28-day case-fatality in the unadjusted regression model and the model adjusted for sex and age. A 1.89-fold higher risk for patients with PAD remained after adjustment for all relevant confounders, but this association was no longer significant (p=0.0733), due to the relatively small sample size compared with other studies [8,15,17,18].

However, previous studies also provided mixed results, which may be explained by different study characteristics [8,11,13-18]. Some of the studies that found an association between PAD and short-term mortality [8,13,16] have also included patients with unstable angina or polyvascular disease [14,15], were restricted to patients with AMI after PCI [17] or did not provide analyses adjusted for comorbidities and treatment [18]. Several studies have chosen in-hospital case-fatality as study outcome and have included patients having died within 24-hours after hospital admission who were in contrast excluded from our study. A current study based on a sample from the MONICA/KORA AMI registry has investigated a sample of 24-hours survivors and additionally included patients aged 75-84 years and those who had a reinfarction [11]. A slightly higher OR of 2.09 was found in this study which remained significant after adjustment in this larger sample with 570 cases with PAD. The study from Spencer et al. [6] had a study population that was quite comparable to ours, but included fatal AMIs within 24 hours after hospital admission. Indeed, the authors were not able to demonstrate a significant association (OR=1.29) between PAD and short-term case fatality, too.

Long-term mortality

Our study confirmed the results from previous studies in terms of a reduced long-term survival after AMI in patients with PAD [6,7,12,14]. However, none of these studies had a mean follow-up >2.8

years. In our study with a median observation time of 5.7 years, we were able to demonstrate that the negative association between PAD and long-term mortality persists even 11 years after the AMI.

Interestingly, younger patients with PAD had a much higher long-term mortality risk than older patients suffering from PAD. To our knowledge, this is the first study on long-term mortality that provided a stratified analysis by age in patients with PAD after AMI. A comparable result was reported by Kirchberger et al. [11] who found a significant, adjusted OR of 3.21 for AMI patients with PAD younger than 69 years and a significant adjusted OR of 1.86 for patients with PAD aged 69 years or older. However, study outcome was 28-day case-fatality, not long term mortality and the age groups were not similar to the present study. An explanation for this finding may be that persons who suffer from both AMI and PAD earlier in life are a particular multimorbid group with severe impairments of the entire cardiovascular system and a corresponding higher mortality risk.

Although the need to investigate CHD risks in women has been highlighted in the last decade [29], sex differences in patients with AMI and PAD were only scarcely investigated [30]. In our study, women with PAD had a slightly higher long-term mortality risk than men. Nevertheless, previous studies provided conflicting results. Subherwal et al. [12] demonstrated in their study a slightly higher long-term mortality risk in men with AMI and PAD compared to women. Another study [31] detected higher 1-year mortality in the unadjusted model in women compared with men with PAD and PCI after ACS.

Diabetes and PAD are strongly related: diabetes is one of the strongest risk factors for PAD [32] and about 20% to 33% of patients with PAD are also suffering from diabetes [32-34]. However, in contrast to the increased risks related with diabetes, the public and the health care providers are still lacking awareness of the risks associated with PAD [35,36]. In our study, the survival curves illustrate that the well-described negative effect of diabetes on long-term survival in AMI is quite comparable with the effect of PAD. AMI patients with both PAD and diabetes showed the worst long-term survival (see Figure 1). Thus, AMI patients with PAD and particularly those with both PAD and diabetes require specific attention by health care providers.

Strenghts and limitations

The present study has a number of strengths. It is based on data collected in the framework of a population-based registry of consecutive cases of death after AMI and survivors with validated AMI which ensures that all patients with incident AMI were included in the sample. In addition, a number of

important covariables that could have an impact on mortality were included. Furthermore, the long observation time gave us the opportunity to evaluate the association of PAD and long-term mortality in patients with AMI over a longer time period than any other study before. Contrary to previous studies [7,12] we stratified by different covariables.

Nevertheless, some limitations of the study should be taken into account. Patients were not older than 74 years, wherefore we were not able to provide evidence for older patients. History of PAD was determined from medical chart review and not confirmed by other diagnostic procedures. Given the universal underdiagnoses of PAD, it is quite likely that patients with asymptomatic PAD are not included in our study. Since our study excluded pre-hospital deaths and patients who died within 24 hours after admission, the 28-day case fatality risk found in our study may underestimate the real magnitude of the problem among the AMI population. Sensitivity analyses also indicated that the inclusion of patients with missing information on covariables would have increased the resulting case-fatality associated with PAD. Finally, results regarding sex differences should be interpreted with caution because of the small number of women.

CONCLUSIONS

In conclusion, our study confirmed that AMI patients with PAD differ considerably from their counterparts without PAD in terms of their pre-AMI risk profile, AMI treatment and post-AMI survival. A significant effect on long-term mortality was found which persisted up to 11 years after AMI and was present in all subgroups according to age, sex and history of diabetes. Patients with PAD who are younger than 63 years had the highest long-term-mortality risk. Further studies are needed to confirm these results.

Conflict of interests

The authors declare that they have no competing interests.

Authors´ contributions

LD and IK conceived the study. LD performed the statistical analysis and drafted the manuscript. IK and UA supervised data analysis and manuscript drafting. CM, BK, CT, CM and AP contributed to the interpretation of the data. CM, MH, BK and CT contributed to data acquisition. CM, AP, MH, BK, CT, IK and UA critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Since the year 2000, the collection of MI-data has been co-financed by the German Federal Ministry of Health to provide population-based MI morbidity data for the official German Health Report (see www.gbe-bund.de). Steering partners of the MONICA/KORA Infarction Registry, Augsburg, include the KORA research platform, Helmholtz Zentrum München and the Department of Internal Medicine I, Cardiology, Central Hospital of Augsburg. We thank all members of the Helmholtz Zentrum München, Institute of Epidemiology II and the field staff in Augsburg who were involved in the planning and conduct of the study. We wish to thank the local health departments, the office-based physicians and the clinicians of the hospital within the study area for their support. Finally, we express our appreciation to all study participants.

REFERENCES

[1] Alzamora MT, Forés R, Baena-Díez JM, et al. The peripheral arterial disease study (PERART/ARTPER): prevalence and risk factors in the general population. BMC public health 2010;10.

[2] Diehm C, Schuster A, Allenberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis 2004;172(1):95–105.

[3] Mehlsen J, Wiinberg N, Joergensen BS, Schultz-Larsen P. High prevalence of peripheral arterial disease in patients with previous cerebrovascular or coronary event. Blood pressure 2010;19(5):308–12.

[4] Perk J, Backer G de, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Atherosclerosis 2012;223(1):1–68.

[5] Reiner Z, Catapano AL, Backer G de, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European heart journal 2011;32(14):1769–818.

[6] Spencer FA, Lessard D, Doubeni C, Yarzebski J, Gore JM, Goldberg RJ. Treatment practices and outcomes of patients with established peripheral arterial disease hospitalized with acute myocardial infarction in a community setting. American heart journal 2007;153(1):140–6.

[7] Inglis SC, Bebchuk J, Al-Suhaim SA, et al. Peripheral artery disease and outcomes after myocardial infarction: an individual-patient meta-analysis of 28,771 patients in CAPRICORN, EPEHESUS, OPTIMAAL and VALIANT. International journal of cardiology 2013;168(2):1094–101.

[8] Froehlich JB, Mukherjee D, Avezum A, et al. Association of peripheral artery disease with treatment and outcomes in acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). American heart journal 2006;151(5):1123–8.

[9] Saw J, Bhatt DL, Moliterno DJ, et al. The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. Journal of the American College of Cardiology 2006;48(8):1567–72.

[10] Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. European heart journal 2009;30(10):1195–202.

[11] Kirchberger I, Amann U, Heier M, Kuch B, Thilo C, Peters A, Meisinger C. Presenting symptoms, pre-hospital delay time and 28-day case fatality in patients with peripheral arterial disease and acute myocardial infarction from the MONICA/KORA Myocardial Infarction Registry. Eur J Prev Cardiol. 2017 Feb;24(3):265-273. doi: 10.1177/2047487316676123.

[12] Subherwal S, Patel MR, Kober L, et al. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. European journal of preventive cardiology 2015;22(3):317–25.

[13] Al-Thani HA, El-Menyar A, Zubaid M, et al. Peripheral arterial disease in patients presenting with acute coronary syndrome in six middle eastern countries. International journal of vascular medicine 2011;2011:815902.

[14] Guerrero M, Harjai K, Stone GW, et al. Usefulness of the presence of peripheral vascular disease in predicting mortality in acute myocardial infarction patients treated with primary angioplasty (from the Primary Angioplasty in Myocardial Infarction Database). The American journal of cardiology 2005;96(5):649–54.

[15] Meizels A, Zeitoun DM, Bataille V, et al. Impact of polyvascular disease on baseline characteristics, management and mortality in acute myocardial infarction. The Alliance project. Archives of cardiovascular diseases 2010;103(4):207–14.

[16] Mukherjee D, Eagle KA, Kline-Rogers E, et al. Impact of prior peripheral arterial disease and stroke on outcomes of acute coronary syndromes and effect of evidence-based therapies (from the Global Registry of Acute Coronary Events). The American journal of cardiology 2007;100(1):1–6.

[17] Jeremias A, Gruberg L, Patel J, Connors G, Brown DL. Effect of peripheral arterial disease on in-hospital outcomes after primary percutaneous coronary intervention for acute myocardial infarction. The American journal of cardiology 2010;105(9):1268–71.

[18] Freisinger E, Malyar NM, Reinecke H. Peripheral artery disease is associated with high in-hospital mortality particularly in males with acute myocardial infarction in a nationwide real-world setting. Vasa. 2016;45(2):169-74. doi: 10.1024/0301-1526/a000512.

[19] Meisinger C, Hoermann A, Heier M, Kuch B, Lowel H. Admission blood glucose and adverse outcomes in non-diabetic patients with myocardial infarction in reperfusion era. International journal of cardiology 2006;113(2):229–35.

[20] Kuch B, Heier M, von Scheidt W, Kling B, Hoermann A, Meisinger C. 20-year trends in clinical characteristics, therapy and short-term prognosis in acute myocardial infarction according to presenting electrocardiogram the MONICA/KORA AMI Registry (1985-2004). Journal of internal medicine 2008;264(3):254–64.

[21] Amann U, Kirchberger I, Heier M, et al. Long-term survival in patients with different combinations of evidence-based medications after incident acute myocardial infarction: results from the MONICA/KORA Myocardial Infarction Registry. Clinical research in cardiology: official journal of the German Cardiac Society 2014;103(8):655–64.

[22] Patel MR, Becker RC, Wojdyla DM, et al. Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: Data from the PLATO Trial. European journal of preventive cardiology 2015;22(6):734–42.

[23] Owens CD, Conte MS. Medical management of peripheral arterial disease: bridging the "gap"? Circulation 2012;126(11):1319–21.

[24] Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286: 1317-24.

[25] Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing;

TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006 Mar 21;113(11):e463-654.

[26] Cotter G, Cannon CP, McCabe CH, et al. Prior peripheral arterial disease and cerebrovascular disease are independent predictors of adverse outcome in patients with acute coronary syndromes: are we doing enough? Results from the Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 study. American heart journal 2003;145(4):622–7.

[27] Subherwal S, Bhatt DL, Li S, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with non-ST-segment-elevation myocardial infarction. Circulation. Cardiovascular quality and outcomes 2012;5(4):541–9.

[28] Januzzi JL, Buros J, Cannon CP. Peripheral arterial disease, acute coronary syndromes, and early invasive management: The TACTICS TIMI 18 trial. Clinical Cardiology 2005(28):238–42.

[29] Mosca L, Hammond G, Mochari-Greenberger H, et al. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. Circulation 2013; 127: 1254-63,

[30] Hirsch AT, Allison MA, Gomes AS, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. Circulation 2012; 125: 1449-72.

[31] Pendyala LK, Torguson R, Loh JP, et al. Comparison of adverse outcomes after contemporary percutaneous coronary intervention in women versus men with acute coronary syndrome. The American journal of cardiology 2013;111(8):1092–8.

[32] Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. Journal of vascular surgery 2015;61(3 Suppl):2–41.

[33] Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes--a review. Diabetic medicine a journal of the British Diabetic Association 2010;27(1):4–14.

[34] Stansby G, Mister R, Fowkes G, et al. High risk of peripheral arterial disease in the United Kingdom: 2-year results of a prospective registry. Angiology 2011;62(2):111–8.

[35] Hirsch AT, Murphy TP, Lovell MB, et al. Gaps in public knowledge of peripheral arterial disease: the first national PAD public awareness survey. Circulation 2007; 116: 2086-94.

[36] Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286: 1317-24.