Association of ankle-brachial index and plaques in the carotid and femoral arteries with cardiovascular events and total mortality in a population-based study with 13 years of follow-up

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Aims Peripheral arterial occlusive disease is associated with a high risk of cardiovascular morbidity and mortality. We prospectively examined the association of the ankle-brachial index (ABI) and arterial plaques in carotid and femoral arteries with incident myocardial infarctions (MIs) and cardiovascular and total mortality in 1325 participants of the population-based MONICA Augsburg Survey 1989/90.

Methods and results At baseline, 6.1% of men and 2.6% of women had an ABI <0.9. At least one plaque in the carotid or femoral arteries was identified in 51.8% of men and 36.3% of women. During a 13-year follow-up, 58 persons (4.4%) suffered a MI before age 75 and 189 persons (14.3%) died, 86 (6.5%) of them from cardiovascular causes. Kaplan–Meier curves confirmed both measurements as strong predictors for all three endpoints (P, 0.0001). Cox regression analysis revealed an increase of the risk for MI and cardiovascular and total mortality of 22 (P = 0.012), 35, and 32% (P < 0.00001), respectively, per 0.1 unit decrease in ABI. Correction for measurement error in ABI increased these estimates. The increase in risk for MI and cardiovascular and total mortality was 52, 70, and 45%, respectively, for each increase in the number of plaque-affected arteries (P < 0.0001).

Conclusion Both ABI and number of plaque-affected arteries are strong predictors for incident MI and cardiovascular and total mortality.

KEYWORDS Ankle-brachial index; Subclinical atherosclerosis; Acute coronary events; Total mortality; Prospective cohort; Population-based study

Introduction

Approximately one-third of patients with peripheral arterial occlusive disease (PAOD) show classical symptoms of intermittent claudication. About 30% of them will die within 5 years, three-quarters of them because of cardiovascular disease (CVD).¹ Therefore, the significant threat for patients with PAOD is premature myocardial infarction (MI) or death. Patients with PAOD frequently also have coronary heart disease or cerebrovascular disease.²,³ Risk factors for these diseases such as diabetes, smoking, and hypertension are also risk factors for PAOD.⁴ Therefore, major diagnostic efforts should be made to identify patients with PAOD, who are at the highest risk for CVD events, especially those being asymptomatic.

Asymptomatic PAOD can be diagnosed by means of the ankle-brachial index (ABI), defined as the ratio of Doppler-recorded systolic blood pressures (BPs) in the lower and upper extremities, a standardized, non-invasive, simple diagnostic tool. ABI values of 0.9 or lower indicate the presence of symptomatic PAOD with a sensitivity of 95% and specificity of 100%.¹,⁵ A low ABI may be a relevant indicator of atherosclerotic burden and is associated with increased CVD morbidity and mortality.⁶–¹⁶

Long-term prospective population-based studies on the value of ABI in subjects with PAOD are still sparse in Europe. Therefore, the aim of the present study is to assess the independent association of ABI for incident fatal and non-fatal MI and cardiovascular and total mortality. Furthermore, the presence of plaques in the carotid and femoral arteries was also prospectively investigated in relation to these endpoints during a 13-year follow-up in this large random subsample of the general population from Southern Germany from the city of Augsburg.
Association of ABI and plaques

Methods

Study population

The population-based MONICA (Monitoring of Trends and Determinants of Cardiovascular Diseases) Augsburg survey was conducted in 1989/90 (S2) in the city of Augsburg, Germany, and the two surrounding counties. Randomly sampled men and women (n = 4940), stratified for age in the range of 25–74 years, participated in this survey. The sampling procedure, study population and baseline examination for classical risk factors, and the follow-up status have been described in detail elsewhere.17–19 For logistic reasons, the presented analysis included a randomly chosen subsample (n = 1388) of all survey participants with main residence in the city of Augsburg, in whom an extended examination of carotid and femoral vessels by ultrasonography and measurement of ABI has been performed.

Baseline vascular examination

The ABI was measured at baseline according to a standardized protocol.20 It was calculated as the ratio of the systolic BP at each ankle to the systolic BP at the right arm, using a Doppler ultrasonic device and a BP cuff. The lower of the two ABI values from both legs was taken for further calculations. Participants with missing ABI (n = 9) or ABI ≥ 1.3 (n = 54) were excluded from the analysis. Values exceeding 1.3 may indicate calcification of the media of the arterial wall, which prohibits accurate pressure measurements in the legs.1 Thus, complete data were available for 1325 subjects. In addition, the carotid and femoral arteries on both sides were examined by high resolution sonography using a single ATL Ultramark IV system with a 7.5 MHz linear transducer (Scientific Medical Systems). Right and left carotid bifurcations were scanned within a predefined window comprising 3 cm of the distal common carotid arteries, the bifurcations, and 1 cm of the internal and external carotid arteries, respectively, for the presence of plaques defined as a distinct area with either mineralization or rising into the lumen above 1.2 mm. Similarly, the femoral arteries were scanned from the subinguinal region to the branching of the profundus and superficial femoral arteries.21 All measurements were carried out by the same experienced sonographer, who had no further information on the subjects. The number of arterial sites affected by plaques was used to define a plaque score ranging from 0 to 4 and representing plaques in the right and left carotid arteries and in the right and left femoral arteries, respectively.

Other baseline characteristics

Other risk factors assessed at baseline were age, gender, smoking status, hypertension, body mass index (BMI), self-reported history of prevalent MI, and diabetes mellitus. Hypertension was defined as a BP ≥ 140/90 mmHg or taking antihypertensive drugs. Smoking status was stratified into current smokers (regular smokers and occasional smokers) and non-smokers.

Definition of outcomes

Morbidity and mortality follow-up data were available up to 13 years with a median of event-free participation of 12 years and 9 months. This information was recorded for all participants until the end of 2002 in the framework of KORA (Co-operative Health Research in the region of Augsburg). Fatal or non-fatal acute MI and sudden cardiac death were identified through the MONICA/KORA coronary event registry of the 25–74-year-old study population and censored at 75 years of age. Case ascertainment was complete for at least 95% of participants.22 The diagnosis of a non-fatal MI categorized as definite or possible was based on acute symptoms, cardiac enzymes, and ECG signs in up to four ECGs according to the MONICA manual.22 Since January 2001, all patients suspect for an MI according to revised ESC and ACC criteria were included.23 The vital status of all participants was ascertained through the local Health Department offices. The information on the cause of death was based on death certificates and coded according to ICD-9.

The outcome variables included three endpoints: first, incident fatal and non-fatal MI including pre-hospital cardiac deaths before 75 years of age; secondly, cardiovascular mortality (including ICD-9. Rev.: 390–459 and 798), and thirdly, total mortality.

Statistical methods

Survival analysis based on Kaplan-Meier curves and log-rank tests was used to assess the unadjusted association between participants with ABI ≤ or > 0.9 and between groups with various numbers of plaque-affected arterial sites with each of the three endpoints. In order to extend the analysis of the dichotomized ABI to a quantitative analysis, the functional form of the continuous variable ABI was checked graphically by means of a P-spline of degree 324 and the deviation from a linear relationship was tested. A spline of degree 3 is a linear combination of cubic functions, which enables us to fit virtually any smooth curve to the data. P-splines were also applied for BMI and plaque score. Additionally, the validity of the proportional hazards assumption for the Cox model was tested. The effect of quantitative or dichotomized ABI values as well as the effect of the plaque score and other classical risk factors on endpoints was determined using age- and sex-adjusted Cox proportional hazards model.25 Furthermore, models with more extended adjustments adding prevalent MI, diabetes, hypertension, or smoking were calculated.

The ABI shows a moderate intra- and inter-observer variability,1 which was accounted for in this analysis by utilizing external validation measurements of the ABI in the Cox regression analysis. Validation data came from the first 4 months of the study period of the KORA F3 follow-up study, conducted since March 2004. The sample came from the same region and we used the same procedures and equipment as in the study sample presented in this analysis. Two standardized ABI measurements from 419 subjects were available to calculate measurement variation.

Measurement error in the explanatory variable of the Cox Model implies a dependency of the induced relative risk at one time point on previous time points. In case of a small event rate (‘rare disease assumption’), which was the case here, this dependency can be expected to be small. Then, classical regression calibration can be conducted:26 for each subject, the observed variable ABI is replaced with values accounting for the measurement error,

\[ \tilde{\text{ABI}} = \text{ABI} - \frac{s_{\text{error}}^2}{s_{\text{ABI}}^2} \]

with \( s_{\text{error}} \) being the sample variance of observed ABI and \( s_{\text{ABI}}^2 \) being the error variance derived as the mean of the within-subject variance from the validation data. The values accounting for the measurement error are entered into the Cox model and parameter estimates are calculated as usual. Note that the measurement error is assumed to be non-differential (i.e., the error variance does not depend on event status),27 which is reasonable because of the prospective design.

All statistical analyses were performed using S-Plus 6.1 and the Design-library in S-Plus.

Results

Baseline characteristics including PAOD prevalence

Baseline characteristics of the 670 men and 655 women (n = 1325), who comprised the study sample, are summarized in Table 1. Whereas age, BMI, and prevalence of diabetes were similar between men and women, the plaque score (the number of plaque-affected arterial sites), the prevalence of MI, and current smoking were more frequent in men than in women. Only 58 subjects (41 men and 17 women) had an ABI ≤ 0.9 at baseline and were considered to have PAOD. These subjects were older, showed a higher
prevalence of diabetes mellitus, hypertension, and previous MI. The most obvious difference was observed for the plaque score: in every other subject with PAOD, plaques could be found in all four examined vascular beds, whereas this was only the case in 8.1% of subjects without PAOD (Table 1).

Figure 1 shows the distribution of the continuous ABI measurements. For the whole sample, a rather symmetric distribution was seen for ABI values between 0.9 and 1.3, with a narrow tail to the left end of the scale. Looking at the subgroups with zero, one, two, three, or four plaque affected arteries, a substantial shift to lower ABI values was observed. Although this correlation was highly significant ($P = 0.004$ by the Spearman rank correlation), the correlation coefficient was rather low with $r = -0.08$.

Stratification of the subjects with PAOD by gender and 10-year age groups (Figure 2) showed a markedly increased prevalence at higher age.

**Prospective follow-up**

During the follow-up period, 58 subjects (4.4%) suffered an incident fatal or non-fatal MI before 75 years of age and 189 persons (14.3%) died, 86 (6.5%) of them from CVD. Unadjusted Kaplan–Meier curves in Figure 3 show a clear association of the plaque score as well as an ABI $\leq 0.9$ at baseline, with each of the three endpoints during follow-up (log-rank: $P < 0.0001$). The ABI threshold of 0.9 clearly separated groups with high and low event rates. It is important to note that 36 of the 58 individuals with ABI $\leq 0.9$ died during follow-up. Only six of them died from acute MI (ICD: 410), 15 died from CVD causes other than acute MI, and in 17 subjects, the cause of death was not related to CVD. Therefore, only a small fraction of patients with ABI $\leq 0.9$ was at risk for incident fatal or non-fatal MI.

In order to utilize the full information contained in the quantitative variable ABI, the linearity of the relationship of ABI with event rate was also checked. The P-spline calculated within an age- and sex-adjusted Cox model revealed an inverse linear relationship for the three endpoints (Figure 4), and the test of non-linearity was not rejected ($P > 0.37$ for all three endpoints). For BMI and plaque score, there was also no evidence for non-linearity (data not shown). Table 2 shows the hazard ratios (HRs) for ABI, plaque score, and other risk factors from Cox regression models for all three endpoints adjusted for age and and sex and for the more extensively adjusted models. It can be seen that the plaque score was a strong predictor of all three endpoints independent of other risk factors, which confirms and extends what we have already seen from Kaplan–Meier curves. Each increase in the number of plaque-affected arterial sites increased the HR between 45 and 70%, depending on the endpoint when adjusted for age and gender. Less extreme HRs were found in further adjusted models. Similar observations were made for ABI with highly significant estimates for cardiovascular and total mortality with HR of 0.81–0.74 per 0.1 unit increase in ABI, respectively. This is equivalent to an increase in the cardiovascular and total mortality of 20–35% for each 0.1 unit decrease in ABI. However, these changes were no longer significant for the endpoint incident MI, when models were not only adjusted for age and gender. Estimates for an ABI categorized at 0.9 are additionally provided in Table 2 for comparison with the literature.

**Correction for regression dilution (regression calibration)**

The coefficient of variation (CV) for the repeated measurements in the validation sample varied between 0 and 18% per subject, with a mean CV of 4.0%. The CV did neither depend on the mean ABI value for each subject nor on time. Thus, an additive homoscedastic measurement error (i.e. a measurement error with constant variance across all subjects and across time) was assumed. The error variance $\sigma^2_{\text{error}}$, calculated in the validation sample was 0.0032. Together with an observed ABI variance, $\sigma^2_{\text{ABI}}$ of 0.0147, the ABI for each subject was calibrated with the factor 0.7823. The resulting coefficients of the ABI effect on the three endpoints correcting for this measurement

### Table 1 Baseline characteristics of the 1989/90 MONICA-Augsburg study subjects who underwent ABI measurement and ultrasonographic examination of the carotid and femoral arteries resulting in a plaque score of 0–4

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 1325)</th>
<th>Men (n = 670)</th>
<th>Women (n = 655)</th>
<th>With ABI $\leq 0.9$ (n = 58)</th>
<th>With ABI $&gt;0.9$ (n = 1267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%) of men</td>
<td>670 (50.6)</td>
<td>323 (48.2)</td>
<td>417 (63.7)</td>
<td>9 (15.5)</td>
<td>731 (57.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.7 + 14.0</td>
<td>50.0 + 14.4</td>
<td>25.6 + 4.8</td>
<td>25.9 + 3.7</td>
<td>50.0 + 14.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 + 4.1</td>
<td>26.3 + 3.4</td>
<td>26.4 + 4.8</td>
<td>26.9 + 3.7</td>
<td>25.9 + 4.2</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>66 (5.0)</td>
<td>36 (5.4)</td>
<td>30 (4.6)</td>
<td>13 (22.4)</td>
<td>53 (4.2)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>536 (40.5)</td>
<td>306 (45.7)</td>
<td>230 (35.1)</td>
<td>45 (77.6)</td>
<td>491 (38.8)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>32 (2.5)</td>
<td>24 (3.5)</td>
<td>15 (2.3)</td>
<td>4 (7.7)</td>
<td>38 (3.0)</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>39 (5.8)</td>
<td>76 (11.3)</td>
<td>37 (5.6)</td>
<td>11 (19.0)</td>
<td>102 (8.1)</td>
</tr>
<tr>
<td>PAOD (defined by ABI $\leq 0.9$) (%)</td>
<td>48 (3.6)</td>
<td>41 (6.1)</td>
<td>17 (2.6)</td>
<td>4 (7.1)</td>
<td>42 (3.3)</td>
</tr>
<tr>
<td>Plaque score (number of plaque-affected arterial sites) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>740 (55.8)</td>
<td>323 (48.2)</td>
<td>417 (63.7)</td>
<td>9 (15.5)</td>
<td>731 (57.7)</td>
</tr>
<tr>
<td>1</td>
<td>184 (13.9)</td>
<td>80 (11.9)</td>
<td>104 (15.9)</td>
<td>3 (5.2)</td>
<td>181 (14.3)</td>
</tr>
<tr>
<td>2</td>
<td>157 (11.8)</td>
<td>94 (14.0)</td>
<td>63 (9.6)</td>
<td>6 (10.3)</td>
<td>151 (11.9)</td>
</tr>
<tr>
<td>3</td>
<td>131 (9.5)</td>
<td>76 (11.3)</td>
<td>37 (5.6)</td>
<td>11 (19.0)</td>
<td>102 (8.1)</td>
</tr>
<tr>
<td>4</td>
<td>131 (9.5)</td>
<td>97 (14.5)</td>
<td>34 (5.2)</td>
<td>29 (50)</td>
<td>102 (8.1)</td>
</tr>
</tbody>
</table>

Values are provided as mean ± SD for continuous variables or as n (%) for categorical variables. Only participants with ABI values of <1.3 are considered in the analysis.
error in ABI was higher when compared with the uncorrected coefficient (e.g. calibrated HR = 0.676 for the age- and sex-adjusted model and the endpoint cardiovascular mortality vs. the naive HR = 0.736) (Table 2).

Discussion

In this population-based prospective study from Southern Germany, we demonstrate that an ABI < 0.9 and ultrasonographic presence of plaque in the carotid and femoral arteries strongly and independently predict cardiovascular and total mortality during long-term follow-up. From a methodological point of view, we showed that the relationship between ABI and future cardiovascular events was clearly linear, and we demonstrated that accounting for ABI measurement error in the analysis using repeated measurements resulted in increased HR estimates compared with uncorrected analysis.

Prevalence of PAOD

The prevalence of PAOD varies widely depending on age, ethnicity, and study design. Sufficiently large cross-sectional studies with participants randomly selected from the general German population are missing. The recently published getABI Study reported an age-adjusted prevalence of ~20% in patients aged 65 and above for both genders. In the Augsburg cohort, we observed a prevalence for men or women of 18.1 and 4.3%, respectively, for subjects aged 65–74. Such differences between studies might be explained by study designs: whereas our study was population-based, the getABI Study recruited consecutive, unselected patients aged 65 and older from 344 general practitioners.

Association of ABI and plaque score with endpoints

The ABI represents a simple and inexpensive non-invasive diagnostic tool to identify individuals with asymptomatic PAOD. Arterial stenoses of the lower limb are considered a surrogate marker for advanced systemic atherosclerosis and future cardiovascular complications. The getABI Study
Figure 3 Univariate Kaplan–Meier curves for subjects with/without PAOD (PAOD defined as an ABI ≤ 0.9) (left) and number of vascular beds affected with plaques (plaque score ranging from 0 to 4) (right) on (A) MI-free survival (MI); (B) cardiovascular disease mortality-free survival (CVD); (C) cumulative total mortality-free survival.
found a 2.5-fold increased 1-year risk to die from cardiovascular causes in elderly primary care patients with low ABI.29 This has been confirmed and extended in our population-based study in generally younger subjects (25–74 years), with an ~two-fold increased risk of cardiovascular mortality for participants with PAOD compared with those without. Our data therefore suggest an important prognostic role of PAOD defined by ABI for cardiovascular events.

In our sample, the association of ABI with incident fatal and non-fatal MI was less striking than in the getABI study, but still detectable, which might be related to competing risks of death: 38 of the 58 patients with ABI ≤0.9 died during follow-up and only six of them died from MI. Although the other 32 fatal events were in 15 cases of other cardiovascular causes, these events were not only in competition with an MI but also decreased the power to detect a significant association.

In the present study, we observed that both ABI and plaque score are not simply redundant predictors for an increased atherosclerotic burden. This is supported by the low correlation between both variables ($r = -0.08$). Additionally, the information of each of the two examinations added to the prediction of future MI events, as well as CVD and total mortality: adjusting each test in the Cox model for the other one revealed that ABI and plaque score independently contributed to risk prediction. Furthermore, it has to be noted that this predictive ability was seen (at least for cardiovascular and total mortality) even in models with extended adjustments. Therefore, estimates for ABI and plaque score do not simply reflect the atherosclerotic burden derived from classical risk factors but provide prognostic information above and beyond these variables.

To our knowledge, there is only one large prospective population-based study from Europe which considered—besides ABI—other non-invasive measures of atherosclerosis for prediction of incident MI.12 All four measures in the Rotterdam Study (ABI, carotid plaques, carotid intima–media-thickness, and abdominal aortic atherosclerosis determined by X-ray) were good predictors of MI independently of traditional CVD risk factors. A composite atherosclerosis score, however, performed better and supports therefore the clinical concept of an extended non-invasive atherosclerosis assessment for future CVD prediction.12

**Risk prediction by ABI: use as a dichotomized or continuous variable**

The ABI cut-point of ≤0.9 to identify patients at risk is widely used but not universally accepted. It is conceivable that the dichotomization using this threshold might result in a loss of information. We, therefore, performed a test of linearity for ABI and observed an inverse linear relationship between ABI and CVD outcomes which even included ABI values between 0.9 and 1.1. Further, Cox regression models included ABI as a continuous variable and showed an increasing risk with decreasing ABI (Figure 4 and Table 2). So far, only a few studies considered ABI as a continuous variable or at least with more than two categories, and most of them observed a graded association between ABI and CVD outcomes.7,11,12,30–32 Recent investigations even described a U-shaped association with an increasing all-cause and CVD mortality risk above an ABI of 1.4,11,31 which is probably caused by media calcification frequently seen in patients with diabetes and kidney disease.33 The number of study participants in the present study with ABI values above 1.3 ($n = 54$) was too small to reliably assess a U-shaped association, and these subjects were thus excluded from our study.

**Regression calibration**

Although being considered a simple diagnostic test, the ABI shows some intra- and inter-observer variability.1 Since research nurses in our study had been trained and certified
for ABI measurements, we found a mean CV for repeated measurements of only 4.0% in the validation sample. Despite this low coefficient, the correction for ABI estimates resulted in stronger HRs. Thus, we would have underestimated HRs if we had not corrected for measurement errors which usually does not alter P-values but provides more accurate estimates. The fact that we used an external validation sample might be considered a limitation. However, since measurements in both samples were done using the same equipment by trained technicians, we considered correction of measurement error rather an advantage than to disregard it completely.

**Strengths and limitations of the study**

The strengths of this study are its population-based design, standardized classical risk factor assessment, the use of two non-invasive tests to detect systemic atherosclerosis, and the long follow-up of almost 13 years, as well as statistical analyses carefully checking model assumptions and providing estimates accounting for measurement errors of ABI.

The main limitation of our investigation is the rather small number of subjects with an ABI < 0.9 among the study population at baseline. This can be explained by the population-based design with a relatively young age-structure at study entry. Compared with the ABI, the plaque score seems to be a more sensitive parameter to identify subjects at risk for endpoints: about 50% of men and 35% of women had at least one plaque-affected arterial site at baseline, and the plaque score showed a stronger association with events during follow-up than the ABI (Table 2).

In summary, the ABI and a plaque score derived from ultrasonographic assessment of the carotid and femoral arteries revealed a high prevalence of PAOD and subclinical...
atherosclerosis. Both surrogate markers of CVD were strong and independent predictors for future cardiovascular events and mortality. Since most affected individuals were asymptomatic and carried potentially significant morbidity and mortality risks, screening for PAOD may be a useful routine practice at the primary care level. Whether the additional assessment for PAOD besides other cardiovascular risk factors for risk stratification improves the outcome of patients has to be investigated in further studies.

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