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ORIGINAL ARTICLE
PERIPHERAL DISEASE

Ankle Brachial Index is a strong predictor of mortality in hypertensive patients: results of a five-year follow-up study

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ABSTRACT

Background: In the hypertensive population, the peripheral arterial disease (PAD) is considered one of the target organ damages. Ankle Brachial Index (ABI) measurement represents the widely accepted clinical method that may objectively detect the presence of PAD. The study aimed to assess how PAD revealed by ABI predicts mortality in patients with hypertension.

Methods: In the follow-up time (5 years period) of the Hungarian ERV Study, a large scale, multicenter observational study, recruiting hypertensive subjects between 50-75 years, the association of PAD with the survival time was analysed. Several multivariate, interval-censored survival models were developed to assess this association.

Results: Among the 21892 enrolled hypertensive patients, the prevalence of PAD (ABI≤0.9) was 14.4%. The crude death rate was 5.44% (1190 cases) over the available observational period. In multivariate models male sex, myocardial infarction in patients' history, diabetes, renal failure, PAD and cardiovascular risk (SCORE risk) were significantly associated with mortality. Lower ABI showed a continuous, close to linear association with worse survival. PAD was predictive for mortality risk in all SCORE patient groups.

Conclusions: Low ABI is a strong predictor of mortality in hypertensive patients between the age 50-75, even after adjustment for several potential confounders. The association is linear, with no apparent cut-off,

suggesting that ABI should be handled as a continuous variable. The detection of PAD in hypertensives may contribute to the determination of total cardiovascular risk in hypertensive population.

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Key words: Ankle Brachial Index; Hypertension; Heart disease risk factors; Mortality; Peripheral arterial disease.

Hypertension is estimated to affect around one-third of the population of the Western world, which makes high blood pressure the most common modifiable risk factor of atherosclerotic cardiovascular disease. As cardiovascular disease is the leading cause of death in Europe and North America, optimal management of high blood pressure is an important health issue with substantial economic impact.[1] Peripheral arterial disease (PAD) is a manifestation of atherosclerosis, and complications of atherothrombotic arterial disease are far more prevalent in these patients than in the general population. On the other hand, hypertension affects the local outcome of PAD, since in patients with lower extremity arterial disease, hypertension is one of the most important determinants of lower extremity amputation.[2]

In the large hypertensive population of the ERV Study (age 50-75 years), we found a 14.4% prevalence of PAD,[3] which is comparable to the prevalence in general population aged 65 years and older as documented in the Cardiovascular Health Study.[4] The most relevant predictor factors for PAD presence in the ERV population were smoking, coexistence of other manifestations of atherosclerotic diseases (previous stroke or MI), decline of renal function, diabetes mellitus, and hyperlipidemia. It was also demonstrated that by stratifying the study population according to the European Systematic COronary Risk Evaluation (SCORE) model risk groups, PAD was also detectable in the low (8.1%) and the moderate categories (11.1%). This observation indicated that PAD detection in these groups of patients with low or moderate cardiovascular risk might even reclassify them in a higher risk category.[3] In this sense, considering total mortality, coronary events or cardiovascular mortalities, the incremental value of PAD in cardiovascular risk prediction was demonstrated in several general population-based studies, deeming.[5-7] Not only the presence of PAD, defined as Ankle Brachial Index (ABI) value below or equal to 0.9, but a borderline value (ABI value of 0.9-0.99 *vs*. 1.00-1.40[1.29]) was also associated with higher risk for mortality.[8, 9] Additionally, high ABI (value above 1.4) was also shown to be associated with increased mortality, although data were not consistent in all patient populations.[10-12] However, data on the hypertensive population in this regard is scarcely available. In a Chinese population, patients with ABI in the range of 0.41-0.90 were more than 1.5 times as likely to die (relative risk= 1.534, 95% CI: 1.199-1.962). This association was even more pronounced in ABI below 0.4. The total mortality risk was 3.105 times (95% CI: 1.936-4.979) higher compared to normal ABI (1.0-1.4). These data supported the need of ABI screening in hypertensive population.[13, 14]

The present research is a follow-up to the cross-sectional analysis of the ERV Study, aimed to analyse the role of ABI with other potential explanatory variables in the mortality prediction of hypertensive patients.

Materials and methods

Study design

The Evaluation of Ankle/Brachial Index in Hungarian Hypertensives (ERV) program is a large-scale, multicenter, observational study with a cross-sectional and a longitudinal part. The study was conducted from April 2007 to September 2014 in 55 hypertension outpatient clinics in Hungary.[3] The trial protocol was designed and written by the study coordinators and has been approved by the Central Ethical Review Board (Scientific Research Ethics Committee of the Medical Research Council of Hungary, chairperson: Zoltán Papp, protocol number: 22-35/2007-1018EKU, date: 29.02.2008) before experiment was started and that has been conducted in accordance with the principles set forth in the Helsinki Declaration.

Study population

During the first phase of the study, every consecutive hypertensive patient, aged 50-75 years attending one of the

55 Hungarian Hypertension centers (maximum 40 patients/month in every center) were included in the study. Control visits were performed depending on the result of the ankle-brachial index measurement. In the case of normal ABI value, patients were controlled after five years, in case of abnormal ABI, yearly. By September 2008, 21 892 hypertensive individuals were asked to participate. Patients with advanced PAD (Fontaine stage III and IV) were excluded. Informed consent was obtained from all eligible patients.

Assessment of risk factors

Clinical history (based on previous medical reports) was taken from all participants, physical examination, blood analysis and measurement of the ankle-brachial index were performed in each case. The recorded risk factors were smoking, diabetes mellitus, hypertension, hypercholesterolemia, high body mass index, high waist circumference, a family history of vascular disease, previous myocardial infarction, angina pectoris, prior angioplasty or coronary bypass surgery, and prior ischemic stroke. The patients' risk profile was calculated according to the SCORE model for high risk regions in Europe.[15]

Laboratory examination

Blood samples were taken from every patient for analysis of serum levels of fasting blood glucose, cholesterol, triglyceride, uric acid and creatinine. Determination of serum HDL-, LDL-cholesterol and microalbuminuria were optional.

Assessment of the ABI

In every center, physicians and research nurses were trained to perform ankle-brachial index measurements according to current guidelines.[16] To calculate ABI, brachial systolic blood pressure was measured in both arms after 5 minutes of rest, followed by the measurement of the systolic pressures in the dorsal pedal and posterior tibial arteries at the malleolar level in both limbs. For the measurement, a continuous wave Doppler device was used in every center (ELITE 200 Doppler /5MHz). The ABI was calculated for each leg by dividing the higher systolic pressure at the ankle by the higher brachial systolic pressure. PAD was diagnosed when ABI was 0.9 or less in at least one leg of the patient. The person who measured ABI was not aware of the medical history of the patient. In the subsequent multivariable analysis, ABI value was defined as the average of measurements on the left and right side.

Statistical analysis

Categorical variables are presented as frequency (percentage), continuous variables are presented as mean±SD. Unfortunately the exact date of death was not known, so interval-censored survival model[17] was used for the analysis of our data.

In this analysis, patients who were alive at the time of the last visit were assumed to be (right) censored at the time of the last visit. Those who were not alive were interval-censored, with the interval being the time from the visit before the last visit to the time of the last visit. These data were modelled with a semi-parametric model for interval censored data using proportional hazards model (*i.e.* Cox-regression).[18] 1000 bootstrap samples were obtained for each model to calculate confidence intervals. Continuous variables in the models were expanded with three degrees-of-freedom natural cubic spline to allow for a potentially non-linear effect.

Four models were created that differed by in covariates and their functional form. Sex, diabetes, renal failure, myocardial infarction, stroke in patients' history and presence of PAD (ABI less or equal to 0.9) as categorical variables were complemented with BMI, age, systolic and diastolic blood pressure as continuous variables in Model 1. In Model 2, the SCORE risk categories were also included by simultaneously omitting the sex variable as it was part of the SCORE estimate. In the Model 3, the analysis was limited to ABI and the SCORE categories. Finally, in Model 4, ABI was considered and used as a continuous variable instead of ABI as a categorical variable. The potential interaction between systolic and diastolic blood pressure and systolic blood pressure and the presence of PAD was also investigated (in separate models).

Results are presented either as hazard ratios (HR) with 95% confidence interval for categorical variables or as predicted log hazards with 95% confidence interval for continuous variables and for interactions involving continuous variables. In the latter type of plot, each variable is varied across its practically whole range (all possible value for categorical variables and from the 1st to 99th percentile for continuous variables) with every other variable fixed at its central value (mode for categorical variables, median for continuous ones). P values are determined using likelihood ratio test. Calculations were performed under the R statistical program package,[19] version 3.4.3, using the package icenReg, version 2.0.14 The whole source code is available at https://github.com/tamas-ferenci/ERVstudy.

Results

At baseline, 21,892 patients were recruited into the ERV Study population. In the follow-up period, 16 patients were excluded from the analysis because of missing essential data. The remaining 21,876 patients were considered as the sample population for our study. Demographics and clinical characteristics of the study population are shown in Table I. The distribution of the ABI values are shown on Figure 1. A decrease of blood pressure was observed already on the 1-year visit compared to baseline levels (139.4±19.9/82.6±9.8 mmHg; and 137.6±17.1/81.0±8.7; respectively), and was stable during the study (137.7±15.0/80.3±7.6 mmHg at 5-years visit). Patients who either participated in the final visit (visit 6) or data was available about their death at the time of the due visit were considered right-censored and uncensored, respectively. They represented 79.5% (17,385 subjects) of the sample population. The remaining 20.5% (4491 subjects) of the patients were interval-censored.

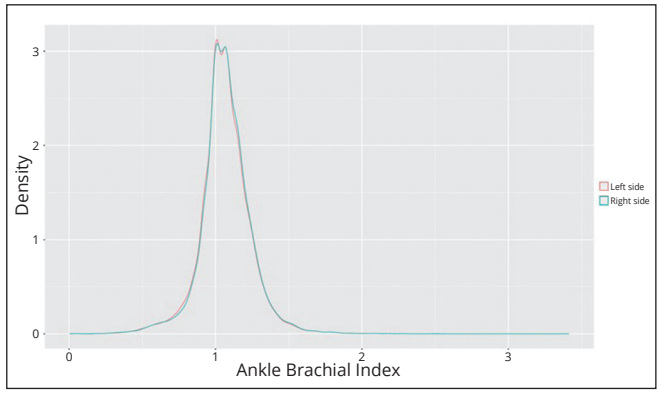

Figure 1.—The density of ABI values in the study population.

Table I.—*Characteristics of the studied subjects (N.=21,876).*

Characteristics	Value
Female/male (%)	12.721/9155 (58.1/41.9)
Age (years, mean±SD)	60.9±8.8
Myocardial infarction in history (%)	11
Stroke in history (%)	4.8
Peripheral vascular disease in history (%)	4.1
Diabetes mellitus (%)*	41
Blood glucose (mmol/L, mean±SD)	6.25±2.24
Hyperlipidemia (%)†	33.6
Serum cholesterol (mmol/L, mean±SD)	5.3±1.2
GFR (mL/min)	74.7±15.9
GFR<60 mL/min (%)	16.2
Serum uric acid (μmol/L) †	311.9±91.6
Hyperuricemia (%)‡	20.2
Smoking (%)	19
Waist circumference (cm, mean±SD)	
Female	98.6±13.5
Male	104.6±12.9
Obesity according to waist circumference (%)§	71
BMI (kg/m²)	28.96±5.05
Obesity according to BMI (%)‖	38.3
Blood pressure mmHg (mean±SD)	139.4±19.9/82.6±9.8
Optimal blood pressure control (%) #	37.7
Number of antihypertensive agents (median±interquartile range)	2±2
SCORE risk ≤2% (%)	18.6
SCORE risk >2% and ≤4% (%)	39.4
SCORE risk >4% and ≤10% (%)	29
SCORE risk >10% (%)	13
PAD prevalence (%)	14.4
High ABI prevalence (%)	9.4 (2.85)

GFR: glomerular filtration rate; ABI: Ankle Brachial Index; SCORE: Systematic COronary Risk Evaluation; PAD: peripheral arterial disease (Ankle Brachial Index ≤0.9); High ABI: Ankle Brachial Index >1.3 (>1.4). *Defined as fasting plasma glucose level ≥7.0 mmol/L, or known previous condition, or concomitant antiglicemic medication; †defined as serum cholesterol ≥ 6.5 mmol/l, or known previous condition, or concomitant Antilipemic medication; ‡defined as serum uric acid level at or above the cut-off (363 μmol/l-females, 488 μmol/l-males), or known previous condition, or concomitant antiuricosuric medication), 11,743 subjects were examined; §defined as waist circumference at or above the cut-off (88 cm-females, 102 cm-males); ‖defined as BMI≥30 kg/m²; #definition based on European Society of Hypertension Guidelines.

The crude death rate was 5.44% (1190 cases) over the available observational period.

In our analysis, we made an effort to explore the association between survival time and several explanatory factors by developing different multivariable models (Models 1-4).

The hazard ratios of the categorical variables of Model 1 are shown in Table II, and continuous variables are presented in Supplementary Digital Material 1 (Supplementary Figure 1). Except stroke in patients history, all categorical explanatory factors were significantly related to death. As far as blood pressure is concerned, log hazard of mortality showed a U-shape curve with a minimum value of 130 mmHg for systolic and 90 mmHg for diastolic pressure, respectively. In the case of BMI, the minimum value was 30, with an increasing tendency to be below and above this value. No interaction between systolic and diastolic blood pressure (P=0.496), or systolic blood pressure and ABI (P=0.773) could have been detected.

In the next model (Model 2) SCORE risk was included that forms the base of the European cardiovascular disease risk assessment model. We excluded all individual constituents of SCORE from the model; results are shown in Table II. In Model 3 we aimed to assess the additive predictive value of lower extremity arterial disease when

Table II.—*Interval-censored proportional death hazard in Model 1 and Model 2.*

	Model 1[a] Hazard ratio (95% confidence interval)	P value	Model 2 Hazard ratio (95% confidence interval)	P value
Male sex	2.12 (1.83-2.44)	<0.001		
Myocardial infarction in patients history	1.34 (1.15-1.57)	<0.001	1.58 (1.34-1.86)	<0.001
Stroke in patients history	0.92 (0.71-1.21)	0.568	1.02 (0.79-1.31)	0.89
Diabetes	1.44 (1.26-1.64)	<0.001	1.55 (1.35-1.78)	<0.001
Renal failure [b]	1.9 (1.63-2.21)	<0.001	2.21 (1.89-2.58)	<0.001
Lower extremity arterial disease [c]	1.87 (1.63-2.16)	<0.001	1.85 (1.59-2.16)	<0.001
SCORE moderate *vs*. low risk			2.38 (1.79-3.17)	<0.001
SCORE high *vs*. low risk			3.27 (2.41-4.45)	<0.001
SCORE very high *vs*. low risk			4.91 (3.49-6.9)	<0.001

SCORE: Systematic COronary Risk Evaluation.
[a]Continuous variables in Model 1 are demonstrated in Supplementary Figure 1; [b]GFR (glomerular filtration rate) ≤60 mL/min; [c]Ankle Brachial Index≤0.9.

Table III.—*Interval-censored proportional death hazard in Model 3 and 4.*

	Model 3 Hazard ratio (95% confidence interval)	P value	Model 4 [a] Hazard ratio (95% confidence interval)	P value
Male sex			2.12 (1.81-2.48)	<0.001
Myocardial infarction in patients history			1.38 (1.18-1.62)	<0.001
Stroke in patients history			0.93 (0.71-1.20)	0.568
Diabetes			1.47 (1.28-1.68)	<0.001
Renal failure [b]			1.9 (1.63-2.21)	<0.001
Lower extremity arterial disease [c]	2.15 (1.82-2.53)	<0.001		
SCORE moderate *vs*. low risk	2.66 (1.99-3.56)	<0.001		
SCORE high *vs*. low risk	3.77 (2.75-5.18)	<0.001		
SCORE very high *vs*. low risk	5.14 (3.61-7.31)	<0.001		

SCORE: Systematic COronary Risk Evaluation.
[a]Continuous variables in Model 4 are demonstrated in Figure 2, 3; [b]GFR (glomerular filtration rate) ≤60 mL/min; [c]Ankle Brachial Index ≤0.9.

added to the SCORE risk alone. In this model, the hazard ratio for PAD was 2.15 (95% CI:1.82-2.53). χ^2 for SCORE was 185.0, for the PAD it was 105.3, indicating a substantial role of PAD (Table III). However, when added to this model, the interaction between PAD and SCORE was not significant (P=0.988), meaning that no significant deviation was observed from the hypothesis that the impact of PAD is the same in all SCORE categories.

In the Model 4, all individual constituents of the models were included, as in Model 1. However, instead of considering ABI to be a categorical variable, it was included as a continuous variable (with spline-expansion, to allow for potential non-linear effects). The hazard ratios of the categorical variables of the model are seen in Table III, continuous variables are shown in Figure 2, 3. In brief, the impact of BMI, systolic blood pressure and diastolic blood pressure on mortality was all U-shaped (on the log hazard scale), with the minimum, *i.e.*, best survival attained at around 30 kg/m^2, 130 mmHg and 90 mmHg, respectively. In contrast, the effect of ABI and age was close to being linear. All of these effects were significant, just as the effect of every categorical variable (GFR>60, sex, diabetes, infarction) with the exception of stroke. No significant interaction between sex and ABI was detected (P=0.9274).

Discussion

Our research focused on the importance of low ABI as a predictor of death in a hypertensive population. Data in this regard were scarcely available in the literature.[13, 14] We made an effort to put this question in a multivariable environment. Beyond the large number of study subjects, the number and the location of the outpatient hypertension clinics (study centres) also supported representativeness. The fact that the prevalence of traditional risk factors (diabetes, renal failure, dyslipidemia, and obesity) was similar to other publications with a similar framework,[20-23] also promises a reasonable external validity.

However, it is a limitation that patients with advanced PAD (critical limb ischemia) and patients with non-compressible arteries (ABI>1.4) were less represented in our

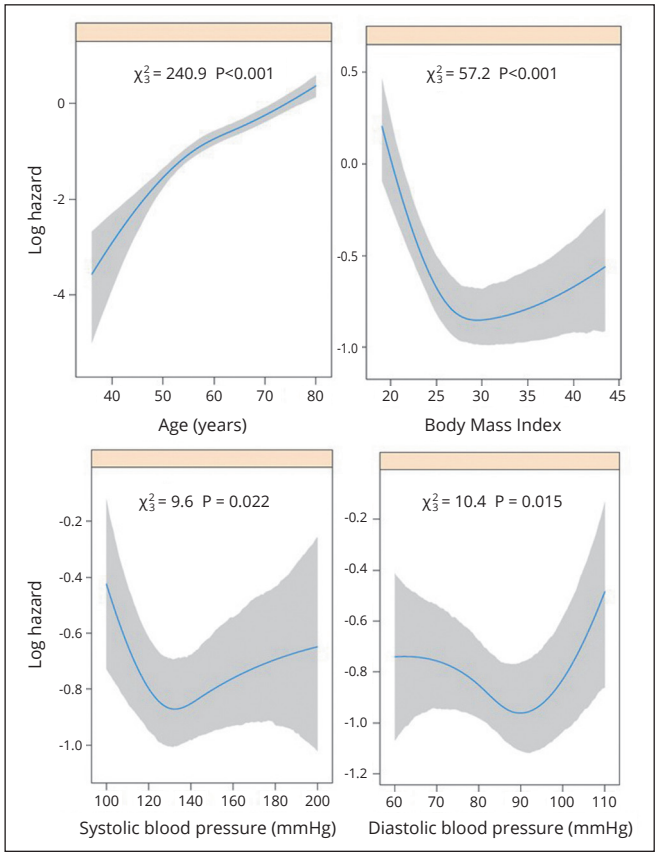

Figure 2.—Predicted log hazards of mortality, considering the continuous explanatory variables (age, BMI, systolic/diastolic blood pressure) in Model 4. Categorical variables in this model are presented in Table III.

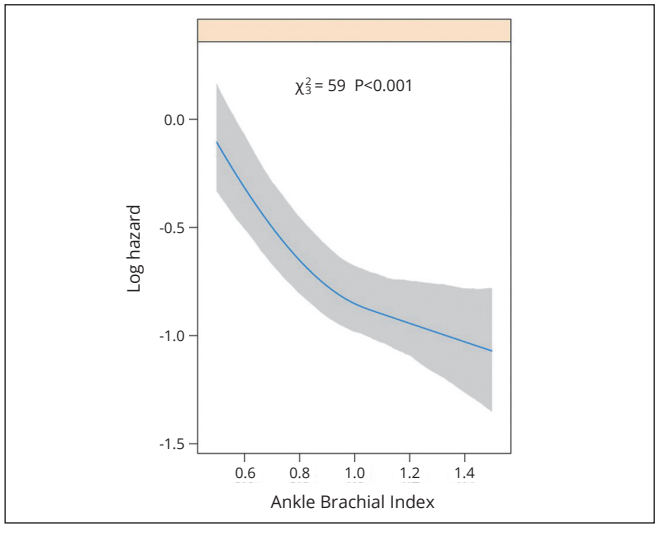

Figure 3.—Predicted log hazards of mortality in Model 4., considering ABI as a continuous explanatory variable. Categorical variables in this model are presented in Table III.

study population (Figure 1). Consequently, patients in our study population, detected with PAD, represented primarily asymptomatic or mildly symptomatic subjects.

The major finding of our study is that low ABI substantially increased the mortality risk, even in asymptomatic or mildly symptomatic hypertensive subjects at the age of 50-75. In addition to low ABI, previous myocardial infarction, diabetes and similar to the male sex, chronic renal failure also increased the risk. The fact that may explain the lack of association between previous stroke and mortality, is that our patients in study centres were adequately treated against high blood pressure that is the main determinant of the risk of recurrent stroke.[24] The decrease in blood pressure was observed already on the second visit compared to baseline levels and was stable during the study.

These results are in line with the findings of the ALLHAT study, in which more advanced patients with PAD were recruited, representing another extreme of the PAD spectrum.[25]

In another subdomain, patients with non-compressible arteries with high ABI were shown to carry a substantial risk of death in a meta-analysis.[10] On the one hand, this group was less represented in our study population and so, based on our data, we cannot reasonably conclude about this association. On the other hand, considering the prevalence of diabetes and chronic renal failure in the ERV population, the impact of low ABI on mortality could have been mitigated by the presence of this phenomenon. Nevertheless, we assume that excluding these patients from the study would have been flawed because of losing representativeness. Accepting the results of meta-analysis above,[10] the association of high ABI and death is limited to a population with high cardiovascular risk; that was not our case. Additionally, we also have to add that without an objective diagnostic method (toe pressure measurement) that separates patients with high ABI and normal extremity blood supply from patients with similar ABI range and compromised circulation, the question cannot be explored.

We also investigated the ESC SCORE Risk Chart values, that calculates 10-year risk of having a fatal cardiovascular disease based on age, gender, smoking, systolic blood pressure, and total cholesterol. In our cohort, the majority (58%) of the patients had low or mildly elevated CV risk, while only 13% of the patients had more than 10% risk. We found that irrespectively of the actual SCORE category, having an ABI≤0.9 substantially increased the risk of mortality in all patient groups. Naturally, we found the highest risk among patients with higher calculated SCORE risk, however it is well-known, that risk estima-

tion systems, like the SCORE system are not accurate in all patient groups and this model may not be accurate in predicting CV mortality risk in patients with high or low cardiovascular risk.[26]

For this reason, we assessed the additive value of ABI only in addition to the SCORE system. In our analysis PAD was predictive of mortality risk in all SCORE patient groups, meaning that low ABI is an independent risk factor for mortality. In this model PAD has been shown as to have an additional independent role to SCORE risk in mortality hazard prediction. These two factors showed no interaction in this regard, meaning PAD status was related to mortality the same way in every SCORE group.

In the recent 2018 ESC/ESH guideline for the management of hypertension it is stated that an ABI<0.9 in asymptomatic patients can be regarded as hypertension-mediated organ damage and documented PAD (either clinical or unequivocal on imaging) classifies patients into the very high risk category.[27] This is in harmony with the results of the metanalysis of Fowkes at al., that showed the impact of a combination of SCORE risk with ABI in general population.[5] However, according to the US Preventive Services Task Force Statement, more evidence and research are needed to assess the additional value of ABI to the traditional cardiovascular risk prediction.[28]

Finally, important conclusions can be drawn from our study regarding the handling of ABI in predictive models. While ABI is often dichotomized (at 0.9), the present study revealed that such cut-off is arbitrary. Although dichotomisation and the application of cut-offs are common in medical research, it also shows serious drawbacks: it may entail losing information, reducing statistical power to detect associations, increasing the risk of a positive result being a false positive, losing detection of non-linearity, and strengthening the impact of the confounders.[29] The continuous and almost linear association of ABI with mortality that was demonstrated is in harmony with the results of other research that found an association not only with the low (ABI≤0.9), but the borderline range (ABI 0.9-0.99).[9]

Limitations of the study

The major limitation of this analysis is that the exact time of death was not known for the investigators. While interval-censored survival analysis, that was employed is the best analytical tool in the present situation as it uses all available information, yet, the uncertainty in the date of death means reduced precision in the obtained estimates. Additionally, our data sample regarding ABI represented a limited range (lower and higher ABI values with a smaller share), including more advanced disease and non-compressible arteries to less extent.

Conclusions

In our follow-up study of a large cohort of treated hypertensive patients aged 50-75 years, low ABI markedly increased the mortality risk in every SCORE risk category. This was demonstrated following a multivariable adjustment for several confounders. The association between ABI and mortality was proven to be linear rather than an abrupt change at a specific cut-off. Measurement of ABI is recommended when an effort is made to assess the total cardiovascular risk in hypertensives.

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Authors' contributions.—Katalin Farkas, as the professional coordinator of the ERV Study, has taken part in the design of the study and in the interpretation of the data and drafted the article as well; Zoltán Járai and Endre Kolossváry have taken part in the design of the study and in the statistical analysis of the data; Tamás Ferenci and András Paksy performed the statistical evaluation of the study; István Kiss as the society (Hungarian Society of Hypertension) coordinator of the ERV Study has taken part in the organisation of the study. Unfortunately, Professor István Kiss deceased, but played an important role in the ERV Study. All authors read and approved the final version of the manuscript.

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