



Association of low ankle brachial index with high mortality in primary care

Curt Diehm^{1*}, Stefan Lange², Harald Darius³, David Pittrow⁴, Berndt von Stritzky⁵, Gerhart Tepohl⁶, Roman L. Haberl⁷, Jens Rainer Allenberg⁸, Burkhard Dasch², and Hans Joachim Trampisch² for the getABI Study Group

¹ Department of Internal Medicine/Vascular Medicine, SRH-Klinikum Karlsbad-Langensteinbach, Affiliated Teaching Hospital, University of Heidelberg, Guttmanstr. 1, D-76307 Karlsbad, Germany; ² Department of Medical Informatics, Biometry and Epidemiology, University of Bochum, Bochum, Germany; ³ Department of Medicine I, Vivantes Neukölln Medical Center, Berlin, Germany; ⁴ Department for Clinical Pharmacology, Medical Faculty, Technical University of Dresden, Dresden, Sachsen, Germany; ⁵ Medical Department, Sanofi-Aventis, Berlin, Germany; ⁶ Vascular Medicine, Munich, Germany; ⁷ Department of Neurology, Hospital Harlaching, Munich, Germany; and ⁸ Department of Vascular Surgery, Ruprecht-Karls University of Heidelberg, Heidelberg, Germany

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Aims We aimed to assess the increased risk of death and severe vascular events in elderly individuals with subclinical or manifest peripheral arterial disease (PAD), evidenced by low ankle brachial index (ABI < 0.9) in primary care.

Methods and results In this monitored prospective observational study, 6880 representative unselected patients aged ≥ 65 years were followed up over 3 years by 344 primary care physicians. Main outcome measures were mortality or a combined endpoint of mortality and severe vascular events. In total, 20 127 patient-years were observed. In the group of PAD patients ($n = 1230$), 134 patients died; in the group without PAD ($n = 5591$), 237 patients died [multivariate hazard ratio (HR) 2.0; 95% confidence interval 1.6–2.5, $P < 0.001$]. Compared with an ABI ≥ 1.1 , the risk of death increased linearly in the lower ABI categories: ABI 0.7–0.89, HR 1.7 (1.2–2.4, $P < 0.001$); ABI < 0.5, HR 3.6 (2.4–5.4, $P < 0.001$).

Conclusion Patients with a low ABI (PAD), who can be readily identified in a primary care setting, have a substantially increased risk of death and severe vascular events. Patients with an ABI between 1.1 and 0.9 should be considered and followed up as borderline PAD cases. Particular attention should be paid to patients with PAD and previous vascular events, as their risk is markedly increased.

Introduction

Atherosclerotic vascular disease is a diffuse progressive condition that usually affects multiple vascular territories at the same time. Its manifestations are coronary heart disease (CHD), cerebrovascular disease (CVD), and peripheral arterial disease (PAD), which, taken together, have been the leading causes of death in adults for many decades.¹

In recent years, our understanding of PAD has undergone a substantial change, as it is now perceived as an indicator disease for generalized atherosclerosis. This is due to the fact that a number of prospective studies have shown the considerable co-prevalence of PAD and the other manifestations of atherosclerosis. Depending on the study population, in patients with PAD, concomitant CHD has been diagnosed by coronary angiography in up to 90% and concomitant CVD in about 50%.² Although screening possibilities

for CHD or CVD in the primary care setting are limited, they are readily available for PAD. The ankle brachial index (ABI) has emerged as an accurate and reliable marker of subclinical or clinical PAD and, at the same time, as a measure of atherosclerosis burden.³ On the basis of epidemiological evidence, current guidelines recommend a cut-off of 0.9 for the diagnosis of PAD.⁴ This threshold value has been reported to have high sensitivity and specificity for arterial stenosis compared with the angiogram as the current gold standard.⁴

Although an ABI < 0.9 had high predictive power for future cardiovascular morbidity and mortality in studies in special settings or population-based studies, the increased risk has not been adequately quantified in typical primary care attendees.⁵ The primary care setting is of particular interest from a public health perspective, because the general practitioner (GP) in his gatekeeper function has an important role in the screening and identification of PAD patients and in the initiation of adequate treatment. Because of the high prevalence of atherosclerotic disease

* Corresponding author. Tel: +49 7202 61 3340; fax: +49 7202 61 6167.
E-mail address: curt.diehm@kkl.srh.de

in the elderly,⁶ screening measures in this group might be most efficient. Therefore, in a large prospective cohort of unselected patients aged 65 years and above, we aimed (i) to quantify the risk of mortality and severe vascular events of patients with PAD vs. those without PAD, (ii) to investigate the risk increase according to different ABI categories including the 0.9–1.1 category, which is conventionally regarded as ‘no disease’, and (iii) to assess the contributions of known risk factors including PAD to the overall risk of death and severe events.

Methods

The German epidemiological study on ankle brachial index (getABI) is a large-scale epidemiological trial with a cross-sectional part and a longitudinal part. The methods and design of the study have been described elsewhere in greater detail.^{7,8} Briefly, 34 vascular physicians across Germany trained and supervised 344 physicians in their vicinity who were representative in terms of location (post-codes) and training (internists and general physicians) for the primary care setting in Germany. A prevalence assessment of primary care attendees, irrespective of their reason for seeing the doctor, was then conducted in a pre-specified week in October 2001. An average of 20 (maximum 25) eligible patients per practice fulfilling the inclusion criteria (age ≥ 65 years, patient being legally competent and able to co-operate appropriately, and providing written informed consent) were recruited, preferably as evenly as possible over this week in order to avoid selection bias. The only exclusion criterion was life expectancy ≤ 6 months, as judged by the GP (e.g. progressive cancer).

The medical history as assessed at baseline included the following conditions: (i) cardiovascular diseases (myocardial infarction or coronary revascularization procedures), (ii) cerebrovascular diseases (stroke or revascularization procedures on the carotid artery), (iii) PAD, i.e. a history of amputation (minor and major forms) of the lower extremities on account of PAD, intermittent claudication (IC, i.e. pain in the calf muscles while walking or during other exertion and disappearing within 10 min at rest), or revascularization procedures on the peripheral arteries, (iv) risk factors, i.e. the existence of arterial hypertension (clinical diagnosis), and disorders of lipid metabolism (clinical diagnosis) or glucose metabolism. Subjects were defined as diabetics if they had been diagnosed as such by their physician, and/or if their HbA1c was $\geq 6.5\%$ (criterion used in 76 cases), and/or if they were being treated with any oral anti-diabetic drug and/or insulin. Glomerular filtration rate was estimated by the Cockcroft–Gault equation on the basis of serum creatinine levels according to the K/DOQI clinical practice guideline.⁹ Other laboratory examinations included measurement of lipids. A smoking history was taken from all study subjects. Consumption was quantified in pack-years, with one pack-year being defined as smoking of 20 cigarettes daily for 1 year. Smokers were categorized as ‘never smoked’ (i.e. < 1 pack-year), ‘former smokers’ (including date of cessation, number of years smoked, pack-years), and ‘current smokers’ (including start date and pack-years). A short physical examination was performed at baseline (body weight and height, blood pressure and heart rate at rest after 5 min in sitting position, auscultation of the carotid arteries, and palpation of peripheral pulses). Fasting plasma total homocysteine was measured in serum with high-performance liquid chromatography according to the method described by Vester and Rasmussen.¹⁰

ABI at rest

GPs were specifically trained to perform ABI measurements under standardized conditions.^{3,11} A standardized Doppler ultrasonic device was used (Kranzbühler 8 MHz, General Electrics, Solingen, Germany). Blood pressure measurements and ABI calculations

were performed according to the recommendations of the American Heart Association.³ The ABI for each leg equals the ratio of the higher of the two systolic pressures (tibial posterior and anterior artery) above the ankle to the average of the right and left brachial artery pressures, unless there is a discrepancy ≥ 10 mmHg in blood pressure values between the two arms. In such a case, the higher reading was used for the ABI. Pressures in each leg were measured and the ABIs calculated separately for each leg. In addition to the ABI determinations, at baseline and at years 1 and 3, patients completed a questionnaire on intermittent claudication.¹²

Prevalence of PAD

PAD was defined as ABI $< 0.90^3$ or history of peripheral vascular revascularization and/or limb amputation. Patients ($n = 59$) with incompressible arteries (e.g. Mönckeberg sclerosis), as indicated by an ABI ≥ 1.5 , were excluded, as in other studies, to avoid misclassification.^{13,14} In cases with missing ABI values ($n = 10$), patients were classified by vascular physicians (study authors) with regard to PAD status (present/not present) on the basis of clinical data.

Primary study endpoints and identification of cardiovascular events

The primary objective of this study was to compare the risk of death from any cause or the risk of severe vascular events in PAD patients with the risk in those without PAD, in representative primary care settings. Severe vascular events were defined as (i) CHD: myocardial infarction and coronary revascularization, (ii) CVD: stroke, revascularization at carotids, and (3) PAD: amputation, or peripheral revascularization because of PAD during follow-up. Information on patients’ deaths and vascular events was obtained from the participating GPs, who were asked after six months, 1 year, and 3 years to fill in a case report form detailing the event. All deaths from cardio- or cerebrovascular causes were further investigated by verifying data from hospital or GP records to ensure that the protocol criteria were fulfilled.

Statistical analyses

Univariate and multivariate Cox regression analyses were performed, and the corresponding hazard ratios [HRs, and their 95% confidence intervals (95% CI)] were calculated for the investigation of associations between PAD and other risk factors and 3-year mortality and cardiovascular morbidity, respectively. The following variables were included in the multivariate statistical model: PAD (yes/no), age (above/below median), gender, smoking status (never/ever), history of severe cardiac or cerebral events (yes/no), presence of diabetes, hypertension, or lipid disorders (each yes/no), homocysteine (below/above 4th quintile).

To best illustrate possible linear relations between low ABI values and the risk of vascular events, the ABI was categorized according to the cut-off points 1.1, 0.9, 0.7, and 0.5. Time-to-event distributions in the individual categories were summarized with Kaplan–Meier curves. Statistical significance was accepted at the two-sided 0.05 level, and all confidence intervals were computed at the 95% level. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC, USA, 1999).

Results

Characteristics of individuals with and without PAD

Of 27 486 screened individuals, a total of 6880 aged ≥ 65 years were included in the study. On the basis of the study definition (ABI < 0.9 or history of amputation or peripheral revascularization), 1230 were categorized as PAD patients and 5591 as individuals without PAD. Fifty-nine patients

had an ABI > 1.5 and were excluded from further analyses. The corresponding PAD prevalence in the total sample was 18.0% (men: 19.8%, women: 16.8%), with rates showing a sharp increase from 11% in the 65- to 70-year-olds to 39% in the ≥85-year-olds. Symptomatic PAD (intermittent claudication) was reported by 2.8% (men: 3.6%, women: 2.3%). Table 1 shows the baseline characteristics of patients in the two groups. Mean ABI was substantially lower in the PAD group, and there were differences in baseline characteristics in that PAD patients were slightly older, had a higher mean systolic blood pressure, were more frequently current or past smokers, and had a higher proportion of concomitant diseases (diabetes mellitus, arterial hypertension, or lipid disorders).

Patient disposition at 3 years

At 3 years, the survival status (dead/alive) of all but one patient was known (>99.9%). In 95 cases, only telephone follow-up was possible, and in 6149, a clinical examination at study end was performed; 137 patients (2.0%) were lost

to follow-up for the morbidity analyses at 3 years (mortality status was known). These patients were included in the corresponding time-to-event analyses, with censoring at the visit-date of last information.

Mortality and morbidity associated with PAD

During follow-up, a total of 376 patients had died. Deaths were due to myocardial infarction (59 cases), stroke (28), coronary revascularization (2), or other reasons (287). Non-fatal severe vascular events were coronary revascularization (131 cases), myocardial infarction (84), ischaemic stroke (120), carotid revascularization (18), revascularization due to critical leg ischaemia (60), or leg amputation (7).

Table 2 shows the mortality from any cause in the respective PAD or ABI category, and the events calculated per 1000 patient-years. The number of events in the PAD groups was more than 2.5-fold increased, and the corresponding HR was doubled after adjustment for other known risk factors. There was an inverse correlation between the ABI category and events: compared with individuals with an

Table 1 Patient characteristics at inclusion

	All patients <i>n</i> = 6821	No PAD <i>n</i> = 5591	PAD <i>n</i> = 1230	<i>P</i> -value ^a
ABI (%)				
Missing (%) (<i>n</i>)	0.1 (10)	0.1 (6)	0.3 (4)	
N.A. (%) (<i>n</i>) ^b	2.4 (161)		13.0 (161)	
<0.5 (%) (<i>n</i>)	0.8 (51)		4.3 (51)	
≥0.5 and <0.7 (%) (<i>n</i>)	3.1 (214)		17.4 (214)	
≥0.7 and <0.9 (%) (<i>n</i>)	11.7 (800)		65.0 (800)	
≥0.9 and <1.1 (%) (<i>n</i>)	50.1 (3414)	61.1 (3414)		
≥1.1 (%) (<i>n</i>)	31.8 (2171)	38.8 (2171)		
PAD according to WHO IC questionnaire (%) (<i>n</i>)	2.8 (191)	1.0 (56)	11.0% (135)	<0.001
Age, mean ± SD (years)	72.5 ± 5.3	72.2 ± 5.1	73.9 ± 5.7	<0.001
65–69 years (%) (<i>n</i>)	37.8 (2581)	39.7 (2221)	29.3 (360)	
70–74 years (%) (<i>n</i>)	31.7 (2160)	32.4 (1811)	28.4 (349)	
75–79 years (%) (<i>n</i>)	20.6 (1405)	19.1 (1067)	27.5 (338)	
80–84 years (%) (<i>n</i>)	8.0 (545)	7.2 (404)	11.4 (141)	
≥85 years (%) (<i>n</i>)	1.9 (130)	1.6 (88)	3.4 (42)	<0.001
Female (%) (<i>n</i>)	58.0 (3959)	58.9 (3295)	54.0 (664)	0.001
Body mass index (kg/m ²)	27.3 ± 4.1	27.3 ± 4.1	27.4 ± 4.3	0.396
Systolic and diastolic blood pressure, mean ± SD (mmHg)	143.7 ± 19.4/ 81.3 ± 9.6	142.7 ± 18.9/ 81.3 ± 9.4	148.4 ± 21.1/ 81.6 ± 10.4	<0.001/ 0.354
Smoking status (%) (<i>n</i>)				
Current	9.3 (634)	7.9 (439)	15.9 (195)	
Past	36.6 (2500)	35.2 (1973)	42.8 (527)	
Never	54.1 (3687)	56.9 (3179)	41.3 (508)	<0.001
Pack years (smokers only) (%) (<i>n</i>)				
<20	23.6 (150)	23.5 (103)	24.1 (47)	
≥20	22.3 (141)	19.6 (86)	34.5 (67)	<0.001
Diabetes mellitus (%) (<i>n</i>) ^c	25.1 (1712)	22.6 (1264)	36.6 (450)	<0.001
Hypertension (%) (<i>n</i>) ^d	64.7 (4411)	61.6 (3442)	78.8 (969)	<0.001
Lipid disorders (%) (<i>n</i>) ^d	51.8 (3536)	50.7 (2832)	57.2 (704)	<0.001
Any previous CHD event (%) (<i>n</i>)	19.2 (1310)	17.0 (950)	28.9 (355)	<0.001
Any previous CVD event (%) (<i>n</i>)	8.9 (607)	7.6 (425)	15.0 (184)	<0.001

All values are presented as mean ± SD unless otherwise specified. CHD: myocardial infarction, coronary revascularization, angina pectoris; CVD: stroke, revascularization of carotids, TIA; IC, intermittent claudication.

^aComparison between PAD and no PAD groups. Tests of significance: *t*-tests, χ^2 -tests.

^bPatients with history of amputation or peripheral revascularization (on account of PAD).

^cSubjects were defined as diabetics, (i) if they had been assigned the clinical diagnosis by their physician, and/or (ii) if their HbA1c was ≥6.5%, and/or (iii) if they received any oral anti-diabetic drug and/or insulin.

^dHypertension and lipid disorders according to physician's clinical diagnoses.

Table 2 Death from any cause in elderly patients according to presence/absence of PAD or according to ABI category

	Number of patients	Number of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate ^a , 95% CI)	P-value
All	6880	376	20 127	18.7 (16.8–20.6)	–	–	–
ABI > 1.5	59	5	172	29.1 (3.6–54.6)	–	–	–
PAD (no)	5591	237	16 445	14.4 (12.6–16.2)	1.00	1.00	–
PAD (yes)	1230	134	3 510	38.2 (31.7–44.6)	2.66 (2.15–3.29)	2.02 (1.61–2.53)	<0.001
ABI category							
Missing	10	3	25	–	–	–	–
ABI ≥ 1.1	2171	80	6 396	12.5 (9.8–15.3)	1.00	1.00	–
1.1 > ABI ≥ 0.9	3414	157	10 031	15.7 (13.2–18.1)	1.25 (0.96–1.64)	1.26 (0.96–1.66)	0.093
0.9 > ABI ≥ 0.7	800	59	2 309	25.6 (19.0–32.1)	2.05 (1.46–2.87)	1.71 (1.21–2.41)	0.003
0.7 > ABI ≥ 0.5	214	33	604	54.6 (36.0–73.3)	4.41 (2.94–6.62)	3.07 (2.01–4.68)	<0.001
ABI < 0.5 ^b	212	39	591	66.0 (45.3–86.7)	5.35 (3.65–7.85)	3.59 (2.40–5.36)	<0.001

PAD: ABI < 0.9 or history of peripheral revascularization or amputation on account of PAD at baseline. PY, patient-years.

^aAdjusted for age, sex, diabetes, hypertension, hyperlipidaemia, smoking, history of severe cardio- or cerebrovascular events (myocardial infarction, cardiac revascularization, stroke, revascularization at carotids), and homocysteine (>4th quintile, 19.1 μmol/L).

^bABI < 0.5 or history of peripheral revascularization or amputation at baseline.

ABI ≥ 1.1, subjects with an ABI < 0.5 had a more than five-fold increase in events and a nearly four-fold risk increase after adjustment for other risk factors.

A similar picture was also seen when including severe vascular events in the analysis (Table 3). Taken together, the resulting HRs for the individual ABI groups in the combined analysis were comparable with those for deaths alone.

Table 4 shows the association between known cardiovascular risk factors and mortality or severe vascular events. All factors, with the exception of hyperlipidaemia, reached statistical significance in the univariate analysis. In the multivariate model, all factors but hypertension and hyperlipidaemia were significant. The strongest risk predictor was PAD as diagnosed at baseline (risk nearly doubled), followed by a history of severe cardiovascular or cerebrovascular events. If present in combination, the two risk factors were associated with a four-fold mortality rate (no PAD/no history of events: 8.1% vs. PAD plus previous CHD/CVD: 31.9%).

Figure 1 shows the Kaplan–Meier estimates of survival and event-free survival delineated for the five ABI categories. Divergence between the individual ABI curves was most pronounced for the two lowest categories, compared with the categories ≥ 0.9.

Discussion

These results confirm the clinical significance of PAD as diagnosed by ABI in primary care. The disease is highly prevalent among the elderly and, depending on its severity, carries a substantially increased risk of premature deaths and severe vascular events.

A number of studies have previously investigated the increase in total and cardiovascular risk associated with PAD (assessed with low ABI).^{15–20} All studies were smaller than the present one, were in part limited to special populations (e.g. American Indians¹⁸ or patients in vascular

Table 3 Death from any cause or severe vascular event (myocardial infarction, cardiac revascularization, stroke, revascularization at carotids, peripheral revascularization, or amputation)

	Number of patients	Number of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate ^a , 95% CI)	P-value
All	6880	796	19 473	40.9 (38.0–43.7)	–	–	–
ABI > 1.5	59	8	165	48.5 (14.9–82.1)	–	–	–
PAD (no)	5591	515	16 038	32.1 (29.3–34.9)	1.00	1.00	–
PAD (yes)	1230	273	3 272	83.4 (73.4–93.3)	2.61 (2.25–3.02)	1.93 (1.66–2.26)	–
ABI category							
Missing	10	3	25	–	–	–	–
ABI ≥ 1.1	2171	177	6258	28.3 (24.1–32.5)	1.00	1.00	–
1.1 > ABI ≥ 0.9	3414	338	9762	34.6 (30.9–38.3)	1.23 (1.02–1.47)	1.23 (1.02–1.48)	0.027
0.9 > ABI ≥ 0.7	800	126	2198	57.3 (47.3–67.3)	2.03 (1.62–2.55)	1.64 (1.30–2.08)	<0.001
0.7 > ABI ≥ 0.5	214	63	551	114.3 (86.1–142.6)	4.09 (3.07–5.45)	2.83 (2.10–3.80)	<0.001
ABI < 0.5 ^b	212	81	516	157.0 (123.0–191.2)	5.64 (4.33–7.33)	3.54 (2.69–4.67)	<0.001

PAD: ABI < 0.9 or history of peripheral revascularization or amputation on account of PAD at baseline.

^aAdjusted for age, sex, diabetes, hypertension, hyperlipidaemia, smoking, history of severe cardio- or cerebrovascular events (myocardial infarction, cardiac revascularization, stroke, revascularization at carotids), and homocysteine (>4th quintile, 19.1 μmol/L).

^bABI < 0.5 or history of peripheral revascularization or amputation at baseline.

Table 4 Association between PAD and other known vascular risk factors and death of any cause or severe vascular event (myocardial infarction, cardiac revascularization, stroke, revascularization at carotids, peripheral revascularization, or amputation)

	HR (univariate, 95% CI)	P-value	HR (multivariate ^a , 95% CI)	P-value
PAD	2.61 (2.25–3.02)	<0.001	1.93 (1.66–2.26)	<0.001
Diabetes	1.87 (1.62–2.16)	<0.001	1.60 (1.38–1.85)	<0.001
Age (>median)	1.68 (1.45–1.94)	<0.001	1.56 (1.34–1.81)	<0.001
Homocysteine > 4th quintile (19.1 μmol/L)	1.58 (1.35–1.85)	<0.001	1.26 (1.08–1.48)	0.004
Male sex	1.89 (1.64–2.18)	<0.001	1.43 (1.21–1.68)	<0.001
Smoker (ever)	1.90 (1.65–2.19)	<0.001	1.34 (1.14–1.58)	<0.001
History of severe cardio- or cerebrovascular events ^b	2.42 (2.08–2.81)	<0.001	1.69 (1.43–1.99)	<0.001
Hypertension	1.33 (1.14–1.55)	<0.001	1.10 (0.94–1.30)	0.231
Hyperlipidaemia	1.14 (0.99–1.31)	0.063	1.02 (0.88–1.18)	0.835

PAD: ABI < 0.9 or history of peripheral revascularization or amputation at baseline.

^aAdjusted for all other variables in the table.

^bMyocardial infarction, cardiac revascularization, stroke, revascularization at carotids.

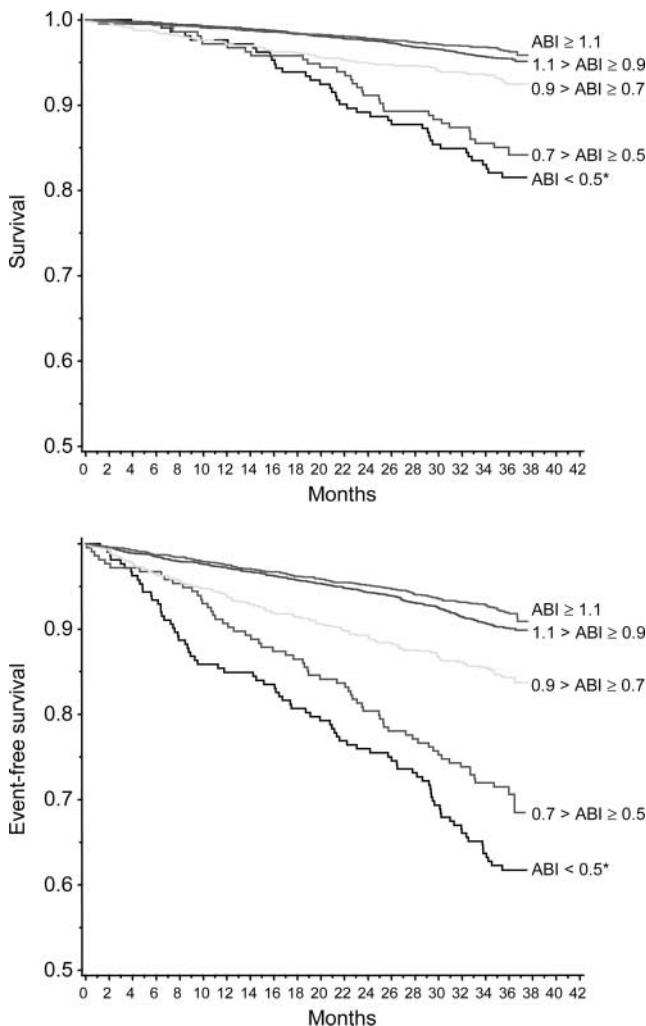


Figure 1 Survival (top) and event-free survival (bottom) according to ABI category over 3 years. Kaplan–Meier estimates of total survival (top) or event-free survival (i.e. no severe vascular events) in the five pre-defined ABI categories during the follow-up period. The risk of death or death/severe events in these categories is shown in Tables 2 and 3. *ABI < 0.5 or history of peripheral revascularization or amputation at baseline.

outpatient clinics¹⁶), and in part used other ABI cut-off values such as 0.7, 0.80,²¹ 0.85,²² or 0.95,¹⁹ as well as various variants of ABI calculations.^{23,24} The cross-sectional and longitudinal characterization of patients by their GPs is likely to be more thorough than would be possible in a community sample, leading to higher data quality. However, only two studies investigated PAD patients in a primary care setting.^{17,19} One was the Edinburgh Artery Study, which followed 1592 patients aged 55–74 years over 5 years and found a 1.6-fold risk increase for death (95% CI 1.1–2.2) in PAD patients compared with those without PAD.¹⁷ Similarly, the Limburg Study, which followed 3649 patients aged 40–78 years over 7 years, reported an HR for PAD vs. no PAD of 1.4 (95% CI 1.1–1.8).¹⁹

The risk increase in PAD patients observed in our study (HR 2.0 for death) is higher than in the previous studies, but may be explained by the higher average patient age in our study. An important finding was the almost linear inverse relationship between ABI and risk. Although in the usual dichotomous categorization of risk factors ABI-values ≥ 0.9 are usually considered ‘normal’, our data show that even individuals with ABI of 0.9–1.1 carry a risk increased by 25% compared with those with ABI > 1.1 . As has been shown for risk factors such as elevated blood pressure or blood lipids, the risks operate on a continuum.²⁵ The risk increases in our study would have been larger if a higher ABI threshold such as 1.1 had been chosen. In analogy to the JNC-VII guidelines on the definition of arterial hypertension, which introduced the ‘pre-hypertension’ category,²⁶ the ABI range between 0.9 and 1.1 should be considered to indicate ‘borderline PAD’. Considering the upper end of ABI categories, spuriously elevated ABI values due to massively calcified vessels might have occurred in the very old and in diabetic patients. Thus, we excluded 59 individuals with ABI values ≥ 1.5 , as is usual in epidemiological studies of this kind. Recent evidence suggests that the effect of a high ABI (> 1.4) on mortality might be equal to that of a low ABI (U-shaped curve), a relationship not explained by comorbidity.^{18,24} However, patient numbers in the high ABI category were too low in our study to corroborate these findings.

As in previous epidemiological studies, GPs performed the Doppler screening and ABI calculations themselves after having been trained by vascular specialists at investigator

meetings. The ABI assessment is easy to learn, although owing to variability of repeated measurements, a misclassification of patients cannot be fully excluded. To account for this possible confounder, we not only divided individuals into the PAD/no PAD strata, but also into five different ABI categories. The almost linear increase in risk towards lower categories and the magnitude of the effect support the results of the main classification into PAD/no PAD.

The major limitation of the present study was the relatively short follow-up. Nonetheless, the present data are informative for a GP: the elderly account for the majority of patients in primary care and usually have one or more cardiovascular risk factors. Further, the study was one of the largest of its kind having sufficient power to distinguish outcomes between the different ABI groups at an early stage without being compromised by the high attrition rates that are a major problem of long-term studies. Compared with previous studies, the present study achieved an unprecedentedly complete follow-up of patients, which was due to regular on-site monitoring of all centres and physician- and patient-binding measures such as newsletters, regular investigator meetings, etc., which in epidemiological studies are the exception rather than a rule.

Medical care during the follow-up period may be a potential source of confounding.²⁷ Although the background anti-diabetic, lipid-lowering, anti-hypertensive, and anti-platelet medication was recorded at baseline, it was not recorded during the follow-up period. It is conceivable that physicians increased interventions, at least in their patients with newly diagnosed PAD, because of the absence of blinding. However, this would have led to an underestimate of the increased risks in PAD patients. It is also likely that GPs did not intensify treatment in PAD patients, as undertreatment seems to be the rule rather than an exception in these patients.²⁸

Among the tested risk factors, PAD had the strongest association with mortality and severe events, followed by CHD/CVD events in the patient's history. The Limburg Study also found co-existing coronary or cerebrovascular disease to be a significant prognostic factor for death and nonfatal vascular events.¹⁹ Interestingly, in this study, as in ours which excluded this covariate from the analyses, PAD became an even stronger factor.

To summarize, primary care patients with a low ABI (including borderline values of 1.1–0.9) had a substantially increased risk of premature death and severe events. Strong PAD effects on both mortality and vascular morbidity were noted after a short time, which underlines the need for early ABI screening and the initiation of further follow-up and adequate secondary prevention measures as are already in place for patients with CHD and CVD.

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manuscript: D.P., C.D., and S.L. Critical revision of the manuscript for important intellectual content: R.L.H., G.T., J.R.A., H.D., and B.v.S. Statistical analysis: S.L. and B.D. Administrative, technical, or material support: B.v.S. Study supervision: C.D., H.J.T., and B.v.S.

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