Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease

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Background—Our aim was to assess the mortality and vascular morbidity risk of elderly individuals with asymptomatic versus symptomatic peripheral artery disease (PAD) in the primary care setting.

Methods and Results—This prospective cohort study included 6880 representative unselected patients ≥65 years of age with monitored follow-up over 5 years. According to physician diagnosis, 5392 patients had no PAD, 836 had asymptomatic PAD (ankle brachial index <0.9 without symptoms), and 593 had symptomatic PAD (lower-extremity peripheral revascularization, amputation as a result of PAD, or intermittent claudication symptoms regardless of ankle brachial index). The risk of symptomatic compared with asymptomatic PAD patients was significantly increased for the composite of all-cause death or severe vascular event (myocardial infarction, coronary revascularization, stroke, carotid revascularization, or lower-extremity peripheral vascular events; hazard ratio, 1.48; 95% confidence interval, 1.21 to 1.80) but not for all-cause death alone (hazard ratio, 1.13; 95% confidence interval, 0.89 to 1.43), all-cause death/myocardial infarction/stroke (excluding lower-extremity peripheral vascular events and any revascularizations; hazard ratio, 1.18; 95% confidence interval, 0.92 to 1.52), cardiovascular events alone (hazard ratio, 1.20; 95% confidence interval, 0.89 to 1.60), or cerebrovascular events alone (hazard ratio, 1.33; 95% confidence interval, 0.80 to 2.20). Lower ankle brachial index categories were associated with increased risk. PAD was a strong factor for the prediction of the composite end point in an adjusted model.

Conclusions—Asymptomatic PAD diagnosed through routine screening in the offices of primary care physicians carries a high mortality and/or vascular event risk. Notably, the risk of mortality was similar in symptomatic and asymptomatic patients with PAD and was significantly higher than in those without PAD. In the primary care setting, the diagnosis of PAD has important prognostic value. **(*Circulation*. 2009;120:2053-2061.)**

Key Words: ankle brachial index ■ coronary disease ■ peripheral vascular disease ■ prevention ■ prognosis screening

Atherosclerosis is a systemic disease that affects coronary, cerebral, and lower-extremity arteries and requires stringent secondary preventive measures to prevent premature mortality and morbidity.[1] The manifestation of atherosclerosis in the legs, peripheral artery disease (PAD), has long been underestimated and underdiagnosed in the primary care setting.[2,3] A series of large-scale epidemiological studies have shown that the disease is widespread, particularly in the elderly and in patients with diabetes mellitus or clusters of cardiovascular risk factors.[4,5] Furthermore, PAD was shown to be associated with increased risk for premature mortality and cardiovascular and cerebrovascular events.[6,7] Only a few studies have been stratified for asymptomatic and symptomatic PAD cases, but they did not provide consistent outcomes. Criqui et al[8] described a progressive increase in patients with PAD who were asymptomatic, symptomatic, or severely symptomatic; Leng et al[9] demonstrated that asymptomatic PAD patients had higher event rates than symptomatic patients. In addition, McDermott et al[10] more recently reported that patients with asymptomatic PAD had poorer functional performance and quality of life than patients

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with intermittent claudication (IC). Overall, current data from the primary care setting on the prevalence and risk of premature mortality and of cardiovascular events associated with PAD are limited.

Editorial see p 2033
Clinical Perspective on p 2061

Against this background, our objectives were to describe the prevalence of asymptomatic and symptomatic PAD in unselected elderly patients in a representative primary care setting in Germany, to investigate the long-term risk for total mortality or major vascular events in patients with PAD by clinical status (asymptomatic versus symptomatic) compared with individuals without PAD, and to quantify the association of PAD with outcomes compared with conventional cardiovascular risk factors.

Methods

The German Epidemiological Trial on Ankle Brachial Index (getABI) is an ongoing prospective observational cohort study initiated in October 2001. The methods and design of the study have been described elsewhere in greater detail.[11,12] Briefly, 34 vascular physicians throughout Germany trained and supervised 344 general physicians (GPs) in their vicinity who were representative in terms of location (ZIP codes) and training (internists and general physicians) of the primary care setting in Germany. A prevalence assessment of primary care attendees, regardless of their reason for seeing the doctor, was then conducted in a prespecified week in October 2001. An average of 20 eligible patients per practice who fulfilled the inclusion criteria (age ≥65 years, legally competent, and able to cooperate appropriately and to provide written informed consent) were recruited evenly over this week to avoid selection bias. The only exclusion criterion was life expectancy ≤6 months as judged by the GP.

Medical History and Definitions at Baseline

A short physical examination was performed at baseline. Medical history assessment included the following conditions: cardiovascular events (myocardial infarction or coronary revascularization procedures); cerebrovascular events (stroke or revascularization procedures on the carotid arteries); lower-extremity peripheral vascular events (ie, a history of amputation [minor and major form] of the lower extremities because of PAD or revascularization procedures on the lower-extremity peripheral arteries); IC (ie, pain in the calf muscles while walking or during other exertion and disappearing within 10 minutes at rest); and risk factors such as arterial hypertension, diabetes mellitus, lipid disorders, or smoking. Subjects were defined as having diabetes mellitus if they had been assigned the clinical diagnosis by their physician, if their hemoglobin A_{1c} was ≥6.5% (criterion used in 94 cases), and/or if they were receiving any oral antidiabetic drug and/or insulin at baseline. Subjects were defined as having hypertension if they had been assigned the clinical diagnosis by their physician and/or if they were receiving AT_1 receptor antagonists, angiotensin-converting enzyme inhibitors, and/or diuretics at baseline. Subjects were defined as having lipid disorders if they had been assigned the clinical diagnosis by their physician, if they were receiving statins and/or fibrates, if their total cholesterol was ≥200 mg/dL at baseline, and/or if their triglyceride level was ≥150 mg/dL at baseline. All laboratory examinations were performed centrally. A cigarette smoking history was taken from all study subjects (never, current, past).

ABI at Rest

GPs were specifically trained to perform ABI measurements under standardized conditions. A standardized Doppler ultrasonic device was used in all centers (8-MHz Kranzbühler, General Electric, Solingen, Germany). Blood pressure measurements and ABI calculations were performed according to the recommendations of the American Heart Association.[13]

The ABI for each leg equals the ratio of the higher of the 2 systolic pressures (tibial posterior and anterior artery) above the ankle to the average of the right and left brachial artery pressures, unless there was a discrepancy ≥10 mm Hg in blood pressure values between the 2 arms. In such a case, the higher reading was used for the ABI. Pressures in each leg were measured, and the ABIs were calculated separately for each leg. The lower of the 2 ABI values was used for analyses.

Asymptomatic PAD was defined as resting ABI <0.90[13] with an absence of prior lower-extremity peripheral vascular events or clinical symptoms indicative of IC. Symptomatic PAD was defined as IC, history of lower-extremity peripheral vascular revascularization, and/or limb amputation because of PAD regardless of ABI value. Total PAD was defined as either symptomatic or asymptomatic PAD. Fifty-nine patients with incompressible arteries (Mönckeberg sclerosis) as indicated by an ABI >1.5 were excluded, as in other studies, to avoid misclassification.[14,15] Cases with missing ABI values (n=8) and no past peripheral events or IC were classified as patients without PAD.

Primary Study Outcomes and Identification of Cardiovascular Events During Follow-Up

Severe vascular events were defined as follows: cardiovascular, including myocardial infarction or coronary revascularization; cerebrovascular, including stroke or carotid revascularization; and lower-extremity peripheral vascular, including peripheral revascularization or amputation because of PAD during follow-up. Information on patients' deaths and vascular events was obtained from the participating GPs, who were asked after 6 months and 1, 3, and 5 years to complete a case record form detailing the event. If possible, deaths resulting from cardiovascular or cerebrovascular causes were further investigated by verifying data from hospital or GP records to ensure that the protocol criteria were fulfilled. Deaths, coronary events, and peripheral events were not adjudicated. However, all strokes were further verified and adjudicated by 2 experienced neurologists independently who were unaware of the PAD status of patients.

Statistical Analyses

Characteristics of subjects at baseline were illustrated descriptively for all 6821 patients and separately by PAD categories. In addition, the differences between symptomatic and asymptomatic PAD patients at baseline were investigated exploratively with χ^2 tests and t tests. To assess associations between PAD, respective ABI categories (and conventional risk factors) and 5-year mortality/vascular morbidity incidence rates were calculated and Cox regression analyses were performed.

Incidence rates and their 95% confidence intervals (CIs) were calculated as events per 1000 person-years. Only the first event and time until first event were taken into account. The constant rate assumption was not met for the risks of interest. Therefore, the reported incidence rates have to be interpreted as a kind of average over the 5 years of the study.

Several unadjusted and adjusted Cox regression analyses were performed, and the corresponding hazard ratios (HRs) and their 95% CIs were calculated. When comparing PAD groups, we used 4 separate models: PAD no/unknown to PAD total (analysis includes all patients), PAD no/unknown to PAD asymptomatic (patients with symptomatic PAD were excluded), PAD no/unknown to PAD symptomatic (patients with asymptomatic PAD were excluded), and PAD asymptomatic to PAD symptomatic (patients without [or unknown] PAD were excluded).

To best illustrate the possible linear relations between low ABI values and the risk of death or vascular events, the ABI was categorized according to the cutoff points of 1.1, 0.9, 0.7, and 0.5 (the last category also includes history of peripheral revascularization or amputation resulting from PAD at baseline). When comparing ABI categories, we also used 4 separate models, with patients with an ABI ≥1.1 and ≤1.5 as the reference group in each case.

Table. Patient Characteristics

	n	All Patients (n=6821)	No/Unknown PAD (n=5392)	PAD (n=1429)	Asymptomatic PAD (n=836)	Symptomatic PAD (n=593)	*P*,* Symptomatic vs Asymptomatic PAD
Age, y	6821	72.5±5.3	72.2±5.1	73.9±5.6	73.9±5.8	73.9±5.4	0.945
Sex, % respondents							
Female	3959	58.0	59.1	54.0	59.6	46.2	≤0.001
Male	2862	42.0	40.9	46.0	40.4	53.8	
Smoking status, % respondents							
Never	3687	54.1	57.2	42.3	48.2	33.9	≤0.001
Past	2500	36.7	35.0	42.8	39.2	47.9	
Current	634	9.3	7.8	14.9	12.6	18.2	
BMI, kg/m^2	6816	27.3±4.1	27.3±4.1	27.4±4.2	27.7±4.4	27.1±3.9	0.006
ABI	6651	1.03±0.16	1.08±0.11	0.81±0.16	0.79±0.11	0.85±0.23†	≤0.001†
Diabetes mellitus, % respondents							
No/unknown	5090	74.6	77.4	64.2	66.0	61.7	0.095
Yes	1731	25.4	22.6	35.8	34.0	38.3	
Hypertension, % respondents							
No/unknown	2102	30.8	34.5	16.9	16.3	17.9	0.425
Yes	4719	69.2	65.5	83.1	83.7	82.1	
Lipid disorders, % respondents							
No/unknown	1158	17.0	17.7	14.3	15.2	13.2	0.279
Yes	5663	83.0	82.3	85.7	84.8	86.8	
History of severe cardiovascular or cerebrovascular events, % respondents							
No/unknown	5730	84.0	86.9	73.1	78.8	65.1	≤0.001
Yes	1091	16.0	13.1	26.9	21.2	34.9	

BMI indicates body mass index. Values are mean±SD when appropriate. Patients with an ABI >1.5 were excluded. ABI was measured at baseline. PAD: ABI <0.9, history of IC, peripheral revascularization, or amputation because of PAD at baseline. Symptomatic PAD: IC, peripheral revascularization, and/or amputation resulting from PAD at baseline. Asymptomatic PAD: ABI <0.9 and no symptomatic PAD at baseline. For definition of diabetes mellitus, arterial hypertension, lipid disorders, etc, see the Methods section.

*Comparison between symptomatic PAD and asymptomatic PAD groups (with *t* or x^2 test).

†Patients with peripheral revascularization or amputation because of PAD at baseline were excluded (431 patients left in symptomatic group).

In addition to PAD groups, respectively ABI categories, the following variables were included in all adjusted statistical models: age (above/below median); gender; smoking status (never/ever); body mass index (≥/<30 kg/m^2); history of severe cardiovascular or cerebrovascular events (yes/no or unknown); presence of diabetes mellitus, hypertension, and lipid disorders (each yes/no or unknown); and homocysteine (below/above the 4th quintile [19.1 μmol/L]). These results were also used to compare the relative prognostic importance of PAD and the other conventional risk factors.

Further, to visualize the findings, time-to-event distributions in the categories were summarized with Kaplan–Meier curves.

Statistical significance was accepted at the 2-sided 0.05 level, and all CIs were computed at the 95% level. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Characteristics of Subjects at Baseline

Of the 6880 patients included in this study, all but 59 (ABI >1.5, defined as patients with mediasclerosis) were analyzed. The survival status of all but 4 patients was known at the 5-year follow-up. According to physician diagnosis, 5392 patients had no PAD (79.0%), 836 had asymptomatic PAD (12.3%), and 593 had symptomatic PAD (8.7%; about one quarter had undergone peripheral artery revascularization or amputation). The Table displays the patient characteristics in the individual groups. Although there were no significant differences in age and most risk factors, in symptomatic PAD patients, the proportions of men, smokers, and patients with a history of cardiovascular or cerebrovascular events were higher. For mean body mass index, the opposite was true. Of note, the mean ABI was higher in symptomatic compared with asymptomatic PAD patients (0.85±0.23 versus 0.79±0.11).

Mortality

Figure 1 provides an overview of mortality events in total and by cause. Of patients without PAD, with asymptomatic PAD, and with symptomatic PAD, 19.5, 41.7, and 53.0 patients per 1000 patient-years had died. Compared with patients without PAD, those with asymptomatic PAD (HR, 1.66; 95% CI, 1.38 to 2.00) or symptomatic PAD (HR, 1.89; 95% CI, 1.55 to 2.30) had a significantly increased risk of premature death. No significant differences between asymptomatic and symptomatic PAD groups were found for death regardless of reason (cardiovascular, cerebrovascular, other, unknown reason).

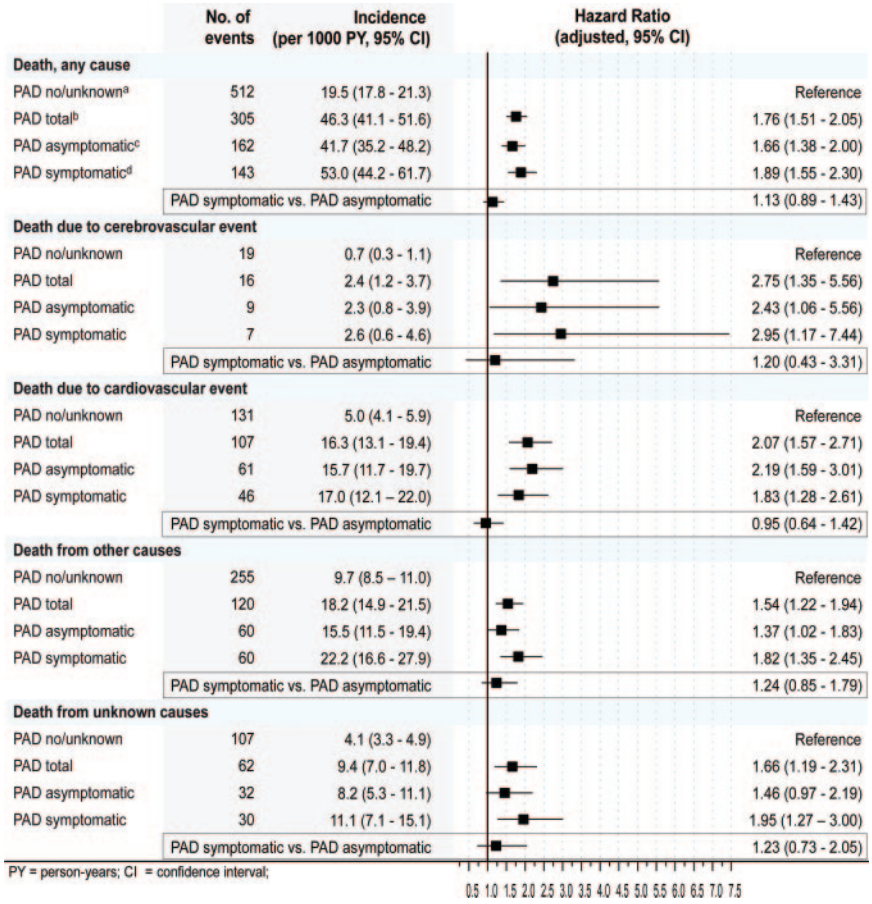

Figure 1. Death from different causes separated by PAD groups. HRs as a result of a Cox regression analysis adjusted for diabetes mellitus, hypertension, lipid disorders, age (above median), sex, body mass index (≥30 kg/m^2), smoking (ever), history of severe cardiovascular or cerebrovascular events, and homocysteine (>4th quintile, 19.1 μmol/L) at baseline. ABI was measured at baseline. PAD if not specified otherwise includes asymptomatic and symptomatic cases: ABI <0.9, history of IC, peripheral revascularization, or amputation because of PAD at baseline. For definition of diabetes mellitus, arterial hypertension, lipid disorders, etc, see the Methods section. Patients with an ABI >1.5 were excluded. [a]n=5,392, PY=26,223; [b]n=1,429, PY=6,583; [c]n=836, PY=3,883; [d]n=593, PY=2,699.

Composite Outcomes of All-Cause Mortality and Vascular Events

The composite end point of all-cause mortality or severe vascular events occurred in 27.2 (no PAD), 60.4 (asymptomatic PAD), and 104.7 (symptomatic PAD) cases per 1000 patient-years (Figure 2, top).

Compared with patients without PAD, those with asymptomatic PAD (HR, 1.81; 95% CI, 1.53 to 2.14) or symptomatic PAD (HR, 2.66; 95% CI, 2.25 to 3.15) had a significantly increased risk to experience the composite outcome, and the difference between the 2 PAD groups was significant (HR. 1.48; 95% CI, 1.21 to 1.80). Times to event for the composite outcomes by PAD status are also illustrated with Kaplan–Meier curves (Figure 3).

The breakdown for the various vascular event types is displayed by PAD status in Tables Ia through If of the online-only Data Supplement. Between symptomatic and asymptomatic PAD, no significant differences were found for myocardial infarction, stroke, peripheral amputation resulting from PAD, and carotid revascularization, whereas rates in the symptomatic PAD group were significantly increased for coronary revascularization and peripheral revascularization.

Figure 2 summarizes these findings and shows the patient-years and event rates for various individual and combined outcomes (all-cause death and/or severe vascular events) in the total PAD group and stratified for asymptomatic and symptomatic PAD, as well as the resulting adjusted risk increase compared with the group of patients without PAD. The relative number of events and the corresponding risk increase were consistently higher in symptomatic PAD patients.

Of note, the number of cerebrovascular events, including ischemic/hemorrhagic stroke, was substantially lower than the number of cardiovascular events. The adjusted HR for cerebrovascular events in the total PAD group was slightly lower than the risk for cardiovascular events (HR, 1.45; 95% CI, 1.06 to 1.98; versus HR, 1.89; 95% CI, 1.56 to 2.28).

Impact of Peripheral Events

The difference between total events in the symptomatic PAD group and the asymptomatic PAD group appeared to be driven by a greater number of peripheral revascularizations performed in the symptomatic group; perhaps these events were triggered by symptoms. Two separate analyses with group comparisons were performed to investigate this finding (Figure 2, middle, and Tables IIa and IIb of the online-only Data Supplement). In the first analysis, lower-extremity peripheral events (lower-extremity peripheral revascularization and amputation resulting from PAD) were excluded from the end point; in the second analysis, lower-extremity peripheral events and all revascularizations (coronary/carotid) were excluded from the end point (Figure 2). In the first analysis, the relative risk of symptomatic PAD patients compared with asymptomatic PAD patients was lower than in the overall end point of all-cause death or severe vascular event (1.32; 95% CI, 1.05 to 1.64; versus 1.48; 95% CI, 1.21 to 1.80), but the

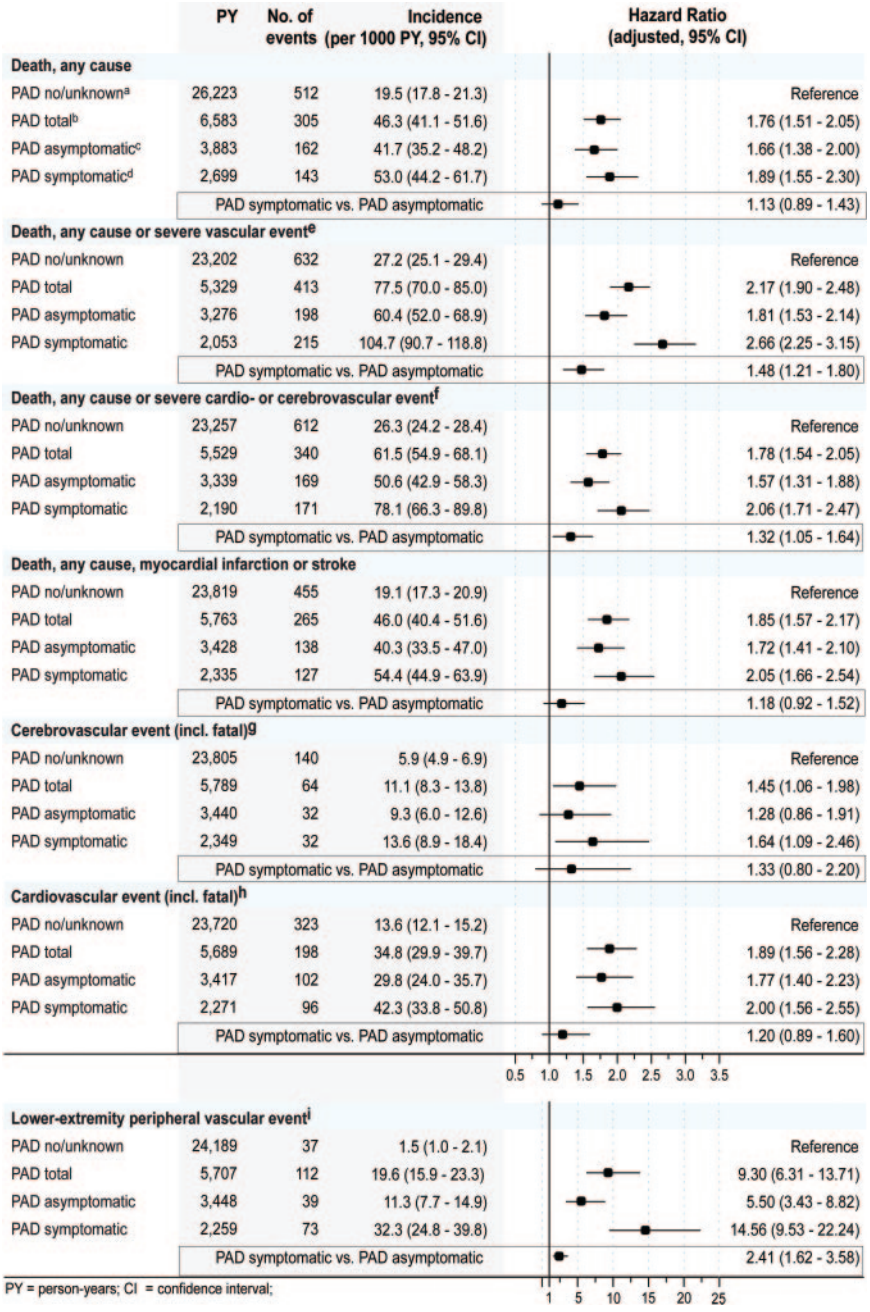

Figure 2. Adjusted risk (hazard rations, 95% CIs) of death and/or severe vascular events in patients with PAD compared to individuals without PAD. HRs as a result of a Cox regression analysis adjusted for diabetes mellitus, hypertension, lipid disorders, age (above median), sex, body mass index (≥30 kg/m^2), smoking (ever), history of severe cardiovascular or cerebrovascular events, and homocysteine (>4th quintile, 19.1 μmol/L) at baseline. ABI was measured at baseline. PAD if not specified otherwise includes asymptomatic and symptomatic cases: ABI <0.9, history of IC, peripheral revascularization, or amputation because of PAD at baseline. For definition of diabetes mellitus, arterial hypertension, lipid disorders, etc, see the Methods section. Patients with an ABI >1.5 were excluded. Patients with events in 2 or 3 categories are mentioned in the respective categories. [a]n=5,392; [b]n=1,429; [c]n=836; [d]n=593; [e]Severe vascular events: myocardial infarction, coronary revascularization, stroke, carotid revascularization, lower-extremity peripheral revascularization, or amputation. [f]Severe cardiovascular events (myocardial infarction or coronary revascularization) or severe cerebrovascular events (stroke or carotid revascularization). [g]Fatal or nonfatal stroke or carotid revascularization. [h]Myocardial infarction, coronary revascularization, or death resulting from a cardiovascular event. [i]Lower-extremity peripheral revascularization or amputation.

difference between symptomatic PAD patients and asymptomatic PAD patients was still significant. In the second analysis, the relative risk of PAD patients compared with non-PAD patients was similar (1.85; 95% CI, 1.57 to 2.17), but the difference between symptomatic PAD patients and asymptomatic PAD patients did not remain significant (1.18; 95% CI, 0.92 to 1.52).

ABI Category

In the analysis by ABI category, patients with an ABI of 1.1 to 1.5 had the lowest event rate per 1000 patient-years (24.3 events), whereas event rates increased substantially with decreasing ABI. In patients with an ABI <0.5, lower-extremity peripheral revascularization, or amputation resulting from PAD, event rates were increased 6-fold (146.3), and the corresponding adjusted risk was increased 4.65-fold (95% CI, 3.57 to 6.05). This finding is illustrated with event-free survival by ABI category in Figure 4, and further details are provided in the Table III of the online-only Data Supplement.

Intermittent Claudication

In a supplementary analysis, ABI was included as a continuous variable in the adjusted statistical model, along with the other risk factors. Patients with IC had lower ABI values than patients without IC, particularly among patients with an ABI <0.9 (Table IVa of the online-only Data Supplement). There was a significant independent prognostic effect of IC for death resulting from any cause in an adjusted model including ABI groups (<0.9/≥0.9); however, in the model with continuous ABI values, it was lower and did not remain signif-

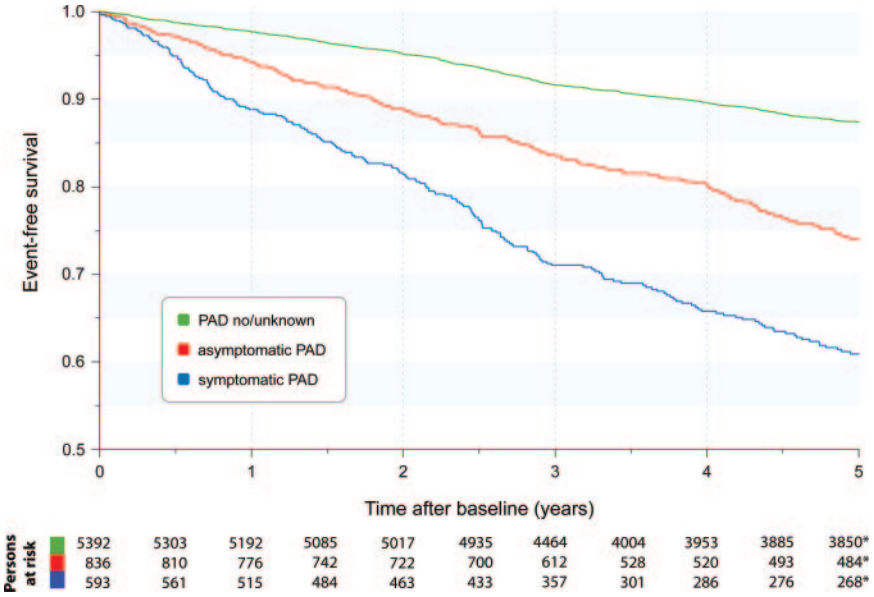

Figure 3. Event-free survival by PAD status at 5 years. Kaplan–Meier estimates showing all-cause mortality or severe vascular events (myocardial infarction, coronary revascularization, stroke, carotid revascularization, peripheral revascularization, or amputation) during the 5-year follow-up. Patients with an ABI >1.5 were excluded. *The number of patients at 5 years reflects a time window of 5±3 months.

icant (Table IVb of the online-only Data Supplement). The prognostic effect of IC for death resulting from any cause or severe vascular event was greater than that for death resulting from any cause alone and was significant in both models (Table IVc of the online-only Data Supplement).

Independent Association of PAD With Outcomes

After adjustment for known conventional risk factors in the adjusted model, PAD had the strongest independent association with death or severe vascular events (HR, 2.17; 95% CI, 1.90 to 2.48). Male gender, previous cardiovascular or cerebrovascular events, diabetes mellitus, high age, smoking, and high homocysteine levels were also significant factors in this model (Figure 5).

Discussion

The present large-scale prospective study shows that 1 in 5 elderly patients visiting their primary care physician has PAD (12.2% asymptomatic, 8.7% symptomatic). With few exceptions, previous epidemiological studies have not differentiated between asymptomatic and symptomatic PAD but have focused on an ABI threshold (usually <0.9) for the diagnosis of PAD.[16–20] In our study, regardless of the event type (death and/or severe vascular events), patients with PAD had a significantly increased risk compared with those without PAD. Within the PAD group, the risk of symptomatic PAD compared with asymptomatic PAD patients was significantly increased by ≈50% (HR, 1.48) for the composite end point of all-cause death or severe vascular event but not significantly for all-cause mortality alone (HR, 1.13), death/myocardial infarction/stroke (ie, excluding any peripheral events and any revascularizations; HR, 1.18), or cardiovascular or cerebrovascular events when assessed separately. Thus, asymptomatic PAD diagnosed through routine screening in the offices of primary care physicians carries a high 5-year mortality and

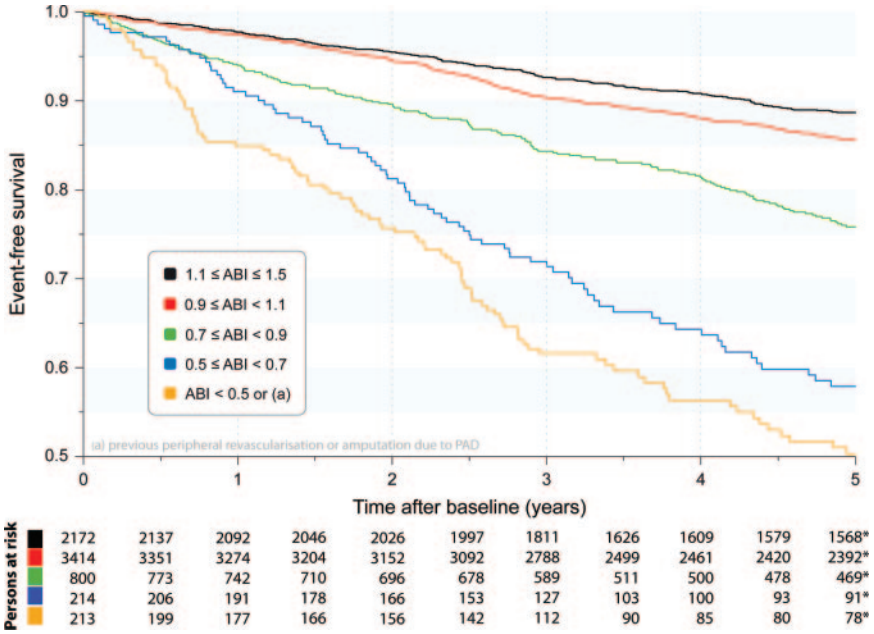

Figure 4. Event-free survival by ABI category. Kaplan–Meier estimates showing all-cause mortality or severe vascular events (myocardial infarction, coronary revascularization, stroke, carotid revascularization, lower-extremity peripheral revascularization, or amputation) during the 5-year follow-up. ABI categories as measured by the physician at baseline. *The number of patients at 5 years reflects a time window of 5±3 months.

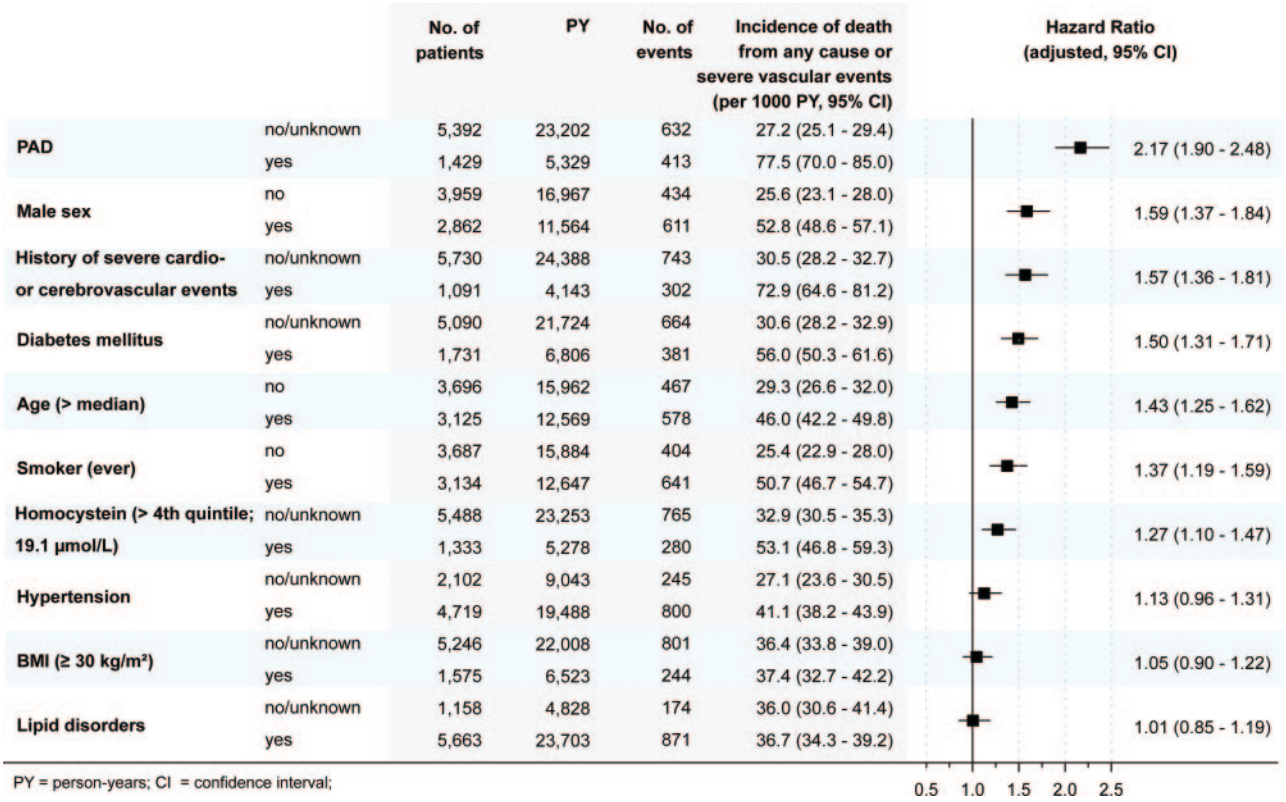

Figure 5. Association between PAD and conventional risk factors with death or severe vascular events by 5 years (adjusted model). HRs as a result of a Cox regression analysis adjusted for all other variables in the Table. Severe vascular events: myocardial infarction, coronary revascularization, stroke, carotid revascularization, lower-extremity peripheral revascularization, or amputation. ABI was measured at baseline. PAD includes asymptomatic and symptomatic cases: ABI <0.9, history of IC, lower-extremity peripheral revascularization, or amputation because of PAD at baseline. For definition of diabetes mellitus, arterial hypertension, and lipid disorders, see the Methods section. Patients with an ABI >1.5 were excluded.

cardiovascular or cerebrovascular event risk that is not substantially lower than that of symptomatic PAD. This early form of PAD has previously been underestimated, underdiagnosed, and undertreated because of a mistaken belief that it is relatively benign.[2,3] The high mortality and vascular event rates, however, show the high risk that these patients face and the importance of treating the condition early.

The majority of earlier observational studies that investigated the risk of PAD patients were population based[8,21–23] or done in high-risk patients.[24] Cohorts in the primary care setting[20,25] (particularly if source data are verified by monitoring as in our study) compared with population-based studies are likely to be characterized more thoroughly in terms of comorbidities and outcomes, and their results are more likely to be directly applicable to routine care. Generally, the risk increase associated with PAD observed in our study is on the same order as in previous population-based studies that used ABI cutoffs of 0.9 (in some studies, 0.85 or 0.5), as systematically reviewed by Doobay and Anand.[6] They found, compared with individuals without PAD, a mean unadjusted relative risk of 3.2 (95% CI, 2.6 to 3.9) and adjusted risks between 1.6 and 3.1, depending on the individual study, for all-cause mortality. Moreover, they found an unadjusted relative risk of 2.3 (95% CI, 1.5 to 3.7) and adjusted risk between 1.4 and 2.7 for cardiovascular events.

Because rates for cerebrovascular events are substantially lower than those for cardiovascular events, large cohorts and/or long follow-up periods are necessary to address the question of whether the respective risk is increased in PAD patients. Thus, compared with coronary morbidity and mortality, cerebrovascular events have been infrequently reported with inconclusive results. The Edinburgh Artery Study[25] and the Atherosclerosis Risk in Communities Study[26] found a significant risk increase for stroke, whereas the Cardiovascular Health Study (after multivariable adjustment) did not.[23] In our study, in the total PAD cohort, the adjusted HR of cerebrovascular events, if not differentiated between type of stroke, was significantly increased (HR, 1.5). Notably, in the group of asymptomatic PAD patients, the risk increase was not significant, which may be due to small power owing to low event numbers.

An important finding of the present study is that PAD (asymptomatic and symptomatic), after adjustment for multiple known cardiovascular risk factors, had a significant association with the composite outcome of death or vascular events. The association between PAD and the composite outcome was considerably stronger than with conventional risk factors, including diabetes mellitus or smoking. This result is in line with the majority of the older investigations focusing on low ABI,[6] showing that PAD provides additional information on risk beyond the assessment of conventional risk factors. Hypertension and lipid disorders had no significant effect in the model, which may be due to pretreatment or the advanced age of the cohort.[27]

Certain types of vascular events are prompted by symptoms, namely revascularizations and amputations in the lower extremities (which are usually performed in patients with claudication), as well as most revascularizations of the carotid and coronary arteries. So, it could be expected that after the exclusion of all events that are influenced by symptoms and consequently physician decision, the risk difference between symptomatic and asymptomatic PAD decreases. Indeed, the difference between asymptomatic and symptomatic PAD patients was reduced somewhat after the exclusion of all lower-extremity peripheral vascular events from the analyses (HR, from 1.48 to 1.32) and to a greater extent after additional exclusion of revascularizations of the carotid and coronary arteries (HR, 1.18, no longer significant).

In our study, the ABI was measured by GPs or their staff. A recent validation study involving getABI investigators showed that between vascular experts, GPs, and nurses, no significant differences exist with respect to measurement variance.[28] Therefore, the ABI measurement can be performed with reliable results after minimal training. It must be noted, however, that the intraobserver and interobserver variability of this investigation is 8% to 9%, which calls for confirmation measurements in patients near the 0.9 threshold to categorize them correctly.[28] Furthermore, as shown in our analysis, the ABI value not only is of high interest for the PAD diagnosis but also conveys relevant information on the individual patient's risk.

Conclusions

The prevalence of PAD in the primary care setting is alarmingly high, which supports the routine use of ABI measurements to identify patients who are at high risk for premature death and vascular events. Measurement of ABI at baseline provides prognostic information that cannot be derived from conventional risk factors alone. Patients with asymptomatic PAD have a significantly increased risk compared with patients without PAD, which calls for risk reduction measures such as stringent lipid-lowering and antiplatelet treatment. In terms of treatment (ie, secondary prevention), the current American Heart Association/American College of Cardiology guidelines or Transatlantic Inter-Society Consensus II guidelines do not differentiate between asymptomatic and symptomatic PAD patients,[4,5] and our results corroborate this approach. The present study confirms the importance of PAD as an indicator disease for generalized atherosclerosis, and its high prognostic utility, in primary care.

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Disclosures

Dr Mahn is a full-time employee of Sanofi-Aventis Pharma, which is one of the sponsors of the study. Dr Mahn had no voting rights. The sponsors have had no influence on the design of the study, research questions, and data interpretation. All analyses were performed by the University of Bochum. The authors report no conflicts of interest related to this study, which does not focus on drug-related research questions.

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CLINICAL PERSPECTIVE

The clinical importance of the early identification and treatment of peripheral arterial disease (PAD) as a manifestation of generalized atherosclerosis is increasingly being acknowledged. However, differences in risk between the asymptomatic and symptomatic manifestations are less clear. Thus, the aim of this study was to compare the risk for all-cause death and vascular events in elderly individuals with asymptomatic PAD (evidenced by low ankle brachial index) and symptomatic PAD in the primary care setting. We found an alarmingly high prevalence of PAD in the primary care setting (12.2% asymptomatic, 8.7% symptomatic). The composite end point of all-cause mortality or severe cardiac, cerebral, or peripheral vascular events occurred in 27.2 (no PAD), 60.4 (asymptomatic PAD), and 104.7 (symptomatic PAD) cases per 1000 patient-years. Thus, asymptomatic PAD diagnosed through routine screening in the offices of primary care physicians carries a high mortality and vascular event risk, which, in cases of all-cause mortality, is not substantially lower than that of symptomatic PAD. This justifies the routine use of ankle brachial index measurements to identify patients who are at high risk for premature death and vascular events. Measurement of ankle brachial index at baseline provides prognostic information that cannot be derived from conventional risk factors alone. In terms of treatment (ie, secondary prevention), the current American Heart Association/American College of Cardiology guidelines or Transatlantic Inter-Society Consensus II guidelines on PAD do not differentiate between asymptomatic and symptomatic PAD patients, and our results corroborate this approach.

Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease

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SUPPLEMENTAL MATERIAL

Supplemental methods

Definitions used in the following tables

ABI: ankle brachial index

PAD: peripheral artery disease: ABI <0.9 or history of intermittent claudication, peripheral revascularization or amputation on account of PAD at baseline;

Symptomatic PAD: intermittent claudication, peripheral revascularization and/or amputation (due to PAD) at baseline;

Asymptomatic PAD: ABI < 0.9 and no symptomatic PAD at baseline;

Total PAD: symptomatic or asymptomatic PAD at baseline;

Diabetes mellitus: Subjects were defined to have diabetes, (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 at baseline;

Hypertension: Subjects were defined to have hypertension, (i) if they had been assigned the clinical diagnosis by their physician, and/or (ii) if they received AT_1-receptor antagonists and/or ACE inhibitors and/or diuretics at baseline;

Lipid disorders: Subjects were defined to have lipid disorders, (i) if they had been assigned the clinical diagnosis by their physician, and/or (ii) if had received statins and/or fibrates and/or (iii) if their total cholesterol was ≥ 200 mg/dl and/or (iv) if their triglycerides were ≥ 150 mg/dl at baseline;

History of severe cardio- or cerebrovascular events: myocardial infarction, cardiac revascularization, stroke or revascularization at carotids until baseline;

Intermittent claudication: Subjects were defined to have intermittent claudication, if they had been assigned the clinical diagnosis by their physician until baseline;

Necrosis/ gangrene: Subjects were defined to necrosis or gangrene, if they had been assigned the clinical diagnosis by their physician until baseline.

Supplemental Tables

Supplemental Table 1a: Myocardial infarction in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	242	29951	8.1 (7.0 - 9.1)	-	-	-
PAD no/unknown	5392	144	24076	6.0 (5.0 - 7.0)	**vs. no/unknown PAD**		
PAD total	1429	98	5876	16.7 (13.3 - 20.0)	2.80 (2.16 - 3.62)	2.08 (1.58 - 2.73)	≤0.001
PAD asymptomatic	836	56	3495	16.0 (11.8 - 20.3)	2.69 (1.97 - 3.66)	2.19 (1.59 - 3.02)	≤0.001
PAD symptomatic	593	42	2380	17.6 (12.3 - 23.0)	2.95 (2.09 - 4.16)	1.92 (1.33 - 2.77)	≤0.001
PAD symptomatic vs. PAD asymptomatic					1.10 (0.74 - 1.65)	0.93 (0.61 - 1.40)	0.724

Patients with an ABI > 1.5 at baseline were excluded; ABI: ankle brachial index at baseline;

PAD: peripheral artery disease; PY: patient years; CI: confidence interval; HR: hazard ratio as a result of a Cox regression analysis.
For definition of PAD, diabetes mellitus, etc see definitions section on the last page.

[a]adjusted for diabetes, hypertension, lipid disorders, age (>median), sex, BMI (≥30 kg/m²), smoking (ever), history of severe cardio- or cerebrovascular events, and homocysteine (> 4th quintile, 19.1 µmol/L) at baseline

Supplemental Table 1b: Coronary revascularizations in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	347	29504	11.8 (10.5 - 13.0)	-	-	-
PAD no/unknown	5392	236	23775	9.9 (8.6 - 11.2)	**vs. no/unknown PAD**		
PAD total	1429	111	5729	19.4 (15.7 - 23.0)	1.97 (1.57 - 2.48)	1.55 (1.22 - 1.97)	≤0.001
PAD asymptomatic	836	51	3436	14.8 (10.7 - 19.0)	1.51 (1.11 - 2.05)	1.30 (0.95 - 1.78)	0.098
PAD symptomatic	593	60	2293	26.2 (19.5 - 32.8)	2.67 (2.01 - 3.55)	1.80 (1.33 - 2.43)	≤0.001
PAD symptomatic vs. PAD asymptomatic					1.77 (1.21 - 2.57)	1.47 (1.003 - 2.16)	0.049

For legend, see table 1a.

Supplemental Table 1c. Strokes in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	183	29915	6.1 (5.2 - 7.1)	-	-	-
PAD no/unknown	5392	121	24048	5.0 (4.1 - 6.0)	**vs. no/unknown PAD**		
PAD total	1429	62	5867	10.6 (7.9 - 13.2)	2.13 (1.56 - 2.90)	1.69 (1.22 - 2.33)	0.002
PAD asymptomatic	836	36	3471	10.4 (6.9 - 13.8)	2.07 (1.42 - 3.01)	1.68 (1.14 - 2.47)	0.009
PAD symptomatic	593	26	2397	10.8 (6.6 - 15.1)	2.21 (1.44 - 3.38)	1.70 (1.08 - 2.66)	0.021
PAD symptomatic vs. PAD asymptomatic					1.08 (0.65 - 1.80)	0.997 (0.59 - 1.68)	0.991

For legend, see table 1a.

Supplemental Table 1d: Revascularizations at carotids in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	43	29917	1.4 (1.0 - 1.9)	-	-	-
PAD no/unknown	5392	30	24031	1.2 (0.8 - 1.7)	**vs. no/unknown PAD**		
PAD total	1429	13	5886	2.2 (1.0 - 3.5)	1.78 (0.92 - 3.42)	1.20 (0.60 - 2.37)	0.605
PAD asymptomatic	836	4	3495	1.1 (0.0 - 2.3)	0.93 (0.32 - 2.64)	0.71 (0.24 - 2.06)	0.527
PAD symptomatic	593	9	2391	3.8 (1.3 - 6.3)	3.02 (1.43 - 6.36)	1.66 (0.75 - 3.65)	0.210
PAD symptomatic vs. PAD asymptomatic					3.30 (1.01 - 10.72)	2.78 (0.83 - 9.25)	0.095

For legend, see table 1a.

Supplemental Table 1e: Peripheral revascularizations in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	141	29919	4.7 (3.9 - 5.5)	-	-	-
PAD no/unknown	5392	35	24193	1.4 (0.9 - 2.0)	**vs. no/unknown PAD**		
PAD total	1429	106	5725	18.5 (14.9 - 22.1)	12.84 (8.75 - 18.82)	9.35 (6.27 - 13.94)	≤0.001
PAD asymptomatic	836	35	3453	10.1 (6.7 - 13.5)	7.08 (4.42 - 11.31)	5.29 (3.24 - 8.65)	≤0.001
PAD symptomatic	593	71	2272	31.2 (23.9 - 38.6)	21.71 (14.47 - 32.57)	14.80 (9.58 - 22.84)	≤0.001
PAD symptomatic vs. PAD asymptomatic					3.08 (2.05 - 4.62)	2.61 (1.72 - 3.95)	≤0.001

For legend, see table 1a.

Supplemental Table 1f: Amputation due to PAD in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	28	30198	0.9 (0.5 - 1.3)	-	-	-
PAD no/unknown	5392	7	24267	0.3 (0.0 - 0.6)	**vs. no/unknown PAD**		
PAD total	1429	21	5931	3.5 (2.0 - 5.1)	12.50 (5.31 - 29.42)	6.60 (2.69 - 16.15)	≤0.001
PAD asymptomatic	836	9	3516	2.6 (0.8 - 4.3)	9.25 (3.44 - 24.84)	5.25 (1.85 - 14.85)	0.002
PAD symptomatic	593	12	2415	5.0 (2.1 - 7.8)	17.44 (6.86 - 44.33)	8.41 (3.09 - 22.83)	≤0.001
PAD symptomatic vs. PAD asymptomatic					1.95 (0.81 - 4.62)	1.70 (0.70 - 4.09)	0.239

For legend, see table 1a.

Supplemental Table 2a: Death from any cause or severe vascular, non peripheral event (myocardial infarction, cardiac revascularization, stroke, or revascularization at carotids) in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	952	28787	33.1 (30.9 - 35.2)	-	-	-
PAD no/unknown	5392	612	23257	26.3 (24.2 - 28.4)	**vs. no/unknown PAD**		
PAD total	1429	340	5529	61.5 (54.9 - 68.1)	2.33 (2.04 - 2.67)	1.78 (1.54 - 2.05)	≤0.001
PAD asymptomatic	836	169	3339	50.6 (42.9 - 58.3)	1.92 (1.62 - 2.28)	1.57 (1.31 - 1.88)	≤0.001
PAD symptomatic	593	171	2190	78.1 (66.3 - 89.8)	2.97 (2.50 - 3.52)	2.06 (1.71 - 2.47)	≤0.001
PAD symptomatic vs. PAD asymptomatic					1.54 (1.24 - 1.91)	1.32 (1.05 - 1.64)	0.014

Patients with an ABI > 1.5 at baseline were excluded; ABI: ankle brachial index at baseline.

PAD: peripheral artery disease; PY: patient years; CI: confidence interval; HR: hazard ratio as a result of a Cox regression analysis.
For definition of PAD, diabetes mellitus, etc see definitions section on the last page.

[a]adjusted for diabetes, hypertension, lipid disorders, age (>median), sex, BMI (≥30 kg/m²), smoking (ever), history of severe cardio- or cerebrovascular events, and homocysteine (> 4th quintile, 19.1 µmol/L) at baseline)

Supplemental Table 2b: Death from any cause, myocardial infarction, or stroke in elderly patients according to presence/absence of PAD

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6821	720	29582	24.3 (22.5 - 26.2)	-	-	-
PAD no/unknown	5392	455	23819	19.1 (17.3 - 20.9)	**vs. no/unknown PAD**		
PAD total	1429	265	5763	46.0 (40.4 - 51.6)	2.39 (2.05 - 2.79)	1.85 (1.57 - 2.17)	≤0.001
PAD asymptomatic	836	138	3428	40.3 (33.5 - 47.0)	2.10 (1.73 - 2.54)	1.72 (1.41 - 2.10)	≤0.001
PAD symptomatic	593	127	2335	54.4 (44.9 - 63.9)	2.83 (2.32 - 3.46)	2.05 (1.66 - 2.54)	≤0.001
PAD symptomatic vs. PAD asymptomatic					1.35 (1.06 - 1.72)	1.18 (0.92 - 1.52)	0.184

For legend, see table 2a.

Supplemental Table 3: Death from any cause or severe vascular event (myocardial infarction, cardiac revascularization, stroke, revascularization at carotids, peripheral revascularization, or amputation) in elderly patients according to presence/absence of PAD or according to ABI category

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (uni-variate, 95% CI)	HR (multivariate[a], 95% CI)	P-value (multivariate)
All	6880	1059	28776	36.8 (34.5 - 39.1)	-	-	-
ABI > 1.5	59	14	245	57.1 (27.1 - 87.0)	-	-	-
Patients without suspected mediasclerosis [b]	6821	1045	28531	36.6 (34.4 - 38.9)	-	-	-
PAD no/unknown	5392	632	23202	27.2 (25.1 - 29.4)	**vs. no/unknown PAD**		
PAD total	1429	413	5329	77.5 (70.0 - 85.0)	2.84 (2.51 - 3.22)	2.17 (1.90 - 2.48)	≤0.001
PAD asymptomatic	836	198	3276	60.4 (52.0 - 68.9)	2.22 (1.89 - 2.61)	1.81 (1.53 - 2.14)	≤0.001
PAD symptomatic	593	215	2053	104.7 (90.7 - 118.8)	3.85 (3.29 - 4.50)	2.66 (2.25 - 3.15)	≤0.001
PAD symptomatic vs. PAD asymptomatic					1.74 (1.43 - 2.11)	1.48 (1.21 - 1.80)	≤0.001
ABI category: Missing	8	2	29	-	-	-	-
1.5 ≥ ABI ≥ 1.1	2172	228	9388	24.3 (21.1 - 27.5)	**vs. 1.5 ≥ ABI ≥ 1.1**		
1.1 > ABI ≥ 0.9	3414	458	14553	31.5 (28.5 - 34.4)	1.30 (1.10 - 1.53)	1.39 (1.18 - 1.64)	≤0.001
0.9 > ABI ≥ 0.7	800	177	3151	56.2 (47.8 - 64.5)	2.31 (1.89 - 2.82)	2.03 (1.64 - 2.50)	≤0.001
0.7 > ABI ≥ 0.5	214	81	734	110.4 (86.3 - 134.5)	4.55 (3.52 - 5.87)	3.43 (2.60 - 4.52)	≤0.001
ABI < 0.5[c]	213	99	677	146.3 (117.4 - 175.2)	5.99 (4.72 - 7.60)	4.65 (3.57 - 6.05)	≤0.001

ABI: ankle brachial index at baseline; PAD: peripheral artery disease; PY: patient years; CI: confidence interval; HR: hazard ratio as a result of a Cox regression analysis. For definition of PAD, diabetes mellitus, etc see definitions section on the last page.

[a]adjusted for diabetes, hypertension, lipid disorders, age (>median), sex, BMI (≥30 kg/m²), smoking (ever), history of severe cardio- or cerebrovascular events, and homocysteine (> 4th quintile, 19.1 µmol/L) at baseline. [b] patients with ABI > 1.5 at baseline were excluded. [c]ABI < 0.5 or history of peripheral revascularization or amputation (due to PAD) at baseline;

Supplemental Table 4a. ABI values separated by intermittent claudication and ABI status

ABI ≥ 0.9	**IC: no**						**IC: yes**					
	Mean	**Std**	**Median**	**N**	**Min**	**Max**	**Mean**	**Std**	**Median**	**N**	**Min**	**Max**
ABI	1.08	0.11	1.07	5384	0.90	1.50	1.05	0.12	1.02	202	0.90	1.42

ABI < 0.9	**IC: no**						**IC: yes**					
	Mean	**Std**	**Median**	**N**	**Min**	**Max**	**Mean**	**Std**	**Median**	**N**	**Min**	**Max**
ABI	0.79	0.11	0.82	836	0.30	0.90	0.68	0.15	0.69	229	0.18	0.90

ABI: ankle brachial index at baseline;

IC: intermittent claudication;

For definition of IC, etc see definitions section on the last page.

Patients with an ABI > 1.5, with missing ABI values, with a peripheral revascularisation or amputation due to PAD at baseline were excluded.

Supplemental Table 4b: Death from any cause in elderly patients according to ABI values or status, and intermittent claudication (IC)

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate, 95% CI)	P-value (multivariate)
Model: IC, ABI status							
ABI ≥ 0.9	5586	541	27141	19.9 (18.2 - 21.7)	**vs. ABI ≥ 0.9**		
ABI <0.9	1065	231	4913	47.0 (40.9 - 53.1)	2.35 (2.01 - 2.75)	1.68 (1.42 - 1.99) [a1]	≤0.001
IC: no	6220	671	30075	22.3 (20.6 - 24.0)	**vs. no IC**		
IC: yes	431	101	1980	51.0 (41.0 - 61.0)	2.30 (1.86 - 2.84)	1.31 (1.04 - 1.65) [a1]	0.018
Model: IC, ABI continuous							
ABI (continuous)					0.10 (0.06 - 0.15)	0.22 (0.14 - 0.33) [a2]	≤0.001
IC: no	6220	671	30075	22.3 (20.6 - 24.0)	**vs. no IC**		
IC: yes	431	101	1980	51.0 (41.0 - 61.0)	2.30 (1.86 - 2.84)	1.18 (0.93 - 1.49) [a2]	0.167

Patients with an ABI > 1.5, with missing ABI values, with a peripheral revascularisation or amputation due to PAD at baseline were excluded.

ABI: ankle brachial index at baseline; IC: intermittent claudication; PY: patient years; CI: confidence interval; HR: hazard ratio as a result of a Cox regression analysis; For definition of diabetes mellitus etc. see definitions section on the last page.

[a1]adjusted for diabetes, hypertension, lipid disorders, age (>median), sex, BMI (≥30 kg/m²), smoking (ever), history of severe cardio- or cerebrovascular events, homocysteine (> 4th quintile, 19.1 µmol/L), and intermittent claudication resp. ABI group at baseline

[a2]adjusted for diabetes, hypertension, lipid disorders, age (>median), sex, BMI (≥30 kg/m²), smoking (ever), history of severe cardio- or cerebrovascular events, homocysteine (> 4th quintile, 19.1 µmol/L), and intermittent claudication resp. ABI (continuous) at baseline

Supplemental Table 4c: Death from any cause or severe vascular event (myocardial infarction, cardiac revascularization, stroke, revascularization at carotids, peripheral revascularization, or amputation) in elderly patients according to ABI values or status and intermittent claudication (IC)

	No. of patients	No. of events	PY	Events per 1000 PY (95% CI)	HR (univariate, 95% CI)	HR (multivariate, 95% CI)	P-value (multivariate)
Model: IC, ABI status							
ABI ≥ 0.9	5586	686	23941	28.7 (26.5 - 30.8)	**vs. ABI ≥ 0.9**		
ABI <0.9	1065	287	4029	71.2 (62.9 - 79.5)	2.48 (2.16 - 2.86)	1.72 (1.47 - 2.01) [a1]	≤0.001
IC: no	6220	828	26449	31.3 (29.1 - 33.5)	**vs. no IC**		
IC: yes	431	145	1520	95.4 (79.8 - 110.9)	3.05 (2.55 - 3.64)	1.74 (1.43 - 2.11) [a1]	≤0.001
Model: IC, ABI continuous							
ABI (continuous)					0.08 (0.05 - 0.11)	0.19 (0.13 - 0.28) [a2]	≤0.001
IC: no	6220	828	26449	31.3 (29.1 - 33.5)	**vs. no IC**		
IC: yes	431	145	1520	95.4 (79.8 - 110.9)	3.05 (2.55 - 3.64)	1.51 (1.23 - 1.86) [a2]	≤0.001

For legend, see table 4b.