Toe pressure should be part of a vascular surgeon's first-line investigation in the assessment of lower extremity artery disease and cardiovascular risk of a patient

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ABSTRACT

Objective: Toe pressure (TP) is an accurate indicator of the peripheral vascular status of a patient and thus cardiovascular risk, with less susceptibility to errors than ankle-brachial index (ABI). This study aimed to analyze how ABI and TP measurements associate with overall survival and cardiovascular death and to analyze the TP of patients with ABI of 0.9 to 1.3.

Methods: The first ABI and TP measurements of a consecutive 6784 patients treated at the Helsinki University Hospital vascular surgery clinic between 1990 and 2009 were analyzed. Helsinki University Vascular Registry and the national Cause of Death Registry provided the data.

Results: The poorest survival was in patients with ABI >1.3 (10-year survival, 15.3%; hazard ratio, 2.2; 95% confidence interval, 1.9-2.6; $P < .0001$; reference group, ABI 0.9-1.3), followed by the patients with TP <30 mm Hg (10-year survival, 19.6%; hazard ratio, 2.0; 95% confidence interval, 1.7-2.2; $P < .0001$; reference group, TP ≥80 mm Hg). The best 10-year survival was in patients with TP ≥80 mm Hg (43.9%). Of the 642 patients with normal ABI (0.9-1.3), 18.7% had a TP <50 mm Hg. The highest cardiovascular death rate (64.6%) was in the patients with TP <30 mm Hg, and it was significantly lower than for the patients with TP >50 mm Hg.

Conclusions: Low TP is associated significantly with survival and cardiovascular mortality. Patients with a normal ABI may have lower extremity artery disease (LEAD) and a considerable risk for a cardiovascular event. If only the ABI is measured in addition to clinical examination, a substantial proportion of patients may be left without LEAD diagnosis or adequate treatment of cardiovascular risk factors. Thus, especially if ABI is normal, LEAD is excluded only if TPs are also measured and are normal. (J Vasc Surg 2021;73:641-9.)

Keywords: Lower extremity artery disease; Ankle-brachial index; Toe pressure; Cardiovascular mortality; Cardiovascular disease; Prognosis

Lower extremity artery disease (LEAD) is an indicator of generalized atherosclerosis.[1] Early diagnosis is important for timely treatment, initiation of secondary prevention, and thus improved prognosis for the patient.[2] The ankle-brachial index (ABI) is a basic tool in diagnosis of LEAD,[3] but it is prone to errors. In patients with medial arterial calcification, the ankle pressure is immeasurable or falsely high,[4] which is the case in 30% of the patients with chronic limb-threatening ischemia (CLTI).[5] Therefore, if ABI is the sole noninvasive measurement used alongside clinical assessment, a significant group of patients may be left without further diagnostic investigations or treatment.

Toe pressure (TP) can be measured alongside the ABI noninvasively. Arterial pressure measured from the toe is less susceptible to error caused by medial arterial calcification because it is minimal in the digital arteries.[6] Information is also provided on the vascular status of the foot. Photoplethysmography and laser Doppler are the principal methods used in the measurement of TP. Previous studies have brought up the question of reliability and repeatability of TP measurement with various devices.[7] Because of this, studies in which TP is measured in a standardized manner and based on a larger number of patients have been called for.[8]

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The association between ABI and survival has been studied widely.[9] There is markedly less evidence of the relationship between TP and survival and cardiovascular risk. Therefore, this study aimed to analyze how ABI and TP measurements compare in the association with survival and cardiovascular mortality.

METHODS

The data for this retrospective registry-based study were collected from the Helsinki University Vascular Registry (HUSVASC) and the Causes of Death Registry of Statistics Finland using individual identity codes. The study has the approval of the University of Helsinki and the Institutional Review Board of Helsinki University Hospital (§45/5.8.2015). Because of the nature of the study, informed consent from the patients was not needed.

Vascular laboratory. TP and ankle pressure are routinely measured from all patients visiting the vascular surgery clinic of Helsinki University Hospital because of LEAD. The measurement is completed in the vascular laboratory by trained nurses in a standardized environment and manner according to current guidelines.[10] During the measurement, the patient is in a supine position with feet at heart level. Toes are routinely warmed before the measurement. Heating was carried out by a heating pad originally, but the method has been changed to the use of a heated probe.[11] The systolic arterial pressure values from all four limbs and big toes are registered, and ABI is calculated for each side. If the ABI measurements are unreliable, the results are confirmed with manual measurement.

TP measurements have been carried out with either the photoplethysmography method (Nicolet VasoGuard; Nicolet Vascular Inc, Madison, Wisc) or the laser Doppler method (PeriFlux System 5000; Perimed, Stockholm, Sweden). Photoplethysmography was used until 2015 and laser Doppler since 2007, so both methods were in use during 2007 to 2015.

HUSVASC. The vascular surgery clinic serves the population of the Helsinki metropolitan area (1.2 million) on all matters of diagnostics and treatment requiring a vascular surgeon. Since 1990, vascular laboratory measurements have been registered to the vascular registry. The vascular laboratory information includes the absolute values of ankle pressure, TP, and arm pressure as well as ABIs and toe-brachial index. The ABI and TP data from the HUSVASC form the basis of this study. The registry also includes most of the vascular interventions that the patients have undergone during the study period.

Data selection and patient grouping. The material consists of all the registered, consecutive measurements from January 1, 1990, to December 31, 2009. The data from 1990 to 2000 contain mostly ABI values. Since 2000, TP has been measured and registered routinely alongside the ABI from all patients thought to have LEAD. If one patient had several measurements, we used the values from the first registered measuring session because we wanted to analyze the baseline measurements for each patient before possible revascularization. All patients undergo ABI and TP measurements at least once before any possible intervention. The measurements that were taken after the baseline measurements were discarded from the material. The limb with the lower ABI was included in the comparing analysis if the lowest ABI and TP were not in the same limb. The patients with at least one intervention for the treatment of LEAD documented in the registry were grouped as having had an intervention.

The patients were analyzed in four ABI and TP groups, as follows: the ABI groups were <0.5, 0.5 to 0.89, 0.9 to 1.3, and >1.3. The TP groups were determined as <30 mm Hg, 30 to 49 mm Hg, 50 to 79 mm Hg, and ≥80 mm Hg. ABI <0.5 is a cutoff point for critical ischemia, and ABI 0.9 to 1.3 is the range of a normal ABI.[12,13] Patients with rest pain usually have TP <30 mm Hg, and 50 mm Hg is a critical cutoff point for wound healing.[10]

Causes of death data. The causes and dates of death were provided for each individual patient by the Cause of Death Registry of Statistics Finland. The registry is based on death certificates of permanent residents of Finland. The coverage is very good; annually, only 0.1% to 0.5% of death certificates are missing.[14] The causes of death are included until the end of 2013; however, dates of death are included until the end of 2014. The causes of death were divided according to the *International Classification of Diseases, Tenth Revision* classification. The deaths caused by cardiovascular disease were analyzed separately.

Diabetes medication data. The Social Insurance Institution provided the data of oral and injectable diabetes

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** Low toe pressures (TPs) were associated significantly with long-term survival and cardiovascular mortality in a data set of 3426 patients. Of the 642 patients with ankle-brachial index of 0.9 to 1.3, 18.7% had a TP <50 mm Hg.
- **Take Home Message:** The diagnosis of lower extremity artery disease should routinely include TP measurements to avoid undertreatment of patients, especially when ankle-brachial index does not indicate severe lower extremity artery disease.

medication purchases according to each patient's social security number between 2000 and 2014. The diabetes medication included medicine with the codes A10AB to A10AF and A10BA to A10BX according to the Anatomical Therapeutic Chemical classification. Patients were categorized as having diabetes if they had purchased at least one package of diabetes medication during the selected time period.

Statistical analysis. The statistical analyses were carried out using SPSS Statistics version 24 (IBM, Armonk, NY). Baseline characteristics were compared using χ^2 test for categorical variables and one-way analysis of variance test for continuous variables. A subgroup analysis of the patients with a normal ABI (0.9-1.3) was done to assess the TP values and association of TP with survival in this group. Kaplan-Meier survival analysis was used for the unadjusted model, and Cox proportional hazards model was used to determine the age- and sex-adjusted survival and hazard ratio (HR) in each group. A subset of the data including only patients from 2000 to 2009 was analyzed separately. For these patients, a survival analysis was performed that included adjustment for diabetes medication. Results were considered statistically significant at $P < .05$.

The assumption of proportional hazards was checked with R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) using a test based on Schoenfeld residuals and visual inspection. With ABI, there were no indications of violation of the assumption. However, with TP, there was a possibility for nonproportionality. Visual inspection suggested that the effect might be slightly smaller during the first 2 years than during the later follow-up. As the violation was not severe, we estimated the Cox model again, stratifying by age and sex and calculating robust standard errors. This did not, however, change the results significantly. The HRs should be interpreted as average effects during the follow-up, meaning in this case that actual differences could be a bit larger than what we report on the basis of our conservative approach.

RESULTS

Baseline characteristics. The original data included 24,894 measuring sessions from 6784 patients during the years 1990 to 2009. During the first recorded session, 6761 patients had ABI measured and 3426 had TP measured. These measurements were used in the analysis. The median follow-up time was 6.3 (range, 0-24) years after ABI and 6.1 (range, 0-18) years after TP measurements. Table I shows the mean age and sex ratio in each TP and ABI group.

Association of ABI with survival. Table II shows the unadjusted median survival of patients in each ABI group. The median survival was higher in the groups with higher ABI. The patient group with ABI >1.3 formed an exception; this group has the lowest median survival of only 3.3 years. The best survival was in the patient group with ABI of 0.9 to 1.3, being 8.9 years. The unadjusted cumulative survival probabilities with standard error in the four ABI groups are presented in Supplementary Table I (online only).

The age- and sex-adjusted 10-year survival for the patients with ABI <0.5, 0.5 to 0.89, 0.9 to 1.3, and >1.3 was 27.6%, 38.3%, 43.2%, and 15.3%, respectively. Compared with ABI of 0.9 to 1.3, ABI >1.3 was the most significant factor predicting mortality (HR, 2.2; 95% confidence interval [CI], 1.9-2.6; $P < .0001$), followed by <0.5 (HR, 1.5; 95% CI, 1.4-1.7; $P < .0001$) and 0.5 to 0.89 (HR, 1.1; 95% CI, 1.0-1.2; $P = .003$). The differences in patient outcome on different ABI levels are illustrated by the age- and sex-adjusted Cox proportional hazards models in Fig 1.

When ABI measurements were analyzed as a continuous variable, the age- and sex-adjusted HR was 0.924 (95% CI, 0.856-0.996; $P = .039$).

The age- and sex-adjusted survival according to ABI results for patients measured after 1996 who also had TP measurements available is presented in Supplementary Fig 1 (online only).

Association of TP with survival. The unadjusted median survival with 95% CIs in the four TP groups is depicted in Table II. For the patients with TP <30 mm Hg, the median survival was only 3.8 years, whereas it was 9.6 years in the patients with TP >80 mm Hg. The unadjusted cumulative survival probabilities in each TP group are presented in Supplementary Table II (online only).

The 10-year age- and sex-adjusted survival for the patients with TP <30 mm Hg, 30 to 49 mm Hg, 50 to 79 mm Hg, and ≥80 mm Hg was 19.6%, 27.8%, 39.0%, and 43.9%, respectively. Compared with TP ≥80 mm Hg, the highest association with mortality was in patients with TP <30 mm Hg (HR, 2.0; 95% CI, 1.7-2.2; $P < .0001$), followed by 30 to 49 mm Hg (HR, 1.6; 95% CI, 1.4-1.8; $P < .0001$) and 50 to 79 mm Hg (HR, 1.1; 95% CI, 1.0-1.3; $P = .053$). Fig 2 shows the age- and sex-adjusted Cox proportional hazards models according to TP as well as the age- and sex-adjusted 5- and 10-year survival rates.

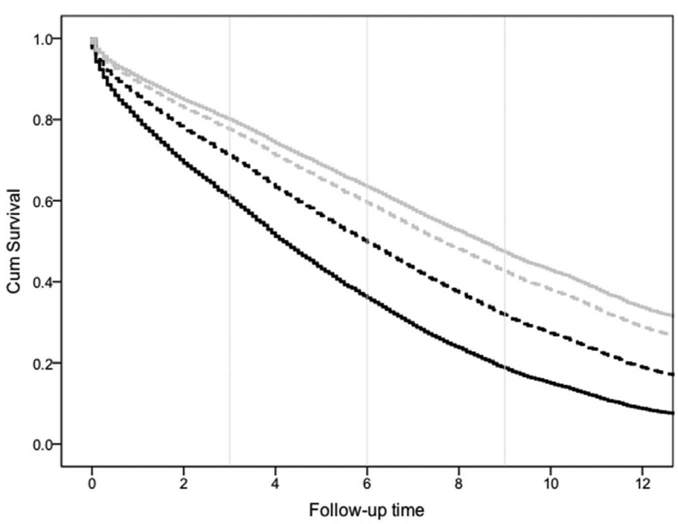
When TP measurements were analyzed as a continuous variable, the age- and sex-adjusted HR was 0.992 (95% CI, 0.991-0.993; $P < .0001$).

Association of TP with survival in patients with ABI of 0.9 to 1.3. There were 642 patients who had a normal ABI (0.9-1.3); 120 (18.7%) of them had TP <50 mm Hg. Moreover, 282 patients (43.9%) had TP <80 mm Hg. The unadjusted median survival of patients with TP <50 mm Hg was 3.9 years (95% CI, 2.7-5.1 years); for patients with TP of 50 to 79 mm Hg, 7.3 years (95% CI 5.8-8.9 years); and for patients with TP ≥80 mm Hg, 9.9 years (95% CI, 9.0-10.8 years). The unadjusted cumulative survival

Table I. Age and sex distribution of patients according to ankle-brachial index (*ABI*) and toe pressure (*TP*)

ABI	<0.5	0.5-0.89	0.9-1.3	>1.3	*P* value
Age, years	71 (12)	68 (11)	67 (12)	70 (13)	<.0001[a]
Female	1365 (50)	929 (37)	338 (27)	98 (40)	<.0001[b]
Male	1369 (50)	1597 (63)	918 (73)	147 (60)	
Total	2734	2526	1256	245	
TP, mm Hg	**<30**	**30-49**	**50-79**	**>80**	***P* value**
Age, years	74 (11)	71 (11)	69 (11)	67 (11)	<.0001[c]
Female	554 (50)	352 (45)	356 (40)	192 (30)	<.0001[b]
Male	550 (50)	428 (55)	539 (60)	455 (70)	
Total	1104	780	895	647	

Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation).
[a]Although the overall difference in age was significant between the four groups, in the post hoc tests, the difference in age was not significant when the group with an ABI of >1.3 was compared with the group with an ABI of <0.5 and 0.5 to 0.89.
[b]*P* values refer to the comparisons between the four groups. *P* values were calculated using χ^2 test for categorical variables and one-way analysis of variance test for continuous variables.
[c]In the post hoc tests, the difference in age was significant between all the groups.



ABI group	5-year survival	10-year survival	Hazard ratio (95% CI)	p-value
<0.5	56.8%	27.6%	1.5 (1.4-1.7)	<0.0001
0.5-0.89	65.6%	38.3%	1.1 (1.0-1.2)	0.003
0.9-1.3	69.2%	43.2%		reference
>1.3	43.8%	15.3%	2.2 (1.9-2.6)	<0.0001

Fig 1. Survival plot for ankle-brachial index (*ABI*). The 12-year survival in the four ABI groups. Age- and sex-adjusted Cox proportional hazards model according to ABI level with 5- and 10-year survival, hazard ratios (HRs) with 95% confidence intervals (*CIs*), and *P* values. To obtain the HR, the other ABI groups were compared with the group with ABI of 0.9 to 1.3. *P* values were calculated using the Wald test. The analysis included 6761 patients in total.

probabilities in the three TP groups are presented in Supplementary Table III (online only).

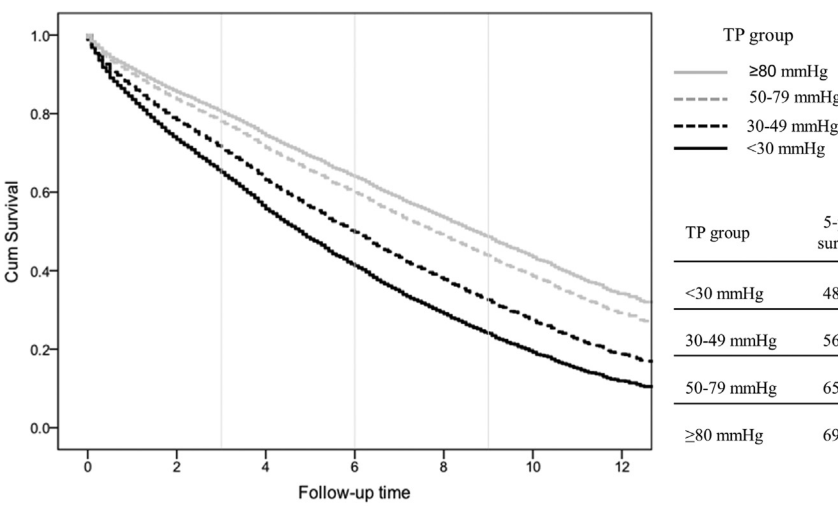
The 10-year age- and sex-adjusted survival for the patients with TP <50 mm Hg, 50 to 79 mm Hg, and ≥80 mm Hg was 19.6%, 40.3%, and 48.4%. Compared with the patients with TP ≥80 mm Hg, the HR was 2.3 (95% CI, 1.8-3.0; $P < .0001$) for the patients with TP <50 mm Hg and 1.3 (95% CI, 1.0-1.6; $P = .083$) for the patients with TP of 50 to 79 mm Hg. The age- and sex-adjusted Cox proportional hazards models according to TP as well as the hazard ratios and 5- and 10-year survival rates of patients with ABI of 0.9 to 1.3 are shown in Fig 3.

The impact of diabetes on the association of ABI and TP with survival. There were 4130 patients included in the study between 2000 and 2009. Of these, 1214 (29.4%) had purchased at least one package of diabetes medication during the study period and were categorized as having diabetes. The distribution of diabetes medication use in the ABI and TP groups is shown in Supplementary Table IV (online only). Compared with the patient group with ABI of 0.9 to 1.3, the age-, sex-, and diabetes-adjusted HR of patients with ABI <0.5 was 1.5 (95% CI 1.4-1.7; $P < .0001$); with ABI of 0.5 to 0.89, 1.2 (95% CI 1.1-1.4; $P < .0001$); and with ABI >1.3, 2.1 (95% CI 1.7-2.6; $P < .0001$).

Table II. Survival of patients according to ankle-brachial index (*ABI*) and toe pressure (*TP*)

ABI	Patients	Median survival, years (95% CI)	TP, mm Hg	Patients	Median survival, years (95% CI)
<0.5	2734	5.3 (5.0-5.5)	<30	1104	3.8 (3.4-4.1)
0.5-0.89	2526	7.8 (7.3-8.2)	30-49	780	5.7 (5.0-6.3)
0.9-1.3	1256	8.9 (8.3-9.6)	50-79	895	8.0 (7.3-8.7)
>1.3	245	3.3 (2.7-4.0)	≥80	647	9.6 (8.8-10.4)

CI, Confidence interval.
Unadjusted median survival of patients in each ABI and TP group from the Kaplan-Meier analysis.



TP group	5-year survival	10-year survival	Hazard ratio (95% CI)	p-value
<30 mmHg	48.5%	19.6%	2.0 (1.7-2.2)	<0.0001
30-49 mmHg	56.6%	27.8%	1.6 (1.4-1.8)	<0.0001
50-79 mmHg	65.8%	39.0%	1.1 (1.0-1.3)	0.053
≥80 mmHg	69.4%	43.9%		reference

Fig 2. Survival plot for toe pressure (*TP*). The 12-year survival in the four TP groups. Age- and sex-adjusted Cox proportional hazards model according to TP with 5- and 10-year survival, hazard ratios (HRs) with 95% confidence intervals (*CIs*), and *P* values. To obtain the HR, the other TP groups were compared with the group with TP ≥80 mm Hg. *P* values were calculated using the Wald test. The analysis included 3426 patients in total.

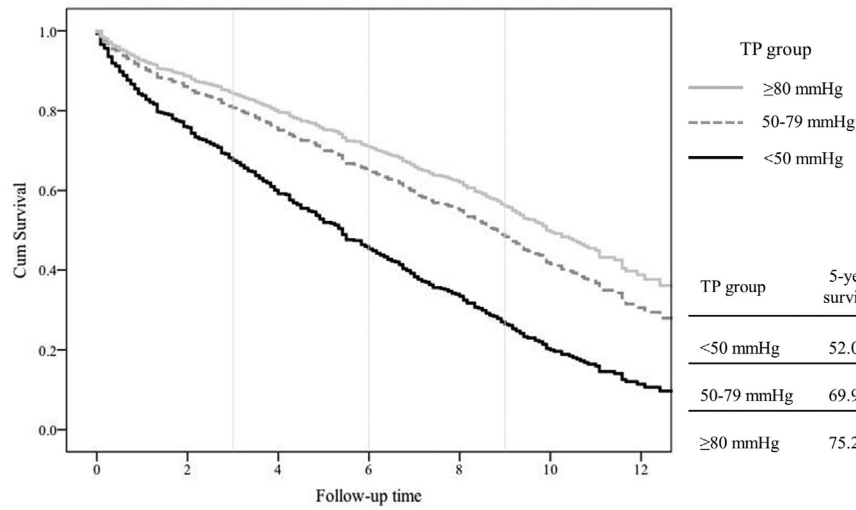
There were 3012 patients who had TP measured during the first measuring session between 2000 and 2009. Compared with the patients with TP ≥80 mm Hg (Supplementary Fig 2, online only), the age-, sex-, and diabetes-adjusted HR of patients with TP <30 mm Hg was 1.8 (95% CI, 1.6-2.1; $P < .0001$); with TP of 30 to 49 mm Hg, 1.5 (95% CI, 1.3-1.7; $P < .0001$); and with TP of 50 to 79 mm Hg, 1.1 (95% CI, 1.0-1.3; $P = .109$).

There were 614 patients with ABI of 0.9 to 1.3 and a TP measurement from the first visit between 2000 and 2009. Of them, 18.1% had TP <50 mm Hg. Compared with the patients with ABI of 0.9 to 1.3 and TP ≥80 mm Hg, the age-, sex-, and diabetes-adjusted HR was 2.4 (95% CI, 1.9-3.2; $P < .0001$) for patients with ABI of 0.9 to 1.3 and TP <50 mm Hg and 1.3 (95% CI 1.0-1.7; $P = .030$) for patients with ABI of 0.9 to 1.3 and TP of 50 to 79 mm Hg.

The impact of interventions on the association of ABI and TP with survival. There were 5420 (80.1%) patients who had undergone a lower limb intervention during the study period. The distribution of patients who had a revascularization in the ABI and TP groups is shown in Supplementary Table V (online only). Compared with the patients with ABI of 0.9 to 1.3, the age-, sex-, and lower limb intervention-adjusted HR of patients with ABI <0.5 was 1.4 (95% CI, 1.3-1.6; $P < .0001$); for ABI of 0.5 to 0.89, 1.1 (95% CI, 1.0-1.2; $P = .129$); and for ABI >1.3, 2.1 (95% CI, 1.8-2.5; $P < .0001$).

Compared with the patients with TP ≥80 mm Hg (Supplementary Fig 3, online only), the age-, sex-, and lower limb intervention-adjusted HR of patients with TP <30 mm Hg was 2.0 (95% CI, 1.7-2.3; $P < .0001$); for patients with TP of 30 to 49 mm Hg, 1.6 (95% CI, 1.4-1.8; $P < .0001$); and for patients with TP of 50 to 79 mm Hg, 1.2 (95% CI, 1.0-1.3; $P = .042$). Compared with the patients with ABI of 0.9 to 1.3 and TP ≥80 mm Hg, the age-, sex-, and lower limb intervention-adjusted HR was 2.1 (95% CI, 1.6-2.8; $P < .0001$) for patients with ABI of 0.9 to 1.3 and TP <50 mm Hg and 1.2 (95% CI, 0.9-1.6; $P = .144$) for patients with ABI of 0.9 to 1.3 and TP of 50 to 79 mm Hg.

Causes of death. At the end of follow-up, 4909 (72.4%) patients had died. There were 4451 patients with ABI and an underlying cause of death recorded. The overall



TP group	5-year survival	10-year survival	Hazard ratio (95% CI)	p-value
<50 mmHg	52.0%	19.6%	2.3 (1.8-3.0)	<0.0001
50-79 mmHg	69.9%	40.3%	1.3 (1.0-1.6)	0.083
≥80 mmHg	75.2%	48.4%		reference

Fig 3. Survival plot for toe pressure (*TP*) in patients with ankle-brachial index (ABI) of 0.9 to 1.3. The 12-year survival of patients with normal (0.9-1.3) ABI according to TP group. Age- and sex-adjusted Cox proportional hazards model with 5- and 10-year survival, hazard ratios (HRs) with 95% confidence intervals (*CIs*), and *P* values. *P* values were calculated using the Wald test. The analysis included 642 patients in total.

proportion of cardiovascular deaths was 59.9%, and it was the highest in the patients with an ABI <0.5 (63.3%; Table III). The corresponding percentage for the patients with ABI of 0.5 to 0.89 was 58.1%; ABI of 0.9 to 1.3, 54.5%; and ABI >1.3. 56.1%. The patients with a lower ABI had a higher percentage of death due to ischemic heart disease and atherosclerosis. However, there was no clear difference in the percentage of death due to cerebrovascular disease between the groups.

There were 2051 patients with TP and the underlying cause of death recorded. Of these patients, the highest death rate due to cardiovascular disease was for the patients with a TP <30 mm Hg (64.6%; n = 525). For patients with TP of 30 to 49 mm Hg, it was 60.8%; and for patients with TP of 50 to 79 mm Hg, 56.2%. The lowest percentage of mortality due to cardiovascular disease was 52.2%, and it was found in the patient group with TP ≥80 mm Hg. There was an association between TP and death from ischemic heart disease and atherosclerosis but again no clear difference in death from cerebrovascular disease between the TP groups.

DISCUSSION

A clear association between TP value and survival was demonstrated by our study. The patient group with ABI >1.3 had the worst survival and even a considerably poorer survival than the groups with the lowest ABI. Of the patients with normal ABI (0.9-1.3), 18.7% had a TP <50 mm Hg, and survival in this group was significantly lower than in the group with normal ABI and TP of 50 to 79 mm Hg and TP ≥80 mm Hg. Thus, even patients with a normal ABI may have substantial atherosclerotic disease that can be distinguished with TP. The addition of diabetes and lower limb interventions as an adjusting factor in the analysis did not change the results substantially. The proportion of deaths due to overall cardiovascular disease, ischemic heart disease, and atherosclerosis was higher in the groups with the lowest TP.

Traditionally, ABI 0.9 has been associated with increased risk of cardiovascular events and higher mortality rate.[12,15] An abnormally high ABI >1.4 is associated with an increased risk of all-cause and cardiovascular mortality.[16] This was also shown in our results as the patients with ABI >1.3 had the poorest long-term survival. A meta-analysis by Xu et al[17] found that the pooled estimate for sensitivity of ABI is 75% in the diagnosis of LEAD. An important factor lowering the sensitivity is medial arterial calcification that may cause ankle arteries to be incompressible, therefore rendering ankle pressure measurements unreliable.

Previous studies of patients with CLTI or those referred for invasive treatment have suggested that TP or toe-brachial index is a useful tool if ankle pressure cannot be measured or the result is abnormally high.[18,19] In CLTI patients, a low TP is associated with increased mortality, and TPs reflect the patient outcomes better than ankle pressure and the ABI do.[20,21] A study demonstrated that only 6% of CLTI patients had an ABI <0.4, whereas the sensitivity of TP was 60%.[22] Furthermore, TP has been shown to be predictive of both cardiovascular and overall mortality.[23]

The major arguments against the routine use of TP are that the instrumentation needed is expensive and thus not widely available and that the measurement is susceptible to errors due to external factors, such as room temperature, as well as systemic factors, such as

Table III. Causes of death due to cardiovascular and pulmonary disease, diabetes, and cancer

	ABI				TP, mm Hg			
Cause of death	**<0.5**	**0.5-0.89**	**0.9-1.3**	**>1.3**	**<30**	**30-49**	**50-79**	**≥80**
Cardiovascular disease	1293 (63.3)	909 (58.1)	360 (54.5)	105 (56.1)	525 (64.6)	297 (60.9)	259 (56.2)	151 (52.2)
95% CI	61.2-65.4	55.6-60.6	50.6-58.3	48.7-63.4	61.2-67.9	56.4-65.2	51.5-60.8	46.3-58.1
Ischemic heart disease	798 (39.1)	579 (37.0)77	210 (31.8)	68 (36.4)	327 (40.2)	184 (37.7)	172 (37.3)	87 (30.1)
95% CI	37.0-41.2	34.6-39.5	28.2-35.5	29.5-43.7	36.8-43.7	33.4-42.2	32.9-41.9	24.9-35.8
Cerebrovascular disease	198 (9.7)	148 (9.5)	48 (7.3)	15 (8.0)	72 (8.9)	40 (8.2)	41 (8.9)	26 (9.0)
95% CI	8.4-11.1	8.1-11.0	5.4-9.5	4.6-12.9	7.0-11.0	5.9-11.0	6.5-11.9	6.0-12.9
Aneurysm or dissection	34 (1.7)	47 (3.0)	44 (6.7)	1 (0.5)	8 (1.0)	14 (2.9)	13 (2.8)	15 (5.2)
95% CI	1.2-2.3	2.2-4.0	4.9-8.8	0.0-2.9	0.4-1.9	1.6-4.8	1.5-4.8	2.9-8.4
Atherosclerosis	136 (6.7)	64 (4.1)	18 (2.7)	10 (5.3)	71 (8.7)	25 (5.1)	16 (3.5)	5 (1.7)
95% CI	5.6-7.8	3.2-5.2	1.6-4.3	2.6-9.6	6.9-10.9	3.3-7.5	2.0-5.6	0.6-4.0
Diabetes	105 (5.1)	91 (5.8)	41 (6.2)	31 (16.6)	49 (6.0)	36 (7.4)	27 (5.9)	18 (6.2)
95% CI	4.2-6.2	4.7-7.1	4.5-8.3	11.6-22.7	4.5-7.9	5.2-10.1	3.9-8.4	3.7-9.7
Pulmonary disease	110 (5.4)	86 (5.5)	25 (3.8)	6 (3.2)	33 (4.1)	19 (3.9)	18 (3.9)	16 (5.5)
95% CI	4.4-6.5	4.4-6.7	2.5-5.5	1.2-6.9	2.8-5.7	2.4-6.0	2.3-6.1	3.2-8.8
Cancer	298 (14.6)	278 (17.8)	123 (18.6)	11 (5.9)	106 (13.0)	63 (12.9)	96 (20.8)	45 (15.6)
95% CI	13.1-16.2	15.9-19.8	15.7-21.8	3.0-10.3	10.8-15.5	10.1-16.2	17.2-24.8	11.6-20.3
Patients with a known cause of death[a]	2042	1564	661	187	813	488	461	289

ABI, Ankle-brachial index; *CI,* confidence interval; *TP,* toe pressure.
Values are reported as number of patients in each group and percentage of deaths of patients with a known underlying cause of death.
[a]Total number of patients in each group with a known underlying cause of death.

increased sympathetic tone leading to vasoconstriction.[11,24,25] However, untreated cardiovascular risk factors may come at a high cost as limb loss, myocardial infarctions, and stroke.[26] The causes of error in measurement can be minimized by using a standardized measuring technique and setting. For example, our unit has used heating probes in TP measurements since 2010 to avoid the influence of vasoconstriction and thus falsely low results.[11]

Medial arterial calcification of patients with diabetes is a major source of error for the ABI measurements; however, pedal arteries are rarely affected, and TP may be more reliable in these patients.[27] To appreciate the role of diabetes in our results, we did a subgroup analysis of patients that included information on diabetes medication purchases. The analysis showed that even if we adjusted for diabetes, the results did not change substantially. Among patients with suspected vascular disease, there may be hyperglycemic patients not yet having a diabetes diagnosis.

The majority of the patients in this study eventually had a lower limb intervention. Interventions were more frequent in the patients with a poor ABI or TP. Having a successful operation will very likely increase the ABI and TP measurements; however, the results show that adjusting for the operation in the survival analysis does not substantially change the results. It may be that a successful operation leading to improved perfusion of the limb may decrease the risk of amputation. The results imply, however, that the overall cardiovascular disease burden of patients with poor ABI and TP will not change significantly.

According to our results, we recommend that TP always be measured also, with or without ABI, as part of a vascular surgeon's examination. Current guidelines acknowledge the use of TP in cases of incompressible ankle arteries, leaving the diagnosis of LEAD to rely solely on ABI in addition to clinical examination in other cases.[3,28] This may lead to patients' being left without adequate treatment of cardiovascular risk factors or a missed diagnosis of LEAD that can be especially harmful for patients with polyvascular disease because they have a clearly heightened risk of serious adverse cardiovascular outcomes.[29]

We divided the patients into four groups according to ABI using commonly accepted values for normal ABI (0.9) and critical limb ischemia (0.5).[3,12,13] The threshold value for an abnormally high ABI in turn has been set at 1.3 to 1.4.[30] Although recent publications have stated the highest normal value as 1.4, we selected 1.3 to avoid highly probable medial calcinosis patients with ABI of 1.3 to 1.4 in the group with normal ABI.

The selected threshold values for the TP groups were 30 mm Hg and 50 mm Hg because those have been determined as the critical cutoff points for TP.[10,31] However, evidence of the threshold value for a normal TP is lacking. According to our results, the use of 50 mm Hg as a threshold value of a significantly lowered TP seems to be justified. It is noteworthy, though, that TP and ABI are both continuous parameters and the association with survival is gradual. This means that all strict cutoff values are always somewhat artificial. Therefore, the use of ABI and TP as tools of identifying LEAD and assessing cardiovascular risk should always be paired with sound clinical judgment.

The results of the association of ABI and TP groups with survival were confirmed by the analysis of ABI and TP as continuous variables. However, the analysis of the measurements as ordinal groups decreases the effect of small variation in the reproducibility of results and provides a more thorough understanding of the association of ABI and TP with survival, especially in the case of ABI, because the association with survival is not linear.

The results of this study concern adult patients thought to have atherosclerosis or who have comorbidities that increase the risk of LEAD. All of the patients included in the study have been specifically referred to a vascular surgeon's consultation. Therefore, the patient data used for this study are highly selected, and the results should not be generalized to the whole population. Previously, the use of ABI and TP has been studied in various sets of the adult population, not all of which may be comparable to the selected patient population of the study at hand.

The limitations of this study include the fact that it is based on registry data. Baseline information is limited as only the social security number and pressure measurements are registered. The strengths of the study are a substantial number of patients and highly standardized vascular laboratory measurements by extremely experienced vascular nurses as they perform >7000 measurements annually. Furthermore, comprehensive long-term mortality data are a strength, despite the fact that the registry is better in identifying all-cause mortality than in classifying specific causes of death.[32]

This study forms the basis for further research on the use of TP as a primary investigation of LEAD. The threshold for a normal TP has been set at 80 mm Hg in this study. However, research is lacking on the optimal cutoff value for a normal TP. In addition, the cost-effectiveness of using TP as opposed to ABI as a first-line investigation in LEAD needs further research. Finally, this study provides a platform for future research on factors affecting patient outcome on different ABI and TP levels.

CONCLUSIONS

In this study, we show a strong association between TP and survival and TP and mortality from cardiovascular causes in a patient data set previously unmatched in size and follow-up time. There is an association between ABI and survival, and the outcome of patients with ABI >1.3 is especially poor. Our study shows that if the ABI is the sole noninvasive investigation in addition to clinical evaluation, a substantial number of patients may be left without treatment or it may be delayed as almost one in five patients with a normal ABI had TP <50 mm Hg. Therefore, we recommend that the diagnosis of LEAD should routinely include TP to avoid undertreatment of patients, especially when ABI does not indicate severe LEAD.

AUTHOR CONTRIBUTIONS

Conception and design: ML, HH, JS, AA, MV
Analysis and interpretation: ML, RS, MV
Data collection: ML, PK, MV
Writing the article: ML
Critical revision of the article: HH, PK, JS, RS, AA, MV
Final approval of the article: ML, HH, PK, JS, RS, AA, MV
Statistical analysis: ML
Obtained funding: ML, MV
Overall responsibility: ML

REFERENCES

1. van Kuijk JP, Flu WJ, Poldermans D. Risk factors and peripheral arterial disease; a plea for objective measurements. Atherosclerosis 2011;214:37-8.
2. Alzamora MT, Forés R, Pera G, Torán P, Heras A, Sorribes M, et al. Ankle-brachial index and the incidence of cardiovascular events in the Mediterranean low cardiovascular risk population ARTPER cohort. BMC Cardiovasc Disord 2013;13:119.
3. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes N, Corriere M, Drachman D, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2017;135:e686-725.
4. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. J Vasc Surg 2008;48:1197-203.
5. Settembre N, Kauhanen P, Albäck A, Spillerova K, Venermo M. Quality control of the foot revascularization using indocyanine green fluorescence imaging. World J Surg 2017;41:1919-26.
6. Potier L, Abi Khalil C, Mohammedi K, Roussel R. Use and utility of ankle brachial index in patients with diabetes. Eur J Vasc Endovasc Surg 2011;41:110-6.
7. Widmer LW, Vikatmaa P, Aho P, Lepäntalo M, Venermo M. Reliability and repeatability of toe pressures measured with laser Doppler and portable and stationary photoplethysmography devices. Ann Vasc Surg 2012;26:404-10.
8. Kröger K, Stewen C, Santosa F, Rudofsky G. Toe pressure measurements compared to ankle artery pressure measurements. Angiology 2003;54:39-44.
9. Oksala NK, Viljamaa J, Saimanen E, Venermo M. Modified ankle-brachial index detects more patients at risk in a Finnish primary health care. Eur J Vasc Endovasc Surg 2010;39:227-33.
10. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45:S5-67.
11. Settembre N, Kagayama T, Kauhanen P, Vikatmaa P, Inoue Y, Venermo M. The influence of heating on toe

pressure in patients with peripheral arterial disease. Scand J Surg 2018;107:62-7.
12. Diehm C, Schuster A, Allenberg JR, Darius H, Haberl R, Lange S, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis 2004;172:95-105.
13. Jelinek HF, Austin M. The ankle-brachial index in clinical decision making. Foot 2006;16:153-7.
14. Statistics Finland. Quality description: causes of death 2013. Available at: http://www.stat.fi/til/ksyyt/2013/ksyyt_2013_2014-12-30_laa_001_en.html. Accessed September 30, 2019.
15. Criqui MH, McClelland RL, McDermott MM, Allison M, Blumenthal R, Aboyans V, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010;56:1506-12.
16. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006;113:388-93.
17. Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. Can J Cardiol 2013;29:492-8.
18. Aboyans V, Criqui MH, Abraham P, Allison M, Creager M, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012;126:2890-909.
19. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (Updating the 2005 Guideline). J Am Coll Cardiol 2011;58:2020.
20. Vallabhaneni R, Kalbaugh CA, Kouri A, Farber MA, Marston WA. Current accepted hemodynamic criteria for critical limb ischemia do not accurately stratify patients at high risk for limb loss. J Vasc Surg 2016;63:105-13.
21. Carter SA, Tate RB. The value of toe pulse waves in determination of risks for limb amputation and death in patients with peripheral arterial disease and skin ulcers or gangrene. J Vasc Surg 2001;33:708-14.
22. Shishehbor MH, Hammad TA, Zeller T, Baumgartner I, Scheinert D, Rocha-Singh KJ. An analysis of IN.PACT DEEP randomized trial on the limitations of the societal guidelines-recommended hemodynamic parameters to diagnose critical limb ischemia. J Vasc Surg 2016;63:1311-7.
23. Wickström JE, Laivuori M, Aro E, Sund R, Hautero O, Venermo M, et al. Toe pressure and toe brachial index are predictive of cardiovascular mortality, overall mortality, and amputation free survival in patients with peripheral artery disease. Eur J Vasc Endovasc Surg 2017;53:696-703.
24. Quong WL, Fung AT, Yu RY, Hsiang YN. Reassessing the normal toe-brachial index in young healthy adults. J Vasc Surg 2016;63:652-6.
25. Pérez-Martin A, Meyer G, Demattei C, Böge G, Laroche J, Quéré I, et al. Validation of a fully automatic photoplethysmographic device for toe blood pressure measurement. Eur J Vasc Endovasc Surg 2010;40:515-20.
26. Vaidya A, Joore MA, ten Cate-Hoek AJ, ten Cate H, Severens JL. Screen or not to screen for peripheral arterial disease: guidance from a decision model. BMC Public Health 2014;14:89.
27. Forsythe RO, Hinchliffe RJ. Assessment of foot perfusion in patients with a diabetic foot ulcer. Diabetes Metab Res Rev 2016;32:232-8.
28. Conte MS, Bradbury AW, Kolh P, White J, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. Eur J Vasc Endovasc Surg 2019;69:3S-125S.
29. Bonaca MP, Nault P, Giugliano RP, Keech A, Pineda A, Kanevsky E, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation 2018;137:338-50.
30. Suominen V, Rantanen T, Venermo M, Saarinen J, Salenius J. Prevalence and risk factors of PAD among patients with elevated ABI. Eur J Vasc Endovasc Surg 2008;35:709-14.
31. Carter SA, Tate RB. Value of toe pulse waves in addition to systolic pressures in the assessment of the severity of peripheral arterial disease and critical limb ischemia. J Vasc Surg 1996;24:258-65.
32. Mieno MN, Tanaka N, Arai T, Kawahara T, Kuchiba A, Ishikawa S, et al. Accuracy of death certificates and assessment of factors for misclassification of underlying cause of death. J Epidemiol 2016;26:191-8.

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Supplementary Table I (online only). Cumulative survival of patients in each ankle-brachial index (*ABI*) group

ABI group	3 years	6 years	9 years	12 years
<0.5	0.656 (0.014)	0.423 (0.014)	0.264 (0.014)	0.156 (0.014)
0.5-0.89	0.740 (0.012)	0.559 (0.013)	0.415 (0.014)	0.296 (0.015)
0.9-1.3	0.789 (0.016)	0.632 (0.019)	0.474 (0.021)	0.312 (0.027)
>1.3	0.539 (0.036)	0.313 (0.034)	0.192 (0.030)	0.136 (0.029)

Cumulative survival of patients at 3, 6, 9, and 12 years from the Kaplan-Meier analysis. Standard error is in parentheses.

Supplementary Table II (online only). Cumulative survival of patients in each toe pressure (*TP*) group

TP group	3 years	6 years	9 years	12 years
<30 mm Hg	0.575 (0.015)	0.356 (0.014)	0.226 (0.013)	0.122 (0.013)
30-49 mm Hg	0.681 (0.017)	0.482 (0.018)	0.309 (0.018)	0.210 (0.019)
50-79 mm Hg	0.791 (0.014)	0.618 (0.016)	0.456 (0.017)	0.336 (0.021)
≥80 mm Hg	0.862 (0.014)	0.671 (0.019)	0.529 (0.021)	0.354 (0.027)

Cumulative survival of patients at 3, 6, 9, and 12 years from the Kaplan-Meier analysis. Standard error is in parentheses.

Supplementary Table III (online only). Cumulative survival of patients with ankle-brachial index (ABI) of 0.9 to 1.3 in the three toe pressure (*TP*) groups

TP group	3 years	6 years	9 years	12 years
<50 mm Hg	0.583 (0.045)	0.392 (0.045)	0.270 (0.043)	0.126 (0.042)
50-79 mm Hg	0.741 (0.034)	0.617 (0.038)	0.454 (0.041)	0.319 (0.080)
≥80 mm Hg	0.872 (0.018)	0.716 (0.024)	0.559 (0.028)	0.338 (0.040)

Cumulative survival of patients with ABI of 0.9 to 1.3 at 3, 6, 9, and 12 years in the three TP groups from the Kaplan-Meier analysis. Standard error is in parentheses.

Supplementary Table IV (online only). Distribution of diabetes medication use in the ankle-brachial index (*ABI*) and toe pressure (*TP*) groups

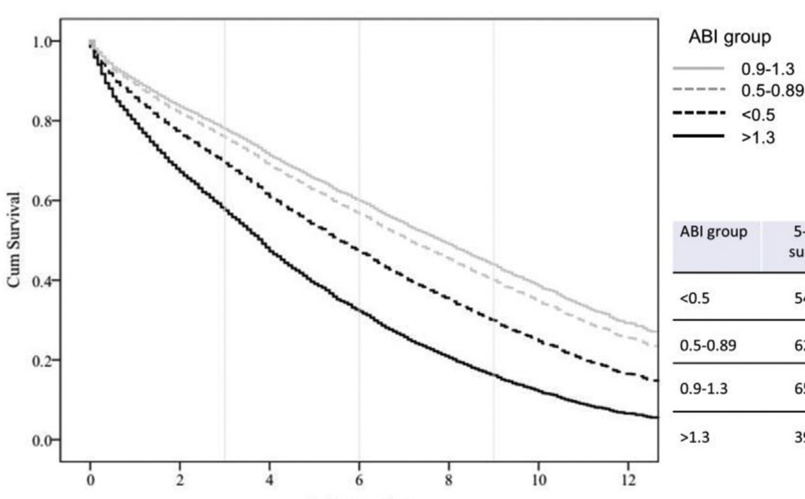
ABI	<0.5	0.5-0.89	0.9-1.3	>1.3	*P* value
No diabetes medication	1024 (70)	1092 (71)	722 (77)	76 (43)	<.0001
Diabetes medication	448 (30)	446 (29)	217 (23)	103 (57)	
Total	1472	1538	939	179	
TP, mm Hg	**<30**	**30-49**	**50-79**	**>80**	***P* value**
No diabetes medication	576 (65)	414 (60)	581 (71)	460 (75)	<.0001
Diabetes medication	309 (35)	281 (40)	242 (29)	150 (25)	
Total	885	695	823	610	

Values are reported as number (%) of patients in each ABI and TP group who use diabetes medication. Data include patients who had first ABI and TP measurements after 2000 and medication data available. *P* value was calculated using χ^2 test.

Supplementary Table V (online only). Distribution of lower limb revascularization in the ankle-brachial index (*ABI*) and toe pressure (*TP*) groups

ABI	<0.5	0.5-0.89	0.9-1.3	>1.3	*P* value
No revascularization	229 (8)	428 (17)	645 (51)	46 (19)	<.0001
Revascularization	2505 (92)	2098 (83)	611 (49)	199 (81)	
Total	2734	2526	1256	245	
TP, mm Hg	**<30**	**30-49**	**50-79**	**>80**	***P* value**
No revascularization	74 (7)	85 (11)	228 (26)	320 (50)	<.0001
Revascularization	1030 (93)	695 (89)	667 (74)	327 (50)	
Total	1104	780	895	647	

Values are reported as number (%) of patients in each ABI and TP group who had a revascularization procedure during the study period. *P* value was calculated using χ^2 test.



ABI group	5-year survival	10-year survival	Hazard ratio (95% CI)	p-value
<0.5	54.2%	24.7%	1.4 (1.3-1.6)	<0.0001
0.5-0.89	62.8%	34.7%	1.1 (1.0-1.3)	0.093
0.9-1.3	65.8%	38.5%		reference
>1.3	39.6%	12.5%	2.2 (1.8-2.7)	<0.0001

Supplementary Fig 1 (online only). The age- and sex-adjusted survival according to ankle-brachial index (*ABI*) results for patients measured after 1996 who also had toe pressure (TP) measurements available. Data include 3417 patients. *CI,* Confidence interval.

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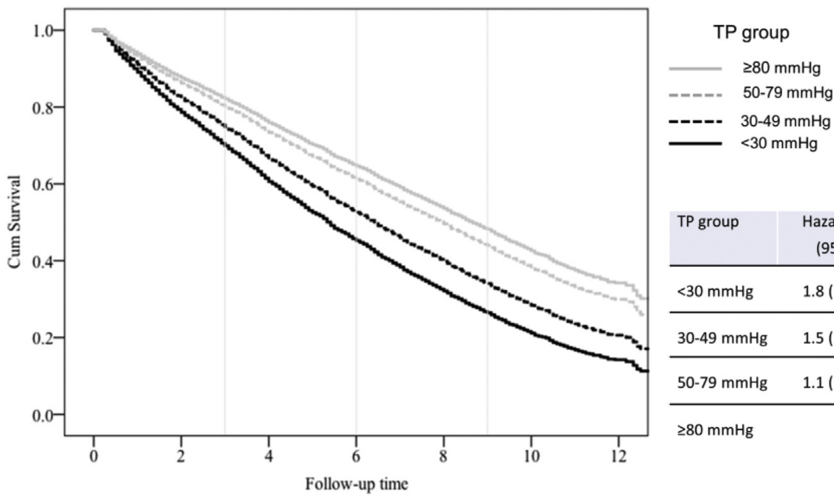
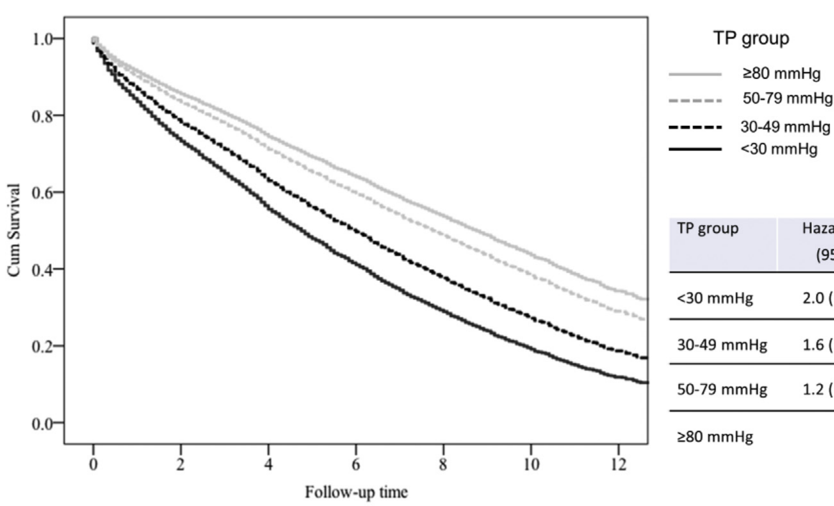


TP group	Hazard ratio (95% CI)	p-value
<30 mmHg	1.8 (1.6-2.1)	<0.0001
30-49 mmHg	1.5 (1.3-1.7)	<0.0001
50-79 mmHg	1.1 (1.0-1.3)	0.109
≥80 mmHg		reference

Supplementary Fig 2 (online only). The 12-year survival in the four toe pressure (*TP*) groups. Age-, sex-, and use of diabetes medication-adjusted Cox proportional hazards model according to TP with hazard ratios (HRs) with 95% confidence intervals (*CIs*) and *P* values. To obtain the HR, the other TP groups were compared with the group with TP ≥80 mm Hg. *P* values were calculated using the Wald test. The analysis included 3012 patients in total.



TP group	Hazard ratio (95% CI)	p-value
<30 mmHg	2.0 (1.7-2.3)	<0.0001
30-49 mmHg	1.6 (1.4-1.8)	<0.0001
50-79 mmHg	1.2 (1.0-1.3)	0.042
≥80 mmHg		reference

Supplementary Fig 3 (online only). The 12-year survival in the four toe pressure (*TP*) groups. Age-, sex-, and revascularization-adjusted Cox proportional hazards model according to TP with hazard ratios (HRs) with 95% confidence intervals (*CIs*) and *P* values. To obtain the HR, the other TP groups were compared with the group with TP ≥80 mm Hg. *P* values were calculated using the Wald test. The analysis included 3426 patients in total.