Journal Pre-proof

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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PII: S0741-5214(20)31577-9

DOI: https://doi.org/10.1016/j.jvs.2020.06.104

Reference: YMVA 11434

To appear in: *Journal of Vascular Surgery*

Received Date: 7 December 2019

Accepted Date: 12 June 2020

Please cite this article as: Laivuori M, Hakovirta H, Kauhanen P, Sinisalo J, Sund R, Albäck A, Venermo M, 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, *Journal of Vascular Surgery* (2020), doi: https://doi.org/10.1016/j.jvs.2020.06.104.

Titles and legends for figures:

Figure 1: Survival plot for ABI

12-year survival in the four ABI groups. Age and sex-adjusted Cox proportional hazard model according to ABI level with 5 and 10-year survival, hazard ratios with 95% confidence intervals (CI) and p-values. To obtain the hazard ratio the other ABI groups were compared to the group with ABI 0.9-1.3. P-values were calculated using the Wald test. The analysis included 6761 patients in total.

Figure 2: Survival plot for TP

12-year survival in the four TP groups. Age and sex-adjusted Cox proportional hazard model according to TP with 5 and 10-year survival, hazard ratios with 95% confidence intervals (CI) and p-values. To obtain the hazard ratio the other TP groups were compared to the group with TP ≥80 mmHg. P-values were calculated using the Wald test. The analysis included 3426 patients in total.

Figure 3: Survival plot for TP in patients with ABI 0.9 – 1.3

12-year survival of patients with normal (0.9-1.3) ABI according to TP group. Age and sex-adjusted Cox proportional hazard model, 5 and 10-year survival, and hazard ratios with 95% confidence intervals (CI) and p-values. P-values were calculated using the Wald test. The analysis included 642 patients in total.

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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Keywords: Lower extremity arterial disease, ankle brachial index, toe pressure, cardiovascular mortality, cardiovascular disease, prognosis

ARTICLE HIGHLIGHTS

Type of Research: A single-center retrospective cohort study.

Key Findings: Low toe pressures were associated significantly with long-term survival and cardiovascular mortality in a dataset of 3426 patients. Of the 642 patients with ankle brachial index 0.9-1.3, 18.7% had a toe pressure of less than 50 mmHg.

Take home Message: The diagnosis of lower extremity artery disease should routinely include toe pressure measurements to avoid undertreatment of patients, especially when ankle brachial index does not indicate severe lower extremity artery disease.

Table of Contents Summary

This retrospective study of 6784 patients found that long-term survival and cardiovascular mortality associated significantly to ankle brachial index (ABI) and toe pressure, however, almost 20% of patients with normal ABI had toe pressure of less than 50 mmHg. This study suggests, that toe pressure should routinely be measured alongside ankle brachial index when diagnosing lower extremity artery disease.

Abstract

Objective: Toe pressure 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. This study aimed to analyse how ankle brachial index and toe pressure measurements associate to overall survival and cardiovascular death and to analyse the toe pressure of patients with ankle brachial index 0.9-1.3.

Methods: The first ankle brachial index and toe pressure measurements of consecutive 6784 patients treated at the Helsinki University Hospital vascular surgery clinic between 1990-2009 were analysed. Helsinki University vascular registry and the national Cause of death registry provided the data.

Results: The poorest survival was in patients with ankle brachial index >1.3, (10-year survival 15.3%; HR 2.2, 95%CI 1.9-2.6; p<0.0001, reference group ankle brachial index 0.9-1.3), followed by the patients with toe pressure <30mmHg (10-year survival 19.6%;HR 2.0; 95%CI 1.7-2.2, p<0.0001, reference group toe pressure ≥80mmHg). The best 10-year survival was in patients with toe pressure ≥80mmHg (43.9%). Of the 642 patients with normal ankle brachial index (0.9-1.3), 18.7% had a toe pressure <50mmHg. The highest cardiovascular death rate (64.6%) was in the patients with toe pressure <30mmHg and it was significantly lower than for the patients with toe pressure >50mmHg.

Conclusions: Low toe pressure associates significantly with survival and cardiovascular mortality. Patients with a normal ankle brachial index may have lower extremity artery

disease and a considerable risk for a cardiovascular event. If only the ankle brachial index is measured in addition to clinical examination, a substantial proportion of patients may be left without lower extremity artery disease diagnosis or adequate treatment of cardiovascular risk factors. Thus, especially if ankle brachial index is normal, lower extremity artery disease is excluded only if also toe pressures are measured and are normal.

Abbreviations:

LEAD: Lower extremity arterial disease

ABI: Ankle Brachial Index

TP: Toe Pressure

TBI: Toe Brachial Index

CLTI: Chronic limb threatening ischemia

MAC: Medial arterial calcification

Introduction

Lower extremity arterial disease (LEAD) is an indicator of generalised atherosclerosis[1]. Early diagnosis is important for timely treatment, initiation of secondary prevention and thus, an improved prognosis of the patient[2]. The ankle brachial index (ABI) is a basic tool in diagnosing LEAD[3], however, 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 non-invasive 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 (MAC) since it is minimal in the digital arteries[6]. Information is also provided on the vascular status of the foot. Photoplethysmography and laser Doppler are principle 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 where TP is measured in a standardised manner and based on a larger number of patients have been called for[8].

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 analyse how ABI and TP measurements compare in the association to survival and cardiovascular mortality.

Methods

The data for the present retrospective registry-based study was 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 IRB of Helsinki University Hospital (§45/5.8.2015). Due to 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 standardised 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 prior to 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, WI) or laser Doppler method (Perimed system 5000, Perimed, Stockholm, Sweden). Photoplethysmography has been used until 2015 and laser Doppler since 2007, so both methods were in use during 2007-2015.

Helsinki University Vascular Registry

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 (TBI). The ABI and TP data from the Helsinki University Vascular Registry 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 1st of January 1990 to 31st of December 2009. The data from 1990 to 2000 contains mostly ABI values. Since 2000 TP has been measured and registered routinely alongside the ABI from all patients with suspicion of LEAD. If one patient had several measurements, we used the values from the first registered measuring session, since we wanted to analyse 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 analysed in four ABI and TP groups as follows: the ABI groups were <0.5, 0.5-0.89, 0.9-1.3, and >1.3. The TP groups were determined as <30mmHg, 30-49mmHg, 50-79mmHg, and ≥ 80mmHg. ABI <0.5 is a cut off point for critical ischemia and

ABI 0.9-1.3 is the range of a normal ABI[12,13]. Patients with rest pain usually have TP<30 mmHg and 50mmHg is a critical cut off 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 0.1-0.5% 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 (ICD-10) classification. The deaths caused by cardiovascular disease were analysed separately.

Diabetes medication data

The Social Insurance Institution provided the data of oral and injectable diabetes 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 (ATC) 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, USA). Baseline characteristics were compared using Chi-squared test for categorical variables and one-way ANOVA 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 to survival in this group. Kaplan-Meier survival analysis was used for the

unadjusted model and Cox proportional hazard 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 2000-2009 was analysed separately. For these patients a survival analysis was performed that included adjustment for diabetes medication. Results were considered statistically significant at $p<0.05$.

The assumption of proportional of hazards was checked with R version 3.4.3 (The 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 non-proportionality. Visual inspection suggested that the effect might be slightly smaller during the first two 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 based on our conservative approach.

Results

Baseline characteristics

The original data included 24894 measuring sessions from 6784 patients during the years 1990-2009. During the first recorded session 6761 patients had their ABI measured and 3426 had their 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 gender ratio in each TP and ABI group.

Association of ABI to 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 0.9-1.3 being 8.9 years. The unadjusted cumulative survival probabilities with standard error in the four ABI groups are presented in table I in the supplemental material.

The age and sex-adjusted 10-year survival for the patients with ABI<0.5, 0.5-0.89, 0.9-1.3 and >1.3 was 27.6%, 38.3%, 43.2% and 15.3%, respectively. Compared to ABI 0.9-1.3, ABI>1.3 was the most significant factor predicting mortality (HR 2.2, 95%CI 1.9-2.6; p<0.0001) followed by <0.5 (HR 1.5, 95%CI 1.4-1.7; p<0.0001) and 0.5-0.89 (HR 1.1 95%CI 1.0-1.2, p=0.003). The differences in patient outcome on different ABI levels are illustrated by the age and sex-adjusted Cox proportional hazard models in figure 1.

When ABI measurements were analysed as a continuous variable, the age and sex adjusted HR was 0.924 (95%CI 0.856-0.996, p=0.039).

The age and sex adjusted survival according to ABI results for patients measured after 1996 that also had TP measurements available is presented in figure I of the supplementary material.

Association of TP to Survival

The unadjusted median survival with 95% confidence intervals in the four TP groups are depicted in table II. For the patients with TP<30mmHg, the median survival was only 3.8 years, when it was 9.6 years in the patients with TP>80mmHg. The unadjusted cumulative survival probabilities in each TP group are presented in table II in the supplemental material.

The 10-year age and sex-adjusted survival for the patients with TP<30mmHg, 30-

49mmHg, 50-79mmHg and ≥80 mmHg was 19.6%, 27.8%, 39.0% and 43.9% respectively. Compared to TP≥80mmHg, the highest association to mortality was in patients with TP<30mmHg (HR 2.0; 95%CI 1.7-2.2, p<0.0001), followed by 30-49mmHg (HR 1.6; 95%CI 1.4-1.8, p<0.0001), and 50-79mmHg (HR 1.1; 95%CI 1.0-1.3, p=0.053). Figure 2 shows the age and sex-adjusted Cox proportional hazard models according to TP as well as the age and sex-adjusted 5- and 10-year survival rates.

When TP measurements were analysed as a continuous variable, the age and sex adjusted HR was 0.992 (95%CI 0.991-0.993, p<0.0001).

Association of TP to survival in patients with ABI 0.9-1.3

642 patients had a normal ABI (0.9-1.3). 120 (18.7%) of them had TP <50mmHg. Moreover, 282 patients (43.9%) had TP<80mmHg. The unadjusted median survival of patients with TP<50mmHg was 3.9 years (95%CI 2.7-5.1 years), for 50-79mmHg 7.3 years (95%CI 5.8-8.9 years), and for ≥80mmHg 9.9 years (95%CI 9.0-10.8 years). The unadjusted cumulative survival probabilities in the three TP groups are presented in table III in the supplemental material.

The 10-year age and sex-adjusted survival for the patients with TP<50mmHg, 50-79mmHg and ≥80mmHg was 19.6%, 40.3% and 48.4%. When compared to the patients with TP≥80mmHg, the HR for the patients with TP<50mmHg was 2.3 (95%CI 1.8-3.0, p<0.0001) and for the patients with TP 50-79mmHg 1.3 (95%CI 1.0-1.6, p=0.083). The age and sex-adjusted Cox proportional hazard models according to TP as well as the hazard ratios and 5 and 10-year survival rates of patients with ABI 0.9-1.3 are shown in figure 3.

The impact of diabetes on the association of ABI and TP to survival

There were 4130 patients included in the study between 2000-2009. 1214 (29.4%) of

them had purchased at least one package of diabetes medication during the study period and were categorised as having diabetes. The distribution of diabetes medication use in the ABI and TP groups is shown in supplementary table IV. The age, sex and diabetes adjusted HR of patients with ABI<0.5 was 1.5 (95%CI 1.4-1.7, p<0.0001), with ABI 0.5-0.89 1.2 (95%CI 1.1-1.4, p<0.0001), and with ABI >1.3 2.1 (95%CI 1.7-2.6, p<0.0001) when compared to the patient group with ABI 0.9-1.3

3012 patients had TP measured during the first measuring session between 2000-2009. The age, sex and diabetes adjusted HR of patients with TP<30mmHg was 1.8 (95%CI 1.6-2.1, p<0.0001), with TP 30-49 mmHg 1.5 (95%CI 1.3-1.7, p<0.0001), and with TP 50-79 mmHg 1.1 (95%CI 1.0-1.3, p=0.109), when compared to the patients with TP≥80mmHg (supplementary figure II).

There were 614 patients with ABI 0.9-1.3 and a TP measurement from the first visit 2000-2009. 18.1% of them had TP<50mmHg. The age, sex and diabetes adjusted HR of patients with ABI 0.9-1.3 and TP<50mmHg was 2.4 (95%CI 1.9-3.2, p<0.0001), and of the patients with TP 50-79mmHg 1.3 (95%CI 1.0-1.7, p=0.030), when compared to the patients with ABI 0.9-1.3 and TP≥80mmHg.

<u>The impact of interventions on the association of ABI and TP to survival</u>

5420 (80.1%) patients had undergone a lower limb intervention during the study period. The distribution of patients that had a revascularization in the ABI and TP groups is shown in supplementary table V. 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<0.0001), for ABI 0.5-0.89 1.1 (95%CI 1.0-1.2, p=0.129), and for patients with ABI>1.3 2.1 (95%CI 1.8-2.5, p<0.0001) when compared to the patients with ABI 0.9-1.3.

The age, sex and lower limb intervention adjusted HR of patients with TP<30mmHg was 2.0 (95%CI 1.7-2.3, p<0.0001), TP 30-49mmHg 1.6 (95%CI 1.4-1.8, p<0.0001) and for patients with TP 50-79mmHg 1.2 (95%CI 1.0-1.3, p=0.042) when compared to the patients with TP≥80mmHg (supplementary figure III). The age, sex and lower limb intervention adjusted HR of patients with ABI 0.9-1.3 and TP<50mmHg was 2.1 (95%CI 1.6-2.8, p<0.0001) and for patients with ABI 0.9-1.3 and TP 50-79mmHg 1.2 (95%CI 0.9-1.6, p=0.144), when compared to the patients with ABI 0.9-1.3 and TP≥80mmHg.

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 proportion of cardiovascular deaths was 59.9% and it was the highest in the patients with an ABI<0.5 (63.3%) (table IV). The corresponding percentage for the patients with ABI 0.5-0.89 was 58.1%, ABI 0.9-1.3 54.5%, and for 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<30mmHg (64.6%, n=525). For patients with TP 30-49mmHg it was 60.8%, and for TP 50-79mmHg 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 mmHg. 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. 18.7% of the patients with normal ABI (0.9-1.3) had a TP<50mmHg and survival in this group was significantly lower than in the group with normal ABI and TP 50-79mmHg and TP≥80 mmHg. Thus, even patients with a normal ABI may have substantial atherosclerotic disease which 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 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[17].

Previous studies on patients with CLTI or those referred for invasive treatment have suggested that TP or TBI 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 or the ABI do[20,21]. A recent 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 is 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 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].

MAC 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. It is also noteworthy to realize, that amongst patients with suspected vascular disease there may be hyperglycaemic 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 to always measure also TP, 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 since 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 1.3-1.4[30]. Although recent publications have stated the highest normal value as 1.4, we selected 1.3 in order to avoid highly probable medial calcinosis patients with ABI 1.3-1.4 in the group with normal ABI.

The selected threshold values for the TP groups were 30 and 50mmHg since those have been determined as the critical cut-off points for TP[10,31]. However, evidence of the threshold value for a normal TP is lacking. According to our results, the use of 50mmHg 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 to survival is gradual. This means that all strict cut-off 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 judgement.

The results of the association of ABI and TP groups to 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 to survival, especially in the case of ABI, since the association to survival is not linear.

The results of this study concern adult patients with a suspicion of 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 is 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, all of which may not 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 standardised vascular laboratory measurements by extremely experienced vascular nurses as they perform over 7000 measurements annually. Furthermore, comprehensive long term mortality data is 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 80mmHg in this study. However, it should be noted, that research is lacking on the optimal cut off 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.

Conclusion

In this study we show a strong association between TP and survival and TP and mortality from cardiovascular causes in a patient dataset 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 non-invasive 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<50mmHg. 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.

Acknowledgments

Acknowledgments: None.

Sources of Funding

This work was supported by the Finnish Society for Angiology and the University of Helsinki doctoral programme in clinical research in the form of a travel grant. (ML)

Conflicts of interest

The authors declare that there is no conflict of interest.

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Table I. Age and gender distribution of patients

ABI	**<0.5**	**0.5-0.89**	**0.9-1.3**	**>1.3**	**p-value**
Mean Age, years (standard deviation)	71 (12)	68 (11)	67 (12)	70 (13)	**p**<0.0001*
Female	1365 (50%)	929 (37%)	338 (27%)	98 (40%)	**p**<0.0001‡
Male	1369 (50%)	1597 (63%)	918 (73%)	147 (60%)	
Total	2734	2526	1256	245	
TP (mmHg)	**<30**	**30-49**	**50-79**	**>80**	**p-value**
Mean Age, years (standard deviation)	74 (11)	71 (11)	69 (11)	67 (11)	p<0.0001†
Female	554 (50%)	352 (45%)	356 (40%)	192 (30%)	p<0.0001‡
Male	550 (50%)	428 (55%)	539 (60%)	455 (70%)	
Total	1104	780	895	647	

Mean age and gender distribution of patients according to ABI and TP. * 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 to the group with an ABI of <0.5 and 0.5-0.89. † In the post hoc tests the difference in age was significant between all the groups. ‡ P-values refer to the comparisons between the four groups. P-values were calculated using Chi-squared test for categorical variables and one-way ANOVA test for continuous variables.

Table II. Survival of patients according to ABI and TP group.

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

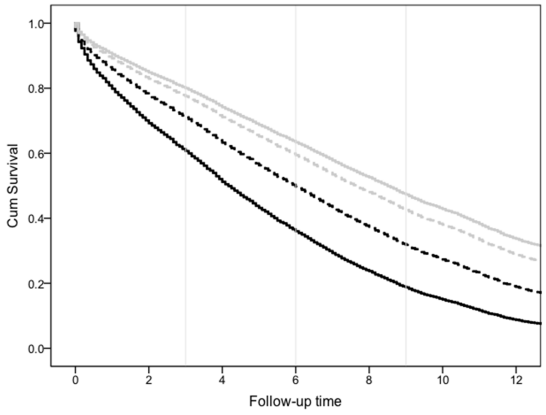
Unadjusted median survival of patients in each ABI and TP group with 95% confidence intervals (CI) from the Kaplan-Meier analysis.

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

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

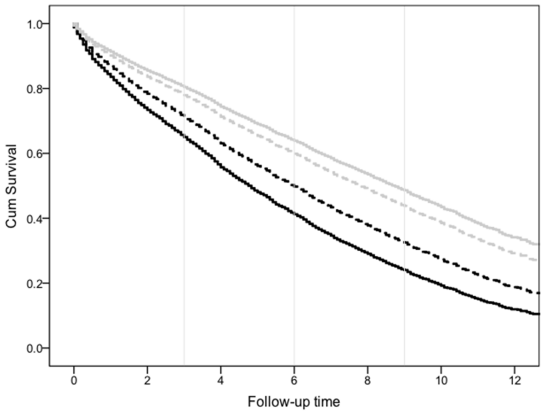
Causes of death. Number of patients in each group and percentage of deaths of patients with a known underlying cause of death with 95% confidence intervals (CI). Patients are grouped

according to ABI and TP measurement. *Total number of patients in each group with a known underlying cause of death.



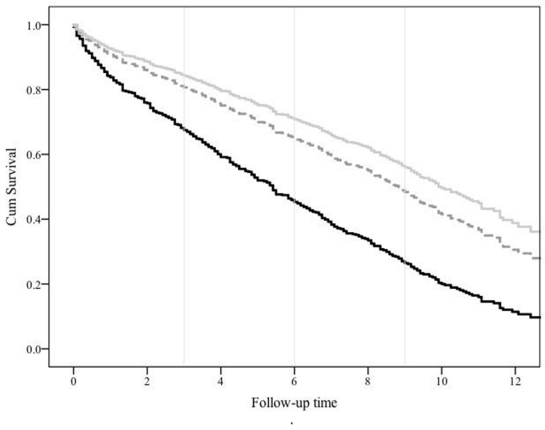
ABI group	5-year survival	10-year survival	Hazard ratio (95% CI)	p-value
<0.5	56.8%	27.6%	1.5 (1.4-1.7)	<0.0001
0.5-0.89	65.6%	38.3%	1.1 (1.0-1.2)	0.003
0.9-1.3	69.2%	43.2%		reference
>1.3	43.8%	15.3%	2.2 (1.9-2.6)	<0.0001

Figure 1.



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

Figure 2.



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

Figure 3.

SUPPLEMENTAL MATERIAL

SUPPLEMENTAL TABLES

Supplemental table I: Cumulative survival of patients in each ABI group.

ABI group	3 years	6 years	9 years	12 years
ABI <0.5	0.656 (0.014)	0.423 (0.014)	0.264 (0.014)	0.156 (0.014)
ABI 0.5-0.89	0.740 (0.012)	0.559 (0.013)	0.415 (0.014)	0.296 (0.015)
ABI 0.9-1.3	0.789 (0.016)	0.632 (0.019)	0.474 (0.021)	0.312 (0.027)
ABI >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 written in parentheses.

Supplemental table II: Cumulative survival of patients in each TP group

TP group	3 years	6 years	9 years	12 years
TP <30 mmHg	0.575 (0.015)	0.356 (0.014)	0.226 (0.013)	0.122 (0.013)
TP 30-49 mmHg	0.681 (0.017)	0.482 (0.018)	0.309 (0.018)	0.210 (0.019)
TP 50-79 mmHg	0.791 (0.014)	0.618 (0.016)	0.456 (0.017)	0.336 (0.021)
TP ≥80mmHg	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 written in parentheses.

Supplemental table III: Cumulative survival of patients with ABI 0.9-1.3 in the three TP groups

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

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

Supplemental table IV: Distribution of diabetes medication use in the ABI and 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%)	p<0.0001
Diabetes medication	448 (30%)	446 (29%)	217 (23%)	103 (57%)	
Total	1472	1538	939	179	

TP (mmHg)	**<30**	**30-49**	**50-79**	**>80**	**p-value**
No diabetes medication	576 (65%)	414 (60%)	581 (71%)	460 (75%)	p<0.0001
Diabetes medication	309 (35%)	281 (40%)	242 (29%)	150 (25%)	
Total	885	695	823	610	

Number and percentage of patients in each ABI and TP group that use diabetes medication. Data includes patients that had first ABI and TP measurements after 2000 and medication data available. P-value was calculated using Chi-squared test.

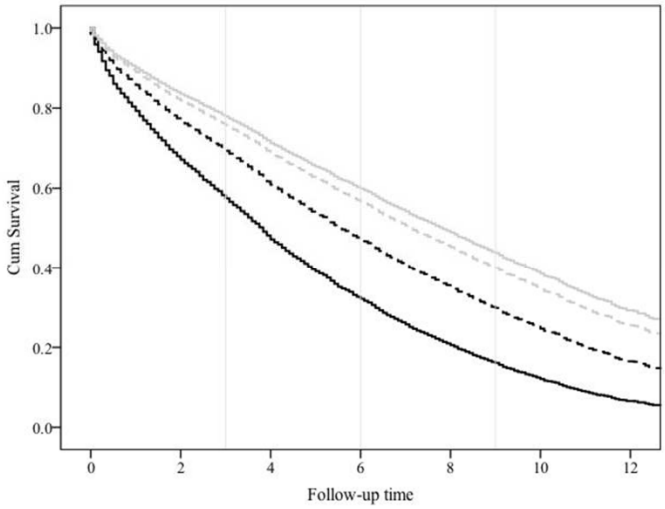
Supplemental table V: Distribution of lower limb revascularization in the ABI and TP groups.

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%)	p<0.0001
Revascularization	2505 (92%)	2098 (83%)	611 (49%)	199 (81%)	
Total	2734	2526	1256	245	

TP (mmHg)	**<30**	**30-49**	**50-79**	**>80**	**p-value**
No revascularization	74 (7%)	85 (11%)	228 (26%)	320 (50%)	p<0.0001
Revascularization	1030 (93%)	695 (89%)	667 (74%)	327 (50%)	
Total	1104	780	895	647	

Number and percentage of patients in each ABI and TP group that had a revascularization procedure during the study period. P-value was calculated using Chi-squared test.

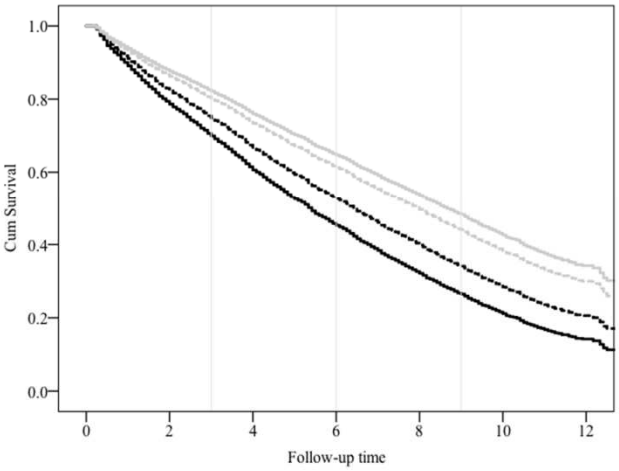
Supplementary figure I.



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

The age and sex adjusted survival according to ABI results for patients measured after 1996 that also had TP measurements available. Data includes 3417 patients.

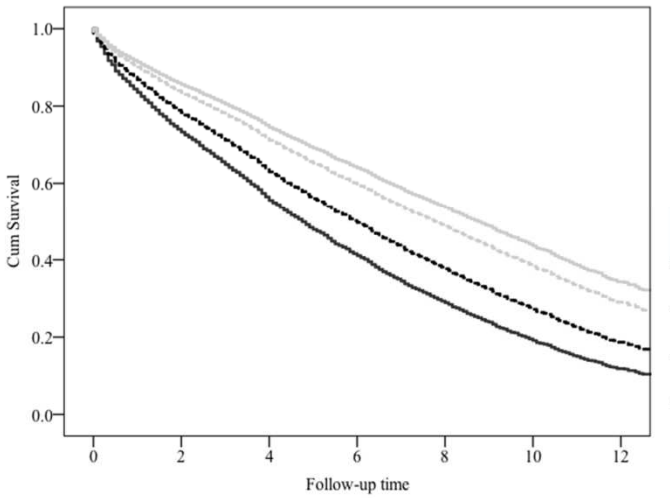
Supplementary figure II.



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

12-year survival in the four TP groups. Age, sex and use of diabetes medication adjusted Cox proportional hazard model according to TP with hazard ratios with 95% confidence intervals (CI) and p-values. To obtain the hazard ratio the other TP groups were compared to the group with TP ≥80 mmHg. P-values were calculated using the Wald test. The analysis included 3012 patients in total.

Supplementary figure III.



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

12-year survival in the four TP groups. Age, sex and revascularization adjusted Cox proportional hazard model according to TP with hazard ratios with 95% confidence intervals (CI) and p-values. To obtain the hazard ratio the other TP groups were compared to the group with TP ≥80 mmHg. P-values were calculated using the Wald test. The analysis included 6769 patients in total.