Bilateral low systolic toe pressure and toe-brachial index are associated with long-term mortality in patients with peripheral artery disease

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ABSTRACT

Objective: Based on our previous reports, ipsilateral systolic toe pressure (STP) and toe-brachial index (TBI) have a strong association with midterm cardiovascular and overall mortality as well as with amputation-free survival in patients with symptomatic lower extremity peripheral artery disease (PAD). The effect of the often overlooked contralateral lower limb on patient outcome remains unknown. This study aimed to resolve the significance of contralateral STP (CL_STP) and contralateral TBI for long-term overall and cardiovascular mortality.

Methods: This is a retrospective cohort study of 727 consecutive patients with symptomatic lower extremity PAD. All patients admitted to the Department of Vascular Surgery at Turku University Hospital for digital subtraction angiography between January 2009 and August 2011 and for whom STP measurements were available were recruited and observed for up to 7 years. Dates and causes of death were collected from the national cause of death registry of Statistics Finland.

Results: In the study cohort, STP was <30 mm Hg in 67 contralateral limbs and 227 ipsilateral limbs. CL_STP <30 mm Hg resulted in a 60-month estimated freedom from cardiovascular death and overall survival of 39% (standard deviation [SD], 0.57) and 25% (SD, 0.41), respectively, and contralateral TBI <0.25, of 45% (SD, 0.54) and 36% (SD, 0.54), respectively. Cumulative freedom from cardiovascular death and overall survival at 60 months for patients with ipsilateral STP <30 mm Hg varied by CL_STP as follows: CL_STP <30 mm Hg: 41% (SD, 0.58) and 25% (SD, 0.43); CL_STP of 30 to 49 mm Hg: 56% (SD, 0.49) and 44% (SD, 0.49); STP ≥50 mm Hg: 62% (SD, 0.52) and 47% (SD, 0.52), respectively. In Cox regression analysis, low STP or TBI of either extremity was associated with significant ($P < .001$) risk of death for cardiovascular or any reason.

Conclusions: Low STP and TBI of both contralateral and ipsilateral lower extremities are associated with high cardiovascular and overall mortality in symptomatic PAD patients. Bilaterally low STP and TBI are associated with a particularly poor prognosis. (J Vasc Surg 2019;70:1994-2004.)

Keywords: Contralateral lower extremity; Toe pressure; Toe-brachial index; Mortality; Peripheral artery disease

Atherosclerosis is the most frequent single cause of death in Western countries. Atherosclerotic disease can be localized into three major vascular beds: cardiac, cerebral, and the extremities. Peripheral artery disease (PAD) is associated with a significant burden of atherosclerosis in cardiac vessels and cerebral circulation.[1] The significance of PAD in low-income countries is increasing.[2,3] In 2010, >200 million people were estimated to have PAD.[4] Both symptomatic and asymptomatic PAD patients have a threefold risk of death and other adverse cardiovascular events compared with people without the disease.[5-7] Patients with asymptomatic low ankle-brachial index (ABI < 0.9) are at increased risk for cardiovascular events, and chronic limb-threatening ischemia (CLTI) further increases the risk of limb loss, adverse cardiovascular events, and death, with myocardial infarction and ischemic stroke accounting for the majority of cardiovascular deaths.[8-11] Short-term and midterm mortality in patients with CLTI is known to be up to four times higher than in patients with intermittent claudication.[12,13]

In a clinical setting, peripheral pressure measurements—systolic ankle pressure (SAP), ABI, systolic toe pressure (STP), and toe-brachial index (TBI)—are widely used for evaluation of the patient and clinical decision-making. The European Society of Cardiology and European Society for Vascular Surgery guidelines on the diagnosis and treatment of PAD recommend ABI as a first-line test for screening and diagnosis of PAD.[14] The prognostic value of ABI is well established and associated with mortality in a U-shaped manner, with both low and abnormally high (>1.3) indices being associated with poor outcome.[15,16] Severe

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arterial stiffening and incompressibility related to diabetes, chronic kidney disease, and high age are the main culprits for this nonlinear association.[15-18] Significant stiffening of the digital arteries is rare, and TBI and STP are often measured in conjunction with SAP and ABI. As an independent clinical workup, STP is an inexpensive, readily available first-line measurement for evaluation of PAD with a small interobserver variability and sufficient reproducibility.[19-22] Nevertheless, toe pressures are not available for patients with extensive tissue loss in the foot, and toes may have previously been amputated. In diabetics, first and second toe pressures have been shown to be comparable, though, so that an amputated great toe does not necessarily preclude a valid STP measurement.[23] Although TBI has been shown to be associated with mortality, its relevant threshold values are not clearly established.[24,25]

STP of the clinically symptomatic or ipsilateral lower extremity has recently been shown to be associated with short-term to midterm cardiovascular mortality, overall mortality, and amputation-free survival.[26,27] As associations of systolic pressure and pressure indices of the contralateral lower extremity with survival have not been studied earlier, we aimed to evaluate the significance of contralateral STP (CL_STP) and contralateral TBI (CL_TBI) for patient outcome.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Bilaterally low systolic toe pressure (STP) and toe-brachial index (TBI) were associated with high cardiovascular and overall mortality in 727 peripheral artery disease patients. Freedom from cardiovascular death at 60 months was 39% (standard deviation, 0.57) and overall survival 25% (standard deviation, 0.41) in patients with contralateral STP <30 mm Hg.
- **Take Home Message:** STP and TBI of lower extremities may be used for risk assessment in peripheral artery disease patients. Those with bilaterally low STP and TBI are at high risk of death.

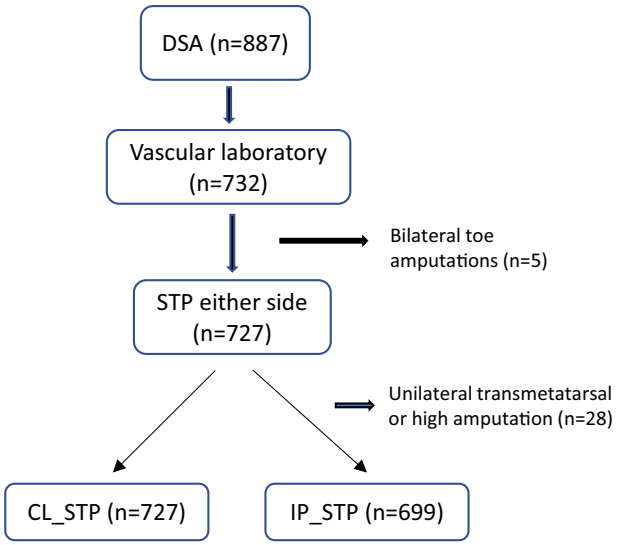

Fig 1. Flow chart for the study. There were 887 patients who entered the study; any peripheral pressure measurements were available for 732 patients, unilateral systolic toe pressure (*STP*) for 699 patients, and bilateral STP for 727 patients. Extremities with no toes were assigned as ipsilateral. *CL,* Contralateral; *DSA,* digital subtraction angiography; *IP,* ipsilateral.

METHODS

Study cohort. Turku University Hospital serves as a primary referral center for 477,000 and as a tertiary referral center for 870,000 inhabitants. During recruitment between January 2009 and August 2011, there were 887 symptomatic (Rutherford category 2-6) patients with acute or chronic onset of PAD symptoms referred to the Department of Vascular Surgery who underwent digital subtraction angiography (DSA). Patients were included in the study irrespective of earlier PAD history or any previous interventions. All patients were retrospectively reviewed. Standardized peripheral pressure measurements were not available for urgent cases outside office hours. Acutely presenting patients with thromboembolic arterial obstruction were thus excluded from the study. A significant number of patients had bilateral CLTI with clinically indistinguishable severity between limbs. Thus, the extremity with the lowest or no measurable STP was defined as the ipsilateral extremity, and the extremity with the highest STP was defined as the contralateral extremity. The study protocol was approved by the local ethical committee of the Hospital District of Southwest Finland. Because of the retrospective nature of the study, patient consent was not required.

Vascular laboratory. Standardized noninvasive hemodynamic measurements were carried out by vascular technicians at the Turku University Hospital Vascular Laboratory. A Nicolet VasoGuard (Nicolet Vascular Inc, Madison, Wisc) photoplethysmography device was used for all measurements. Measurements were obtained from supine patients with preheated feet at heart level. When stable signals were obtained, brachial, ankle, and digital cuffs were inflated until disappearance of the photoplethysmography signal or up to 250 mm Hg. Brachial, ankle, and toe pressures were determined by gradual deflation of the cuffs to the moment of reappearance of a pulsatile signal. Toe pressure was preferentially measured from the great toe or from the nearest available toe.

Table I. Demographics of patient cohort (727 patients) by contralateral systolic toe pressure (*CL_STP*) categories

	CL_STP			
	<30 mm Hg	30-49 mm Hg	≥50 mm Hg	*P* value[a]
Age, years	75.5 (11)	75.6 (11)	74.7 (10)	.622
Female sex	26 (39)	52 (40)	224 (42)	.783
CAD	33 (49)	58 (44)	221 (42)	.357
CVD	11 (16)	17 (13)	95 (18)	.405
HT	47 (70)	98 (75)	361 (68)	.540
DM	38 (57)	58 (44)	202 (38)	.011
COPD	6 (9.0)	14 (11)	72 (14)	.495
Sleep apnea	5 (7.5)	10 (7.6)	29 (5.5)	.499
Renal dysfunction	8 (12)	13 (9.9)	49 (9.3)	.728
Statin use	21 (31)	48 (37)	200 (38)	.600
Antithrombotic	42 (69)	87 (66)	380 (72)	.401
Anticoagulation	16 (24)	31 (24)	114 (22)	.651
Smoking history	10 (15)	31 (24)	171 (32)	.003
Conservative	22 (33)	26 (20)	81 (15)	.003
Endovascular	36 (54)	73 (56)	325 (61)	.267
Surgery	21 (31)	56 (43)	195 (37)	.258
CL_ABI	0.884 (0.80)	0.940 (0.65)	1.04 (0.51)	.050
CL_STP	15.3 (11)	39.4 (8.8)	82 (24)	<.001
IP_ABI	0.694 (0.76)	0.688 (0.65)	0.756 (0.58)	.439
IP_STP	11.9 (11)	27.0 (14)	48.4 (23.9)	<.001
No. of cases	67	131	529	

CAD, Coronary artery disease; *CL_ABI,* contralateral ankle-brachial index; *COPD,* chronic obstructive pulmonary disease; *CVD,* cerebrovascular disease; *DM,* diabetes; *HT,* hypertension; *IP_ABI,* ipsilateral ankle-brachial index; *IP_STP,* ipsilateral systolic toe pressure.
Categorical variables are presented as number (%). Continuous variables are presented as mean (standard deviation). Subsequent treatment modalities (endovascular, open surgical): percentage receiving one or more revascularizations of given type during follow-up. Mean (standard deviation) of ABI and STP is shown in addition to baseline medication and medical conditions.
[a]Fisher exact test.

Table II. Causes of death by contralateral systolic toe pressure (*CL_STP*) categories

	CL_STP				
Cause of death[a]	<30 mm Hg	30-49 mm Hg	≥50 mm Hg	Total	*P* value[b]
Cardiovascular	35 (71)	50 (64)	125 (57)	210 (61)	<.001
Malignant disease	3 (6.1)	9 (12)	39 (18)	51 (15)	.832
Endocrine	1 (2.0)	7 (9.0)	12 (5.5)	20 (5.8)	.138
Dementia	4 (8.1)	3 (3.8)	6 (2.7)	13 (3.7)	.020
Gastroenterologic	2 (4.1)	4 (5.1)	10 (4.5)	16 (4.6)	.532
Miscellaneous	1 (2.0)	1 (1.3)	5 (2.3)	7 (2.0)	.456
Accident or violent	1 (2.0)	3 (3.8)	8 (3.6)	12 (3.5)	.705
Pulmonary	0 (0.0)	1 (1.3)	6 (2.7)	7 (2.0)	1.000
Urologic	1 (2.0)	0 (0.0)	3 (1.4)	4 (1.2)	.442
Alcohol	0 (0.0)	0 (0.0)	3 (1.4)	3 (0.9)	1.000
Neurologic	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.6)	.208
Not available	0 (0.0)	0 (0.0)	2 (0.90)	2 (0.6)	1.000
Total	67	131	529	727	

Values are reported as number (%).
[a]According to Statistics Finland.
[b]Fisher exact test.

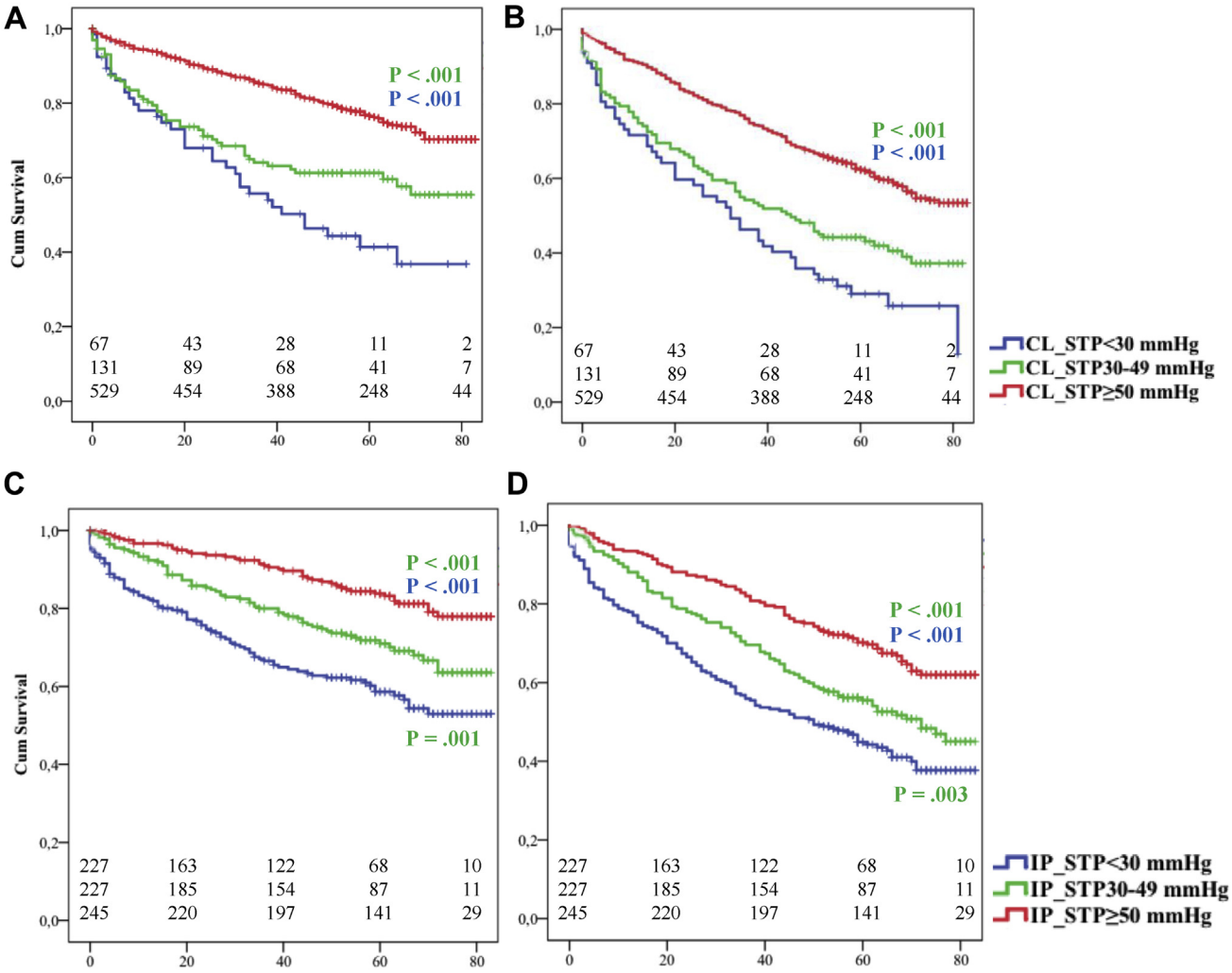

Fig 2. Kaplan-Meier survival curves showing freedom from cardiovascular death **(A)** and overall survival **(B)** by contralateral systolic toe pressure (*CL_STP*) and freedom from cardiovascular death **(C)** and overall survival **(D)** by ipsilateral systolic toe pressure (*IP_STP*). Numbers of patients at risk entering intervals are shown at *bottom*. *P* values significant in pairwise comparison are shown in color corresponding to compared curve.

Data collection and statistical analysis. The primary end point for the study was death for any reason. The secondary end point was death due to cardiovascular reasons, defined as any *International Classification of Diseases, Tenth Revision*-coded immediate cause of death between I00 and I42.5 and I42.7 and I99. Dates and causes of death were obtained from Statistics Finland. Demographic patient data were retrospectively collected from the hospital electronic database. Baseline characteristics at the time of DSA, which served as the index date for follow-up, were used. *International Classification of Diseases, Tenth Revision*-coded diagnoses were registered. Risk factors collected for analysis included coronary artery disease, cerebrovascular disease, hypertension, current smoking, diabetes, sleep apnea, chronic obstructive pulmonary disease, end-stage renal disease, dyslipidemia, SAP, ABI, STP, TBI, and serum creatinine concentration. Baseline medication including statins, clopidogrel, aspirin, warfarin, and novel anticoagulants was registered from within electronic patient files. For the purpose of analysis, toe pressure was pooled into three categories (<30 mm Hg, 30-49 mm Hg, and ≥50 mm Hg [reference]), and TBI was pooled into three categories (<0.25, 0.25-0.49, and ≥0.50 [reference]). Contralateral and ipsilateral limb pressures were analyzed separately as described before.

All statistical analyses were performed using SPSS version 25 (IBM, Armonk, NY) with R statistics extension. Group-specific baseline characteristics were presented as percentages and continuous variables as mean ± standard deviation (SD). Group variables were compared using Fisher exact test. Normality of distribution for continuous variables was tested with a Shapiro-Wilk test. Variables were then compared by analysis of

Table III. Association between systolic toe pressure (*STP*) and toe-brachial index (*TBI*) of contralateral and ipsilateral lower extremity with cardiovascular and overall mortality in multivariable analysis

	STP	HR	95% CI	*P* value		TBI	HR	95% CI	*P* value
Cardiovascular mortality	Age	1.018	1.01-1.06	.05	Cardiovascular mortality	Age	1.017	1.00-1.03	.12
	CAD	1346	1.02-1.77	.35		CAD	1.365	1.04-1.80	.27
	HT	1318	0.957-1.82	.91		HT	1.284	0.932-1.77	1.00
	DM	1.222	0.920-1.63	1.00		DM	1.228	0.923-1.63	1.00
	Renal insufficiency	1.461	0.992-2.15	.55		Renal insufficiency	1.443	0.980-2.13	.63
	Statin use	0.734	0.549-0.982	.38		Statin use	0.738	0.551-0.988	.41
	Smoking history	0.466	0.320-0.678	<.001		Smoking history	0.463	0.318-0.674	<.001
	STP contralateral limb					**TBI contralateral limb**			
	≥50 mm Hg	Reference				≥0.50	Reference		
	30-49 mm Hg	1.928	1.38-2.68	<.001		0.25-0.49	1.549	1.14-2.10	.05
	<30 mm Hg	2.771	1.89-4.08	<.001		<0.25	2.527	1.71-3.74	<.001
	C index (SD): 0.688 (0.021)					C index (SD): 0.681 (0.021)			
	Age	1.019	1.01-1.02	.08		Age	1.018	1.01-1.03	.08
	CAD	1.403	1.06-1.87	.20		CAD	1.428	1.07-1.90	.14
	HT	1.199	0.860-1.67	1.00		HT	1.140	0.819-1.59	1.00
	DM	1.279	0.954-1.72	1.00		DM	1.242	0.926-1.67	1.00
	Renal insufficiency	1.656	1.10-2.49	.15		Renal insufficiency	1.531	1.03-2.29	.37
	Statin use	0.738	0.547-0.994	.45		Statin use	0.771	0.573-1.04	.87
	Smoking history	0.486	0.333-0.708	<.001		Smoking history	0.474	0.325-0.691	<.001
	STP ipsilateral limb					**TBI ipsilateral limb**			
	≥50 mm Hg	Reference				≥0.50	Reference		
	30-49 mm Hg	1.642	1.11-2.43	.13		0.25-0.49	1.981	1.08-3.63	.27
	<30 mm Hg	2.870	1.99-4.14	<.001		<0.25	3.296	1.81-6.02	<.001
	C index (SD): 0.702 (0.021)					C index (SD): 0.695 (0.021)			
Overall mortality	Age	1.020	1.01-1.03	<.001	Overall mortality	Age	1.018	1.01-1.03	<.001
	CAD	1.116	0.900-1.38	1.00		CAD	1.125	0.908-1.39	1.00
	HT	1.219	0.956-1.56	1.00		HT	1.185	0.929-1.51	1.00
	DM	1.042	0.834-1.30	1.00		DM	1.049	0.838-1.31	1.00
	Renal insufficiency	2.118	1.55-1.14	.05		Renal insufficiency	1.515	1.11-2.07	.09
	Statin use	0.740	0.590-0.929	.09		Statin use	0.743	0.592-0.933	.10
	Smoking history	0.568	0.434-0.743	<0.001		Smoking history	0.567	0.434-0.741	<0.001
	STP contralateral limb					**TBI contralateral limb**			
	≥50 mm Hg	Reference				≥0.50	Reference		
	30-49 mm Hg	1.788	1.38-2.32	<.001		0.25-0.49	1.624	1.29-2.05	<.001
	<30 mm Hg	2.444	1.78-3.36	<.001		<0.25	2.077	1.50-2.88	<.001
	C index (SD): 0.658 (0.017)					C index (SD): 0.653 (0.016)			
	Age	1.019	1.01-1.03	<.001		Age	1.020	1.01-1.03	<.001
	CAD	1.156	0.926-1.44	1.00		CAD	1.172	0.939-1.46	1.00
	HT	1.150	0.893-1.48	1.00		HT	1.106	0.859-1.42	1.00
	DM	1.076	0.855-1.36	1.00		DM	1.052	0.835-1.33	1.00
	Renal insufficiency	1.714	1.24-2.37	.01		Renal insufficiency	1.620	1.18-2.23	.03

Table III. Continued.

STP	HR	95% CI	*P* value	TBI	HR	95% CI	*P* value
Statin use	0.745	0.590-0.940	.13	Statin use	0.774	0.613-0.977	.31
Smoking history	0.569	0.433-0.748	<.001	Smoking history	0.552	0.419-0.726	<.001
STP ipsilateral limb				**TBI ipsilateral limb**			
≥50 mm Hg	Reference			≥0.50	Reference		
30-49 mm Hg	1.468	1.10-1.96	.09	0.25-0.49	2.011	1.29-3.15	.02
<30 mm Hg	2.235	1.70-2.95	<.001	<0.25	2.735	1.74-4.29	<.001
C index (SD): 0.659 (0.016)				C index (SD): 0.655 (0.017)			

CAD, Coronary artery disease; *CI,* confidence interval; *DM,* diabetes; *HR,* hazard ratio; *HT,* hypertension; *SD,* standard deviation.
Reference ≥50 mm Hg for STP and ≥0.50 for TBI categories. Confounding factors forced into Cox regression analysis were selected according to significance in univariate analysis. Age: HR per 1-year increase.

variance as continuous variables in each group were normally distributed.

Survival was assessed by Kaplan-Meier and log-rank statistics. A Cox regression analysis was performed to assess the final predictive value of factors associated with survival. Factors with $P < .2$ in univariate analysis were forced into a Cox proportional hazards model. Multivariable analysis was carried out to assess the risk of death. To reduce the probability of false-positive observations, *P* values were Bonferroni adjusted for multiple exposures. $P < .05$ was considered statistically significant.

RESULTS

Standardized peripheral pressure measurements—SAP, STP, or both—were available for 732 patients. STP and TBI of either lower extremity were available for 727 patients and for both extremities of 699 patients; 28 patients had undergone previous amputation or had extensive tissue loss in the foot (Fig 1).

Demographic factors by corresponding CL_STP categories (727 patients) for the study cohort are shown in Table I. Risk factors did not significantly differ between CL_STP categories, with the exception of diabetes and smoking history. There were more diabetics and less ever-smokers with decreasing CL_STP. The proportion of patients who eventually did not receive invasive treatment also differed significantly between groups, with an increasing percentage of patients treated conservatively (17.7% of all cases) as CL_STP decreased. Of all cases, 59.7% underwent at least one endovascular revascularization, 37.4% at least one surgical revascularization, and 14.9% at least one hybrid revascularization during follow-up.

Causes of death. Median follow-up time was 55.5 months for the whole study cohort and 67.0 months for survivors. At 7 years, 347 patients (48%) had died. Cardiovascular causes of death were most common, accounting for 210 (61%) deaths. Cardiovascular causes of death were significantly ($P < .001$) more common among patients with CL_STP <30 mm Hg (71%) compared with those with higher CL_STP. Furthermore, patients with CL_STP <30 mm Hg died more frequently of reasons associated with dementia (Table II).

STP and mortality. Estimated freedom from cardiovascular death and overall survival at 60 months was significantly better in patients with CL_STP ≥50 mm Hg (75% [SD, 0.46] and 60% [SD, 0.46], respectively) compared with other CL_STP categories ($P < .001$). Freedom from cardiovascular death and overall survival differed significantly between all ipsilateral STP (IP_STP) categories ($P < .001$-.003; Fig 2).

In multivariable analysis, the risk of all-cause death and cardiovascular death increased significantly with CL_STP <30 mm Hg and 30 to 49 mm Hg ($P < .001$) compared with CL_STP ≥50 mm Hg. IP_STP <30 mm Hg but not 30 to 49 mm Hg significantly increased ($P < .001$) the risk of both cardiovascular and overall mortality compared with IP_STP ≥50 mm Hg (Table III).

Estimated freedom from cardiovascular death ($P = .005$) and overall survival ($P = .002$) of patients with IP_STP <30 mm Hg and CL_STP ≥50 mm Hg (62% [SD, 0.52] and 47% [SD, 0.52], respectively) were significantly better compared with those with STP <30 mm Hg bilaterally (41% [SD, 0.58] and 25% [SD, 0.43], respectively). Overall survival of patients with IP_STP of 30 to 49 mm Hg and CL_STP ≥50 mm Hg (57% [SD, 0.52]) was significantly better compared with those with CL_STP of 30 to 49 mm Hg (38% [SD, 0.47]; $P = .014$; Fig 3).

TBI and mortality. Estimated freedom from cardiovascular death at 60 months differed significantly between all CL_TBI categories ($P < .001$-.001), and overall survival was significantly higher for CL_TBI ≥0.50 (65% [SD, 0.58]) compared with lower TBI categories ($P < .001$). All ipsilateral TBI (IP_TBI) categories differed significantly with respect to freedom from cardiovascular death and overall survival ($P < .001$-.013; Fig 4).

In multivariable analysis, the risk of all-cause death and cardiovascular death increased significantly with

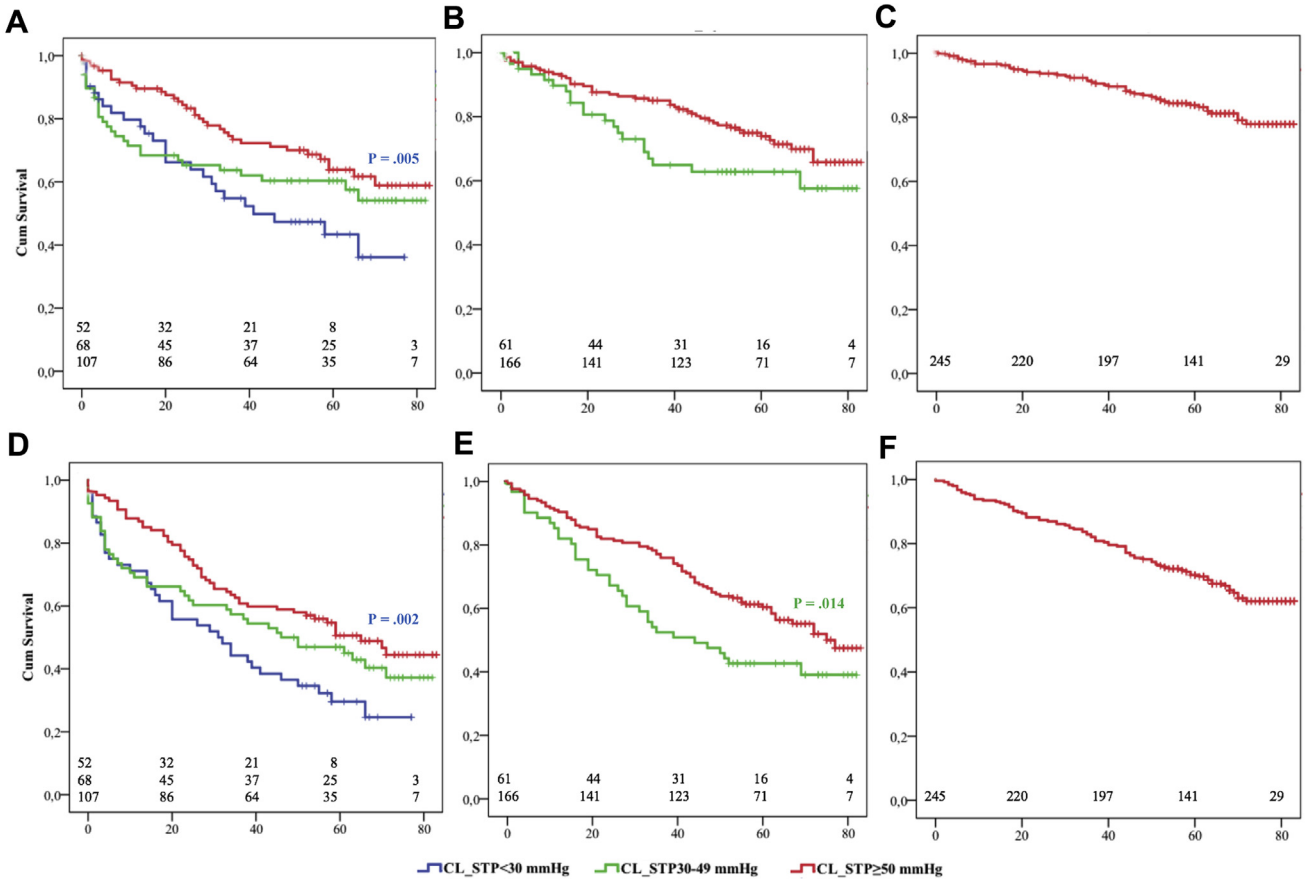

Fig 3. Kaplan-Meier survival curves showing freedom from cardiovascular death **(A-C)** and overall survival **(D-F)** by contralateral systolic toe pressure (*CL_STP*) for patients with ipsilateral systolic toe pressure (IP_STP) <30 mm Hg **(A** and **D)**, 30 to 49 mm Hg **(B** and **E)**, and ≥50 mm Hg **(C** and **F)**. Numbers of patients at risk entering intervals are shown at *bottom*. *P* values significant in pairwise comparison are shown in color corresponding to compared curve.

decreasing CL_TBI and IP_TBI. TBI <0.25 of either side significantly ($P < .001$) increased the risk of both cardiovascular and overall mortality (Table III).

Estimated freedom from cardiovascular death and overall survival of patients at defined IP_TBI categories at 60 months differed further by CL_TBI. Freedom from cardiovascular death of patients with IP_TBI <0.25 and CL_TBI ≥0.50 (64% [SD, 0.53]) was significantly higher compared with those with CL_TBI <0.25 (49% [SD, 0.57]; $P < .038$), and both freedom from cardiovascular death ($P = .018$) and overall survival ($P < .001$) of patients with IP_TBI of 0.25 to 0.49 and CL_TBI ≥0.50 (80% [SD, 0.42] and 67% [SD, 0.42], respectively) were significantly higher compared with patients with CL_TBI of 0.25 to 0.49 (66% [SD, 0.50] and 44% [SD, 0.50], respectively). CL_TBI had no significant effect on overall survival in patients with IP_ TBI <0.25 (Fig 5).

DISCUSSION

The study delineated the association of STP and TBI of the contralateral lower extremity with long-term mortality in 727 symptomatic PAD patients. Low CL_STP and CL_TBI were both associated with high mortality. Patient outcome also differed significantly between high and low CL_STP within the group of patients with low IP_STP. A linear time- and pressure-dependent association with regard to both cardiovascular and overall mortality was observed for both CL_STP and IP_STP.

An increased rate of adverse cardiovascular events and overall mortality with both abnormally high and low ABI has been demonstrated in previous large population studies and investigations.[6,28] This relationship is U shaped because comorbidities such as diabetes and end-stage renal disease render distal leg arteries incompressible.[15,16] Patients with symptomatic PAD and ABI >1.3, with and without diabetes, have increased amputation rates.[29] Although there is a strong body of evidence on both low and pathologically high ABI yielding an increased risk for adverse cardiovascular events and death, studies regarding the association of STP, TBI, and patient outcome are scarce, with some reports demonstrating that TBI is prognostic for cardiovascular mortality and morbidity.[16,30] This study, with >700 patients with STP and TBI measurements, shows a linear correlation

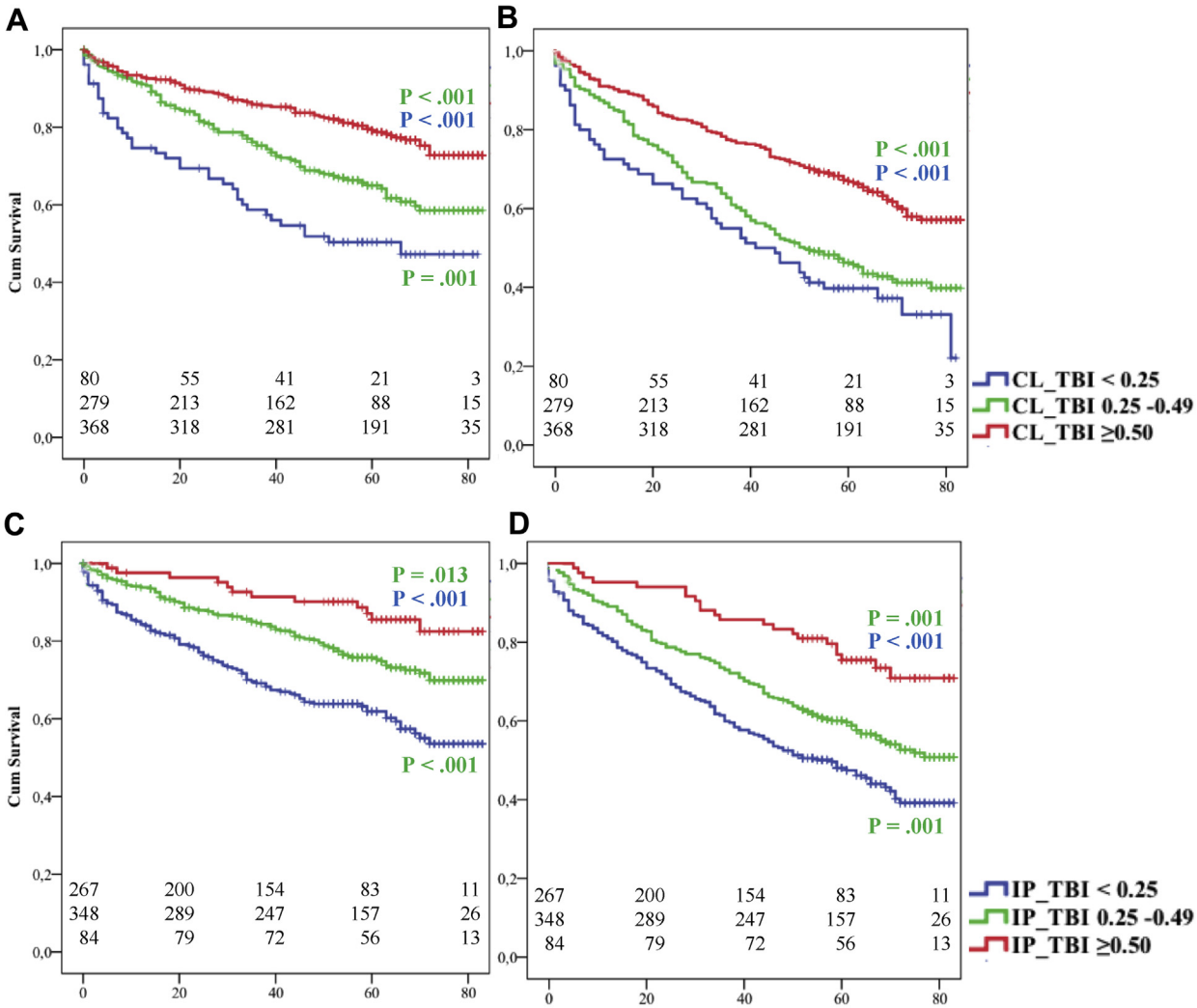

Fig 4. Kaplan-Meier survival curves showing freedom from cardiovascular death **(A)** and overall survival **(B)** by contralateral toe-brachial index (*CL_TBI*) and freedom from cardiovascular death **(C)** and overall survival **(D)** by ipsilateral toe-brachial index (*IP_TBI*). Numbers of patients at risk entering intervals are shown at *bottom*. *P* values significant in pairwise comparison are shown in color corresponding to compared curve.

of these indices with long-term cardiovascular and overall mortality. The data further suggest that CL_STP and CL_TBI are associated with patient outcome, stratifying patients with similar IP_STP or IP_TBI.

According to these data, CL_STP <50 mm Hg and CL_STP <30 mm Hg in particular are significantly associated with poor patient outcome. Cutoff values for STP for this study were selected according to generally accepted criteria for CLTI.[31-33] It is generally accepted that CLTI is associated with poor patient outcome,[28,34] and our results further support the notion of CLTI's having a malignant nature. The role of TBI in evaluating the severity of PAD is largely undefined. Previous guidelines recommend <0.70 as a cutoff between pathologic and normal TBI, but this cutoff is not evidence based.[35] There are no data confirming the utility of TBI in early detection of PAD among diabetics. The results of a Dutch study suggest that diabetes may indeed falsify both ABI and TBI.[20]

Low STP values are associated with a high risk of amputation.[36-38] We have previously observed a strong association between IP_STP and midterm cardiovascular and overall mortality as well as amputation-free survival. Similar results for all-cause mortality have been reported earlier in a study including 76 limbs in 53 patients.[37] Our study analyzes STP and TBI measurements for both lower limbs in 699 patients. STPs fulfilling CLTI criteria for the symptomatic limb were observed in 227 patients (TP <30 mm Hg) and TBI in 267 patients (TBI <0.25). Although recent guidelines consider ABI a principal tool for cardiovascular risk stratification, our findings support the use of both STP and TBI as powerful noninvasive tools for detecting patients at highest risk of death, notably from cardiovascular events, in need of aggressive

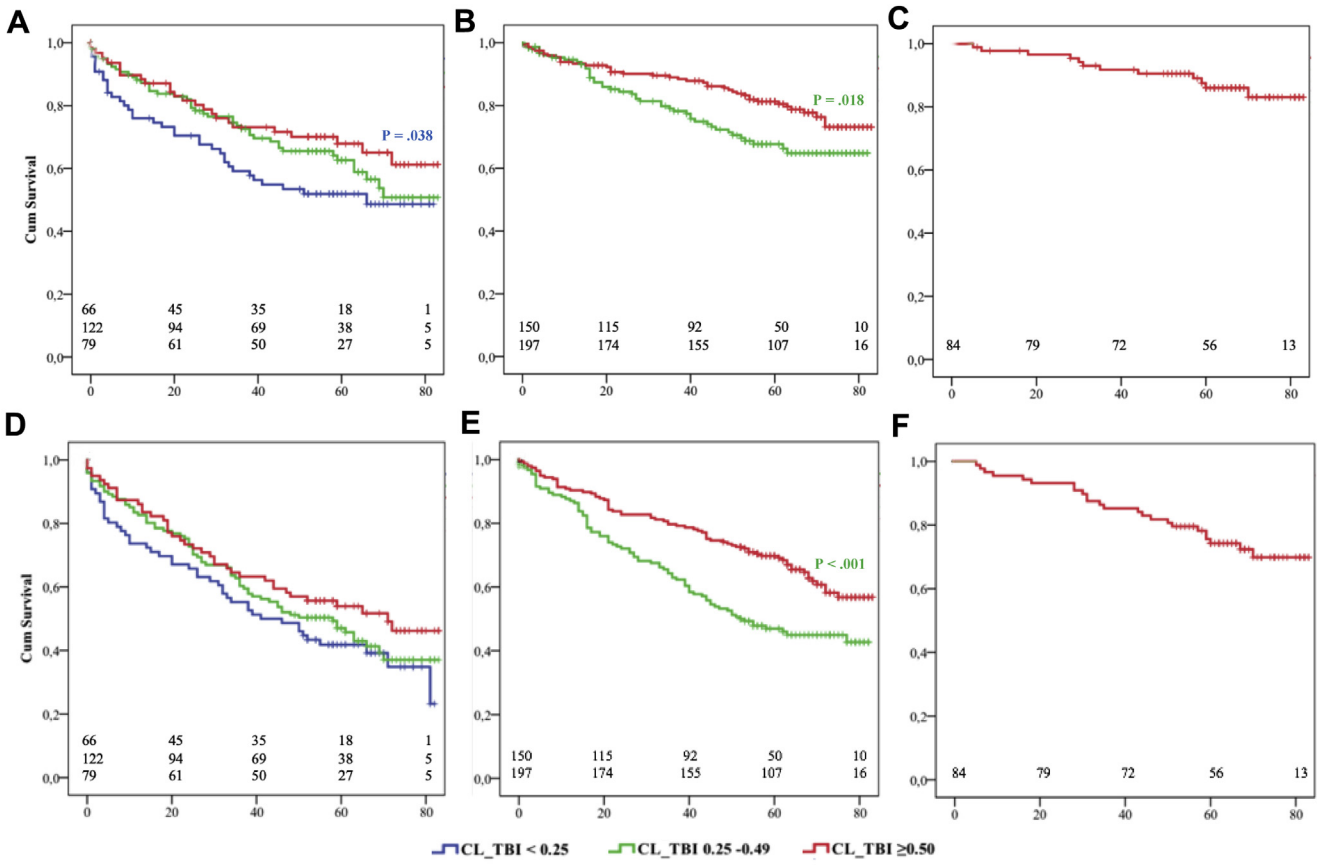

Fig 5. Kaplan-Meier survival curves showing freedom from cardiovascular death **(A-C)** and overall survival **(D-F)** by contralateral toe-brachial index (*CL_TBI*) for patients with ipsilateral toe-brachial index (IP_TBI) <0.25 **(A** and **D)**, 0.25 to 0.49 **(B** and **E)**, and ≥0.50 **(C** and **F)**. Numbers of patients at risk entering intervals are shown at *bottom*. *P* values significant in pairwise comparison are shown in color corresponding to compared curve.

medical therapy to avoid these events.[14] Both measurements are available at a general practitioner's office.[35] They may provide an alternative tool to ABI for screening high-risk patients at diabetes outpatient clinics because of a linear risk stratification. CL_STP and CL_TBI might serve as a valuable tool for comprehensive noninvasive risk stratification, even among CLTI patients. This study emphasizes the importance of bilateral pressure measurements in all PAD patients.

All patients included in the study had symptomatic (Rutherford category 2-6) PAD and were referred to DSA by a vascular specialist. DSA, at the time of the study, was the primary imaging modality for any such patient with an accessible femoral artery. The cohort does not include individuals who do not primarily fulfill criteria for invasive treatment. Randomly selected age- and risk factor-matched nonsymptomatic individuals were not available as a reference group. Even so, the study population is large, and it contains peripheral pressure measurements from patients irrespective of their diabetic status or PAD history. Because of these delineations, the results should further support the use of STP and TBI for cardiovascular risk evaluation in everyday clinical practice.

CONCLUSIONS

The U-shaped association of ABI with cardiovascular morbidity and mortality has been well documented, and ABI has been shown to be a potent noninvasive tool in PAD screening. In many vascular units, SAP, ABI, STP, and TBI are first-line investigations for clinical decision-making and routinely used in everyday practice. Although STP is rarely affected by incompressible digital arteries, it has been shown to be sensitive to changes in skin temperature and patient comorbidities, and it is device dependent.[22,39] To minimize the influence of these confounding factors on results, only standardized vascular laboratory pressure measurements were accepted into this study.

With a recent emergence of particularly aggressive medical therapies showing promise of decreased cardiovascular mortality in PAD patients, identifying those patients at highest risk of cardiovascular death may allow targeting them with novel treatment regimens. Statin therapy at moderate doses is generally considered safe and effective in lowering the risk of cardiovascular events in patients with PAD.[40] High-dose statin therapy reduces this risk even further, but concerns about

potentially serious adverse effects of high-dose statin therapy have been raised, and it has been proposed that this treatment should be reserved for those PAD patients at highest risk for cardiovascular death. With emerging novel lipid-lowering and antithrombotic therapies showing promise of even further risk reduction, justifying the risk of treatment-related adverse events in light of the sinister prognosis of patients at greatest risk of cardiovascular death may become increasingly important.[41,42] Based on our observations, noninvasive measurement of STP and TBI of both lower extremities is linearly prognostic of long-term cardiovascular and overall survival in symptomatic PAD patients, with low STP and TBI in the contralateral limb having an additive effect on long-term mortality. Therefore, they provide a valuable means to identify patients with highest cardiovascular mortality.

AUTHOR CONTRIBUTIONS

Conception and design: JW, MV, HH
Analysis and interpretation: JW, JV, EA, MV, HH
Data collection: JW, JJ, HH
Writing the article: JW, JV, EA, JJ, MV, HH
Critical revision of the article: JW, EA, MV, HH
Final approval of the article: JW, JV, EA, JJ, MV, HH
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