The instrumental diagnostic and screening tests of the peripheral artery disease, with a special focus on the automated, four-limb blood pressure monitors

Ph.D. Thesis Summary

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1. List of abbreviations

ABI	ankle-brachial index
AHA/ACC	American Heart Association/American College of Cardiology
AUC	area under the curve
baPWV	brachial-ankle pulse wave velocity
cfPWV	carotid-femoral pulse wave velocity
CI	confidence interval
CT	computer tomography
CV	cardiovascular
dia BP	diastolic blood pressure
DPA	dorsal pedal artery
DSA	digital subtraction angiography
ecfPWV	estimated carotid-femoral pulse wave velocity
ESC	European Society of Cardiology
ESH	European Society of Hypertension
LD	laser Doppler
LEAD	lower extremity artery disease
MAC	medial arterial calcification
MAP	mean arterial pressure
PAD	peripheral artery disease
PPc	central aortic pulse pressure
PSV	peak systolic velocity
PPG	photoplethysmographic
PTA	posterior tibial artery
PWV	pulse wave velocity
PWVao	aortic pulse wave velocity
ROC	receiver operating characteristic
sens.	sensitivity
SD	standard deviation
spec.	specificity
SPSS	Statistical Product and Service Solutions
sys BP	systolic blood pressure
TBI	toe-brachial index

2. Prologue

2.1. Peripheral artery disease – Epidemiology, symptoms

Peripheral artery disease (PAD) is a progressive atherosclerotic disorder which, if left untreated, leads to stenosis or occlusion of the affected vessels. It is the third leading cause of atherosclerotic mortality, following coronary heart disease and stroke. Due to the systemic nature of atherosclerosis, the diagnosis of PAD can be an indicator of the involvement of other vascular beds as well. PAD is a disease associated with a high prevalence rate, affecting more than 230 million individuals worldwide. Despite its high prevalence and association with adverse clinical outcomes, PAD is unfortunately very often recognised late, in the stage of critical limb ischaemia or remains unrecognised. The delayed diagnosis has a negative impact on the patients' quality of life and imposes extra burden on the health care system. On one hand, the underdiagnosis can be led back to the wide-ranging symptoms. On the other hand, the delayed diagnosis can be often contributed to the low use of conventional diagnostic tools and a frequent failure to systematically identify high-risk individuals. The 2017 European Society of Cardiology (ESC) guideline on PAD recommends screening for PAD over the age of 65, as well as under the age of 65 with an at least high CV risk, over the age of 50 with a positive family history of PAD and in the presence of certain comorbidities (abdominal aortic aneurysm, chronic kidney disease, heart failure, other atherosclerotic diseases).

2.2. Ankle-brachial index measurement

2.2.1. Ankle-brachial index measurement using the traditional Doppler method

The non-invasive test of choice after clinical examination to diagnose symptomatic and asymptomatic PAD is the Doppler-based ankle-brachial index (ABI) measurement. After a few minutes of rest, systolic blood pressure is measured on the arms (brachial artery) and the ankles [over the dorsal pedal (DPA) and the posterior tibial artery (PTA)] in the patient's supine position, using a manual sphygmomanomether and a continuous wave Doppler device. This test is cost-effective and is widely available, also in primary care.

According to the current guidelines, ABI is defined as a ratio of the higher systolic blood pressure of the PTA or the DPA of each lower limb and the higher systolic blood pressure of the upper limbs. However, some studies suggested that to increase sensitivity and more accurate risk classification, the use of the modified ABI, i.e., taking the lower systolic blood pressure of the two ankle arteries as the numerator, is more appropriate.

The disadvantage of the Doppler method is that it is relatively time-consuming. The average examination time of 10 minutes is difficult to fit into the time frame of primary care or non-angiological specialist appointments. The correct implementation requires skills on the part of the examiner.

2.2.2. Ankle-brachial index measurement using the automated devices

To overcome these limitations, automated, four-limb blood pressure monitors have been developed in recent years, which are specially designed for ABI measurement. The simultaneous and automated blood pressure measurement on all four limbs helps to eliminate measurement inaccuracies due to blood pressure fluctuations and lack of experience by the examiner and reduces the time required to perform the examination.

They can basically be divided into two large groups, devices operating on the photo- or air plethysmography and the ones operating on the oscillometric principle. The photoplethysmographic (PPG) devices operate with a photosensor which emits infrared light and then detects its reflection during deflation of the cuffs. These devices are less widespread. Based on the few available studies, their sensitivity ranges widely (20-100%). Oscillometric devices are more widespread, and more data are available about them.

However, despite the limitations of these devices, including low measurement accuracy in low ABI ranges and a tendency to slightly overestimate ABI values compared to the Doppler measurement, a recent meta-analysis concluded that oscillometric devices have an acceptable diagnostic accuracy and feasibility, and they may be useful especially in mass screening programmes for PAD. Due to their limitations, current guidelines recommend the traditional hand-held Doppler method over automated ABI measurement for PAD diagnostics.

2.3. Additional functions of the automated devices

To improve the sensitivity in detecting PAD, some automated devices have been equipped with additional functions, like measuring the pulse wave velocity (PWV) or toe-brachial index (TBI).

2.3.1. Toe pressure measurement

Toe pressure measurement helps to overcome the constraints of resting ABI measurement in patients with incompressible ankle arteries due to medial arterial calcification (MAC), which is most frequently associated with diabetes, chronic kidney disease or advanced age. Current guidelines recommend alternative tests, such as TBI measurement to detect PAD in patients with incompressible ankle arteries or in case of a high ABI (>1.4). Toe pressure measurement is usually carried out by measuring systolic blood pressure on the hallux or, in its absence, on the second toe using PPG or laser Doppler (LD) principle. Despite the clinical importance of toe pressure measurement, it is an almost neglected screening method in outpatient settings.

2.3.2. Measurement of the pulse wave velocity

The measurement of aortic inelasticity, in particular, the aortic PWV (PWVao) is considered a partially accepted cardiovascular biomarker. The measurement of the PWVao may be suitable for detecting persons at high CV risk and is considered an independent predictor of subsequent cardiovascular events. The non-invasive gold standard for measuring the PWVao is the measurement of the carotid-femoral pulse wave velocity (cfPWV). In contrast to the traditional

method of determining cfPWV, the applanation tonometry, PWV measurement utilising automated, oscillometric devices requires lower operator skills and a shorter examination duration. According to the current guideline of the European Society of Hypertension (ESH), a cfPWV above 10 m/s can be considered an independent predictor of organ damage. However, PWV is not included in the current PAD guidelines.

3. Focus and aim of the studies

Despite its high prevalence, screening for peripheral artery disease does not receive enough attention. To overcome the limitations of the Doppler method, automated, four-limb blood pressure monitors have been designed. Their use does not require a special learning curve, the user-friendly and quick implementation aims to shorten the examination time. However, due to the aforementioned disadvantages, their use is not supported by current guidelines. The additional functions which were developed to increase their sensitivity, have been less investigated so far.

The purpose of our study was to evaluate the measurement accuracy, sensitivity and specificity of two automated, oscillometric, four-limb blood pressure monitors (BOSO ABI-system 100 PWV and MESI mTablet) compared to generally accepted measurement methods. Oscillometric ABI measurement was compared to the standard Doppler method, the role of the modified ABI calculation in the PAD screening was also evaluated. Automated TBI measurement was compared to the LD method and to another portable device operating also with PPG.

Our investigation aimed to provide new knowledge by calculating the sensitivity and specificity values of the various measurements based on results of vascular imaging techniques.

Our further goal was to investigate two additional functions of the automated devices, namely estimated cfPWV (ecfPWV) and TBI whether they could contribute to the screening of PAD.

4. Patients and methods

4.1. Study design

A total of 230 adult patients were enrolled in our study with the BOSO ABI-system 100 PWV device, 117 of them also participated in the investigation with the MESI mTablet. Patients were recruited from January 2022 to November 2022 in the outpatient clinic and in the ward of the Division of Angiology at the University of Pécs Clinical Centre. Patients were screened prospectively and consecutively. The included individuals were divided into the following subgroups: control group, patients with previously confirmed PAD, patients with high CV risk, patients with very high CV risk and patients with other non-atherosclerotic CV diseases. Patients of the latter three groups were not previously diagnosed with PAD. The control group consisted of non-smoking individuals, matched for sex and age (within ±5 years tolerance compared to all patients) who did not have diabetes and any CV diseases, except for essential,

uncomplicated, medically properly treated arterial hypertension. Patients with at least moderate stenosis of the arteries of the lower extremities (luminal stenosis greater than 50% of the lumen) were considered as PAD patients. High and very high CV risk was defined according to the 2021 ESC "Guidelines on cardiovascular disease prevention in clinical practice". The group of patients with non-atherosclerotic CV diseases ("other CV") involved mainly patients treated in our angiology ward afflicted with venous thromboembolic diseases.
The investigation followed the principles of the Declaration of Helsinki and was approved by the Regional Committee for the Research Ethics of the University of Pécs (No 9343 - PTE 2022). Informed consent was obtained from all subjects prior to being included in the study.

4.2. Methods

4.2.1. ABI measurement

4.2.1.1. Hand-held Doppler method

Systolic blood pressure in the PTA and DPA of both legs as well as in the brachial artery of both arms was measured using a hand-held Doppler ultrasound device (Bidop ES-100V3, Hadeco Inc., Kawasaki, Japan) operated with an 8-MHz probe and a manual sphygmomanometer following the same measurement sequence (right arm – right leg – left leg – left arm). ABI was calculated in two different ways – taking the higher or the lower systolic blood pressure in the PTA and the DPA of each ankle as the numerator, giving the Doppler ABI or the modified Doppler ABI. The higher systolic blood pressure of both arms was taken as the denominator.

4.2.1.2. Automated measurement

4.2.1.2.1. BOSO ABI-system 100 PWV device

Arterial blood pressure measurements were performed on all four extremities simultaneously based on the oscillometric principle. After reaching a suprasystolic blood pressure of more than 30 mmHg above the expected systolic blood pressure, the device started to deflate the cuffs. Systolic and diastolic blood pressure values are calculated based on predefined percentages of the maximal oscillation amplitude, the systolic blood pressure corresponds to the first, the diastolic blood pressure to the last major oscillation amplitude.

4.2.1.2.2. MESI mTablet device

ABI measurements were conducted using the dedicated software installed on the tablet connected via Bluetooth to a wireless four-limb blood pressure monitor. The measurements were carried out using the oscillometric principle. In the first step, the arm cuffs were inflated, and the arm with the higher systolic pressure was selected based on the Smartarm™ algorithm. In the second step, the two ankle cuffs and the selected arm cuff were inflated simultaneously. In addition to the calculated both-sided ABI value, oscillation graphs and pulse waves were also displayed. By analysing the morphology of the pulse waves, the PADsense™ algorithm raises the possibility of severe PAD (usually ABI ≤0.5) or incompressible arteries due to media sclerosis.

An ABI value ≤0.9 was considered abnormal, and a value >1.4 was considered indicative of media sclerosis.

4.2.2. ecfPWV measurement with the automated oscillometric devices

Upon completion of measuring the ABI in both legs, both automated devices performed the oscillometric measurement of the ecfPWV. Through simultaneous inflation of the upper and lower cuffs, the devices determined the pulse transit time between the brachial and tibial arteries by analysing the oscillometric amplitudes. The pulse transit time is used to calculate the brachial-ankle pulse wave velocity (baPWV), from which the cfPWV can be estimated based on the following formula: ecfPWV=0.833 x baPWV- 2.33 (m/s). Values above a cut-off level of 10 m/s were considered abnormal. The user manual of the BOSO device also supported this cut-off level.

4.2.3. TBI measurement

Systolic toe pressure was measured using three different devices, first using LD flowmetry (PeriFlux System 5000, Perimed AB, Sweden), followed by measurement using a portable device operating on the PPG principle (SysToe, Atys medical, France). In 117 patients, TBI was also measured using the MESI mTablet.

The TBI for each lower limb was determined by dividing the systolic toe pressure with the higher systolic arm pressure. A TBI value ≤0.7 was considered abnormal.

4.2.4. Vascular imaging techniques

Except for pre-known, chronic, non-intervenable PAD cases [19 patients, documented by a previous digital subtraction angiography (DSA)], all other patients were examined by a vascular imaging technique. 47 patients with, at minimum, Fontaine stage IIb, underwent DSA with subsequent intervention. In 160 cases, a colour-coded duplex ultrasound was performed, and in 4 cases, a CT angiography was performed.

PAD was defined by the presence of at least one significant (at least 50%) stenosis of the lower limb arteries. Using the duplex ultrasound, stenoses were evaluated with the PSV ratio (ratio of PSV at stenosis to the PSV measured directly proximal to the stenosis), considered as significant when >2. Atherosclerotic plaques were defined as an intima-media thickness exceeding one of the neighbouring sites by at least 50%.

4.2.5. Statistical analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) statistical software, version 28.0.0.0 (SPSS Inc. Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation (SD). The between- and within-groups analyses of continuous variables were performed by one-way ANOVA. Homogeneity of variances was analysed by Levene's test; in cases of equal variances, Tukey post hoc test was performed, and in cases of inhomogeneity of variances, Welch's statistics and Tamhane's post hoc test were

performed. The association between the Doppler-assisted and oscillometric measurements was determined by the Pearson product-moment correlation, in which a correlation coefficient (r) greater than 0.5 was considered to demonstrate a strong correlation. The means of the automated and manually adjusted TBI values were compared using paired samples *t*-test.
The intermodality agreement of various measurements was analysed by the Bland-Altman method. The proportional bias was evaluated by linear regression analysis of the differences between the measurements.
The diagnostic efficiency of the various methods was compared using receiver operating characteristic (ROC) curve analysis. The accuracy of the diagnostic tests was estimated by the area under the curve (AUC) value. The optimal cut-off value for each method was calculated using Youden's J statistic based on the „sensitivity + specificity -1" equation. The cut-off value belonging to the highest Youden's J index was selected. The corresponding AUC values of the independent ROC curves were compared using the Hanley–McNeil algorithm, the ones of correlated ROC curves based on the DeLong algorithm using the Jamovi statistical software, version 2.3.28. A p value <0.05 was considered to indicate a statistical significance.

5. Results

5.1. ABI measurement

5.1.1. BOSO ABI-system 100 PWV device

A total of 455 lower limbs of 230 patients were analysed. ABI was not measurable in four limbs due to major amputations and in one limb due to ankle ulcerations.
A detailed analysis and comparison of the ABI values for each patient subgroup can be found in the full thesis.

To evaluate the correlation between the Doppler, modified Doppler and the oscillometric ABI measurements, 45 cases (9.9%) needed to be excluded, in which the BOSO ABI was "0", while the Doppler ABI was a non-zero value. Of these cases, 28 patients were diabetic and 17 were non-diabetic (16.4% of all ABI measurements of diabetic and 6.0% of non-diabetic patients). In 100% of these cases significant PAD lesions were detected by vascular imaging. A significant correlation was found between the Doppler and BOSO ABI values ($r=0.614$, $p<0.001$) and a slightly more pronounced correlation between the modified Doppler and BOSO ABI values ($r=0.641$, $p<0.001$).
The analysis of the intermodality agreement between the Doppler and BOSO ABI measurements with the Bland–Altman method showed a mean difference of 0.075 between the two methods, with the limits of agreement from −0.577 to 0.727. The linear regression analysis of the differences revealed no proportional bias ($p=0.876$). *Figure 1* highlights the differences with the circled sections resulting from oscillometric "0" readings in which the Doppler ABI values differed from "0", as well as the cases in which the Doppler ABI values indicated media sclerosis, while the BOSO ABI values did not.

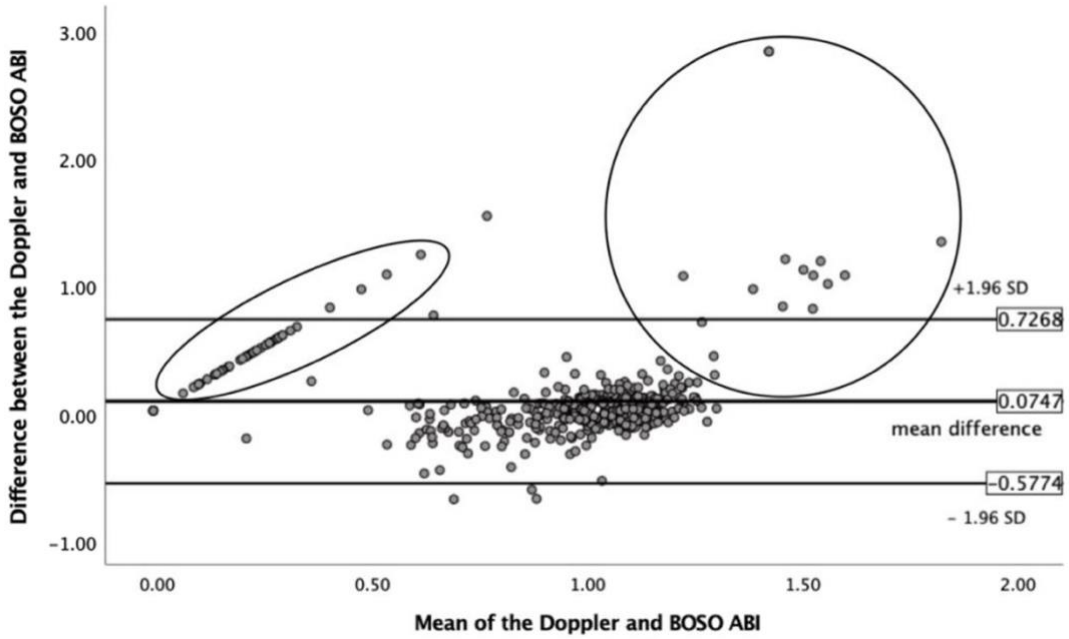
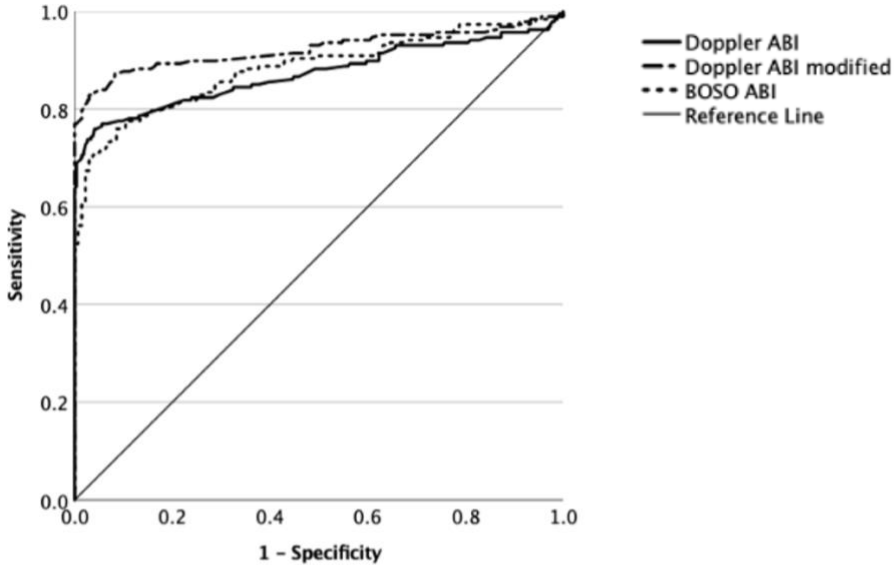


Figure 1. Analysis of the intermodality agreement between the Doppler and BOSO ABI measurements with the Bland-Altman method. The circled part on the left indicates the measurements for which the oscillometric ABI resulted "0", while the Doppler ABI showed a non-zero value. The circled area on the right demonstrates the cases where Doppler ABI values indicated media sclerosis, yet the BOSO ABI values did not.

The diagnostic efficacy of using the Doppler, modified Doppler and BOSO ABI values was compared through ROC curve analysis, taking the results of the vascular imaging as a reference (*Figure 2*). At a cut-off point of 0.9, the Doppler ABI [AUC=0.873 (95% CI 0.833–0.912), p<0.001] showed a sensitivity/specificity of 70.6%/98.1%, the modified Doppler ABI [AUC=0.923 (95% CI 0.891–0.954), p<0.001] showed a sensitivity/specificity of 84.0%/94.4%, and the BOSO ABI [AUC=0.882 (95% CI 0.846–0.917), p<0.001] showed a sensitivity/specificity of 61.5%/97.8%. At a cut-off level of 1.0, the BOSO ABI revealed a sensitivity of 80.7% and a specificity of 79.1%. The optimal cut-off value was considered 0.94 for the Doppler ABI, 0.87 for the modified Doppler ABI and 0.96 for the BOSO ABI.



		cut-off 0.9	
	AUC (95% CI)	sensitivity (%)	specificity (%)
Doppler ABI	0.873 (0.833-0.912)	70.6	98.1
Doppler ABI modified	0.923 (0.891-0.954)	84.0	94.4
BOSO ABI	0.882 (0.846-0.917)	61.5	97.8

Figure 2. Diagnostic efficacy of the Doppler, modified Doppler and BOSO ABI measurements with ROC curve analysis (all patients).

Table 1 demonstrates the diagnostic efficacy of the three different ABI measurement methods with an indication of the sensitivity and specificity values at a cut-off level of 0.9 in the high, very high CV risk and confirmed PAD patient subgroups. No statistically significant differences were found regarding the diagnostic efficacy of the Doppler and modified Doppler ABI assessment between the analysed subgroups. The AUC values of the BOSO ABI measurement revealed significant differences between high CV risk and confirmed PAD patients (p=0.028) and between very high CV risk and confirmed PAD patients (p=0.041). No statistically significant differences were found comparing the diagnostic efficacy of the Doppler and BOSO measurements in the subgroups of high CV risk (p=0.521), very high CV risk (p=1.000) and confirmed PAD patients (p=0.104).

Table 1. Diagnostic efficacy of the Doppler, modified Doppler and BOSO ABI measurements in the subgroups of patients with high CV risk, very high CV risk and in patients with previously confirmed PAD by ROC curve analysis (sens. – sensitivity, spec. – specificity).

	High CV risk (n=46)			**Very high CV risk (n=65)**			**Confirmed PAD (n=75)**		
		cut-off 0.9			**cut-off 0.9**			**cut-off 0.9**	
	AUC (95% CI)	**sens. (%)**	**spec. (%)**	**AUC (95% CI)**	**sens. (%)**	**spec. (%)**	**AUC (95% CI)**	**sens. (%)**	**spec. (%)**
Doppler ABI	0.932 (0.848-1.000)	60.0	98.8	0.877 (0.793-0.961)	75.0	96.7	0.830 (0.767-0.893)	70.1	100.0
Doppler ABI modified	0.945 (0.856-1.000)	70.0	98.8	0.904 (0.830-0.978)	82.5	86.7	0.884 (0.831-0.937)	84.6	90.0
BOSO ABI	0.909 (0.796-1.000)	70.0	97.5	0.877 (0.795-0.959)	57.5	97.8	0.701 (0.555-0.848)	62.5	80.0

5.1.2. MESI mTablet device

In total, 233 lower limbs of 117 patients could be examined, due to a previous unilateral major amputation of one subject. A comparison of the mean values for each subgroup is presented in the full thesis.

The MESI mTablet showed numerical ABI data in 210 cases. In another 23 cases, a text signal of "Possibility of severe PAD or incompressible arteries" was displayed. The ratio of patients who lacked numerical data was 14.6% in the subgroup of diabetic patients (n=41, 12 text data of 82 readings) and 7.6% in non-diabetic patients (n=76, 11 text data of 151 ABI measurements). By comparing these readings with the results of the vascular imaging, it could be ascertained that 100% of these limbs could be diagnosed with PAD lesions. However, these 23 measurements had to be excluded from further statistical analysis.

The Pearson correlation analysis revealed a significant correlation between the Doppler-assisted and oscillometric MESI ABI readings ($r=0.471$, $p<0.001$). The correlation was stronger in non-diabetic ($r=0.652$, $p<0.001$) than in diabetic ($r=0.284$, $p<0.001$) patients.

The Bland–Altman plot (*Figure 3*) displayed a mean difference of -0.038 between the Doppler and MESI ABI measurements, with the limits of agreement of 0.413 and −0.489. The linear regression analysis indicated the presence of proportional bias ($R^2 = 0.314$, $F(1,208) = 95.133$, $p<0.001$). *Figure 3* highlights with the circled section the cases in which the Doppler ABI values indicated media sclerosis, while the MESI ABI values did not.

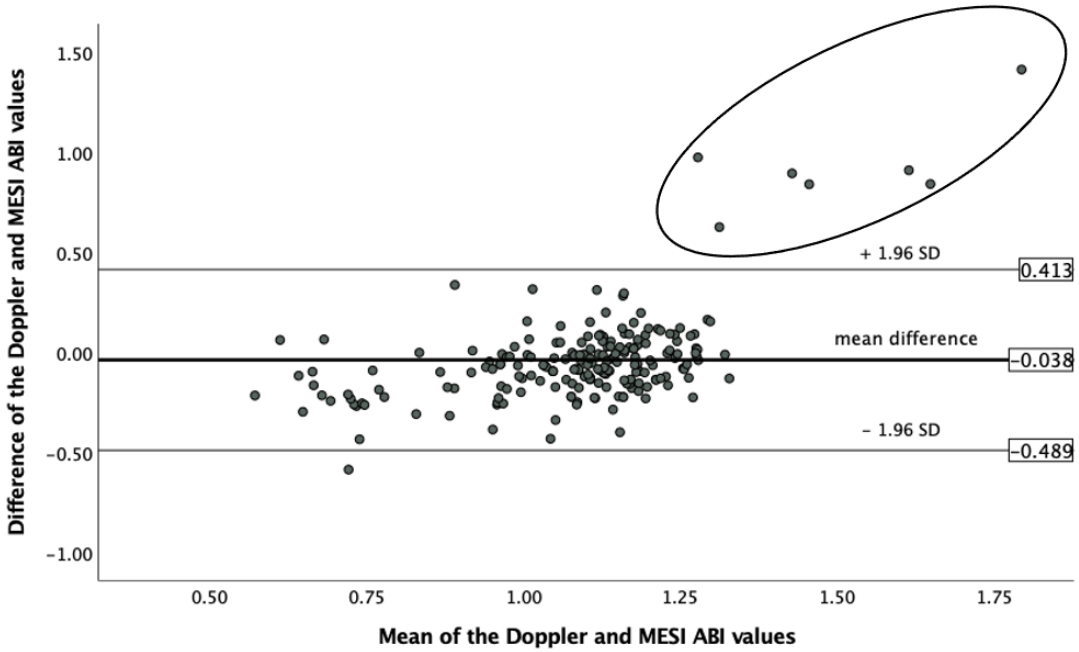
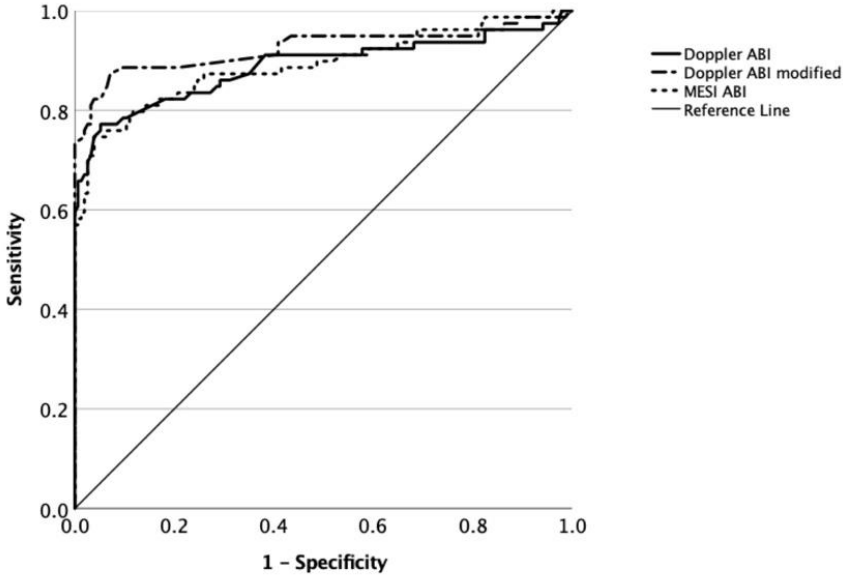


Figure 3. Analysis of the intermodality agreement between the Doppler and MESI ABI measurements using the Bland–Altman method. The circled area demonstrates the cases where Doppler ABI values indicated media sclerosis, yet the MESI ABI values did not.

The diagnostic efficacy of the three different ABI readings in recognising PAD with reference to the vascular imaging was analysed based on ROC curves (*Figure 4*).

For the cut-off value of 0.9 ABI, the Doppler ABI [AUC=0.888 (95% CI 0.832–0.943), p<0.001] showed a sensitivity/specificity of 67.1%/97.4%, the modified Doppler ABI [AUC=0.925 (95% CI 0.878–0.972), p<0.001] revealed 82.3%/95.5%, and the MESI ABI [AUC=0.891 (95% CI 0.839–0.942), p<0.001] showed 57.0%/100%.

For the cut-off value of 1.0, the MESI ABI showed a sensitivity of 74.7% and a specificity of 94.8%. The optimal cut-off value was calculated as 0.99 for the oscillometric MESI ABI determination.



		cut-off 0.9	
	AUC (95% CI)	**sensitivity (%)**	**specificity (%)**
Doppler ABI	0.888 (0.832–0.943)	67.1	97.4
Doppler ABI modified	0.925 (0.878–0.972)	82.3	95.5
MESI ABI	0.891 (0.839–0.942)	57.0	100.0

Figure 4. Diagnostic efficacy of the Doppler, modified Doppler and MESI ABI measurements based on ROC curve analysis in all patients.

The diagnostic efficacy of the Doppler, modified Doppler and MESI ABI measurement methods with an indication of the sensitivity and specificity values at a cut-off level of 0.9 in the high, very high CV risk and confirmed PAD patient subgroups is demonstrated in *Table 2.* Regarding the diagnostic efficacy of the Doppler and modified Doppler ABI assessment between the subgroups of patients with high CV risk, with very high CV and with previously confirmed PAD, no statistically significant differences were found. The AUC values of the MESI ABI measurement revealed significant differences between very high CV risk and confirmed PAD patients (p<0.001). No statistically significant differences were found comparing the diagnostic efficacy of the Doppler and MESI ABI measurements in the subgroups of high CV risk (p=0.305) and very high CV risk (p=0.418) patients.

Table 2. Diagnostic efficacy of the Doppler, modified Doppler and MESI ABI measurements in the subgroups of patients with high CV risk, very high CV risk and in patients with previously confirmed PAD by ROC curve analysis (sens. – sensitivity, spec. – specificity).

	High CV risk (n=28)			**Very high CV risk (n=28)**			**Confirmed PAD (n=31)**		
		cut-off 0.9			**cut-off 0.9**			**cut-off 0.9**	
	AUC (95% CI)	**sens. (%)**	**spec. (%)**	**AUC (95% CI)**	**sens. (%)**	**spec. (%)**	**AUC (95% CI)**	**sens. (%)**	**spec. (%)**
Doppler ABI	0.885 (0.759-1.000)	33.3	98.0	0.876 (0.720-1.000)	66.7	95.5	0.892 (0.812-0.971)	70.0	100.0
Doppler ABI modified	0.895 (0.742-1.000)	50.0	98.0	0.888 (0.737-1.000)	75.0	88.6	0.883 (0.802-0.965)	86.7	100.0
MESI ABI	0.737 (0.460-1.000)	33.3	100.0	0.947 (0.888-1.000)	33.3	100.0	0.650 (0.529-0.771)	63.3	100.0

5.2. TBI measurement

Out of the 117 patients involved in the study using the MESI mTablet device, toe pressure measurement was performed using the three different devices on 230 lower limbs. In one case, toe pressure could not be obtained due to major amputation; in two cases, it was due to minor amputations; and in one case, it was due to toe gangrene. The toe pressure values of the automated MESI TBI measurement had to be corrected manually in most cases due to movement artifacts, which were recognised as a reappearance of the perfusion curve by the device. The automatically measured toe pressure values were noticed in 165 cases. However, the corrected values compared to the manually adjusted values showed no statistically significant difference (mean of the automated measurement 90.99 ± 40.88 mmHg, mean of the corrected values 86.81 ± 37.36 mmHg; paired samples t-test, $t(164) = -1.087$, $p=0.279$).

The mean TBI was 0.66 ± 0.24 using PeriFlux LD, 0.68 ± 0.23 using SysToe and 0.65 ± 0.29 when measured using MESI, respectively.

Welch's ANOVA revealed no significant differences between the three measurement techniques ($p=0.333$). Tamhane's post hoc test also showed no significant differences between the PeriFlux LD and SysToe measurements ($p=0.778$), between the PeriFlux LD and MESI measurements ($p=0.868$) and between the SysToe and MESI ($p=0.372$) measurements.

The Bland–Altman analysis showed a mean difference of 0.017 between the TBI assessment using the PeriFlux LD and the MESI measurements. The limits of agreement covered a range from −0.267 to 0.301. The circled section on *Figure 5* demonstrates 11 cases in which the PeriFlux LD measured a numerical value, but the MESI device did not detect a pulse wave on the affected toe.

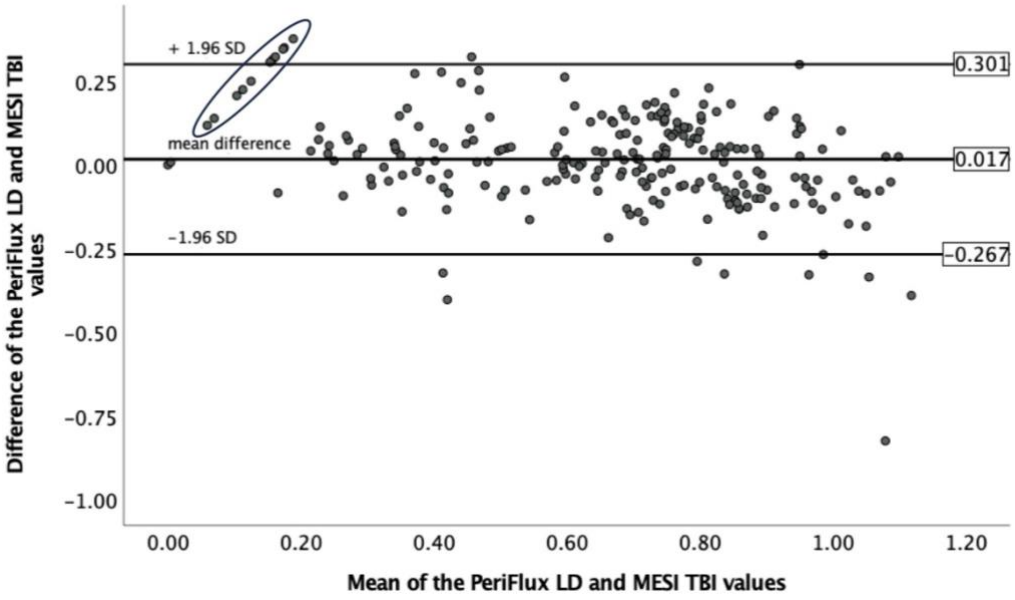
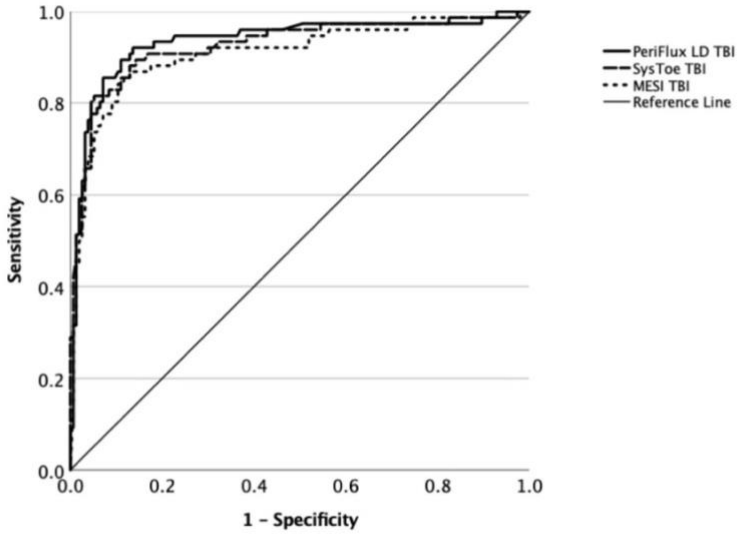


Figure 5. Analysis of the intermodality agreement between the PeriFlux LD and MESI TBI measurements using the Bland–Altman method. The circled section demonstrates 11 cases in which the PeriFlux LD measured a numerical value, but the MESI device did not detect a pulse wave on the affected toe.

The ROC curve analysis of all three measurement techniques (*Figure 6*) revealed an excellent diagnostic efficacy, with the PeriFlux LD TBI measurement showing an AUC of 0.935 (95% CI 0.895–0.974), SysToe showing a value of 0.926 (95% CI 0.884–0.967) and MESI showing a value of 0.909 (95% CI 0.862–0.955), with a significance of $p<0.001$ for all analyses. PeriFlux LD showed a sensitivity/specificity of 94.7%/76.0%, SysToe revealed 90.8%/76.6%, and MESI revealed 92.1%/67.5% at a cut-off value of 0.7. The optimal cut-off value for the MESI TBI assessment was calculated to be 0.61.



		cut-off 0.7	
	AUC (95% CI)	sensitivity (%)	specificity (%)
PeriFlux LD TBI	0.935 (0.895–0.974)	94.7	76.0
SysToe TBI	0.926 (0.884–0.967)	90.8	76.6
MESI TBI	0.909 (0.862–0.955)	92.1	67.5

Figure 6. Comparison of the diagnostic efficacy of the PeriFlux LD, SysToe and MESI TBI measurements based on ROC curve analysis.

5.3. ecfPWV measurement

5.3.1. BOSO ABI-system 100 PWV device

The detailed comparison of the mean ecfPWV values of the different patient subgroups is shown in the full dissertation. The ecfPWV was immeasurably low in 6.5% of the high CV risk, in 10.8% of the very high CV risk and in 46.7% of the confirmed PAD patients. The BOSO device was not able to perform an ecfPWV measurement when the higher BOSO ABI value of the patient's two lower limbs was below 0.9 (n=46). Vascular imaging confirmed atherosclerotic PAD lesions in 100% of these cases.

The diagnostic performance of the ecfPWV measurement to predict atherosclerotic lesions was also analysed with ROC curves. Data analysis with measurable ecfPWV values [AUC=0.896 (95% CI 0.851–0.941), p<0.001] showed that the suggested cut-off level of 10.0 m/s was linked with a sensitivity of 63.2% and a specificity of 100%. The optimal cut-off value of 9.95 m/s practically corresponded to the cut-off value suggested by the manufacturer.

The ROC analysis of the ecfPWV measurement in predicting PAD lesions affecting at least one lower extremity showed an AUC value of 0.693 (95% CI 0.610–0.776, p<0.001). At a cut-off level of 10.0 m/s, a sensitivity of 69.4% and a specificity of 66.1% were obtained. The optimal cut-off level was calculated as 10.25 m/s.

5.3.2. MESI mTablet device

The mean MESI ecfPWV values of patient groups are demonstrated and compared in the full thesis. In contrast to the BOSO ecfPWV measurement, in cases where the higher MESI ABI value of the patient's two lower limbs indicated the presence of PAD, the ecfPWV values were inconsistent.

The ROC curve analysis of the MESI ecfPWV measurement in predicting atherosclerotic lesions revealed a moderate diagnostic efficacy [AUC=0.642 (95% CI 0.540–0.743), p=0.013]. The cut-off level of 10.0 m/s was linked with a sensitivity of 25.6% and a specificity of 92.3%. The optimal cut-off value based on the Youden-index was calculated to be 8.75 m/s.

The MESI ecfPWV measurement showed an insufficient diagnostic efficacy in predicting PAD lesions affecting at least one lower extremity [AUC=0.467 (95% CI 0.348–0.585), p=0.547]. The AUC value <0.5 was obtained by assuming, as suggested by the manufacturer, that higher ecfPWV values indicated the presence of PAD. The non-significant p value also indicated the lack of discriminatory ability.

5.4. Screening using the various methods

5.4.1. BOSO ABI-system 100 PWV device

We further analysed how the measurement of the BOSO ecfPWV contributes to PAD screening. Out of 187 lower extremities affected by PAD (considering both pre-known and newly diagnosed cases), Doppler ABI recognised 72.7% and the modified Doppler ABI 84.5%. The discrepancies with the data of the ROC curves result from the ABI values >1.4, which were also considered abnormal. The BOSO ABI was positive in 61.5% at an ABI cut-off level of 0.9

and in 80.7% at a cut-off level of 1.0, as already shown in the corresponding ROC curve. The ecfPWV measurement gave abnormal results in 82.9% of all PAD patients. If the BOSO ABI was combined with the ecfPWV measurement, 89.5% of the PAD patients were identified. If, in addition to the ecfPWV measurement, the cut-off level for the BOSO ABI was raised to 1.0, 92.4% of all PAD patients were recognised by the BOSO device.
TBI measurement proved to be the most effective in PAD screening - with a cut-off level of 0.7, PeriFlux LD TBI was positive in 96.2% and SysToe TBI was positive in 94.1% of all PAD limbs.

5.4.2. MESI mTablet device

Out of the 79 lower limbs of 44 patients affected by PAD (pre-known and newly diagnosed), the Doppler ABI calculation gave abnormal results in 56 cases (70.9%), while the modified Doppler ABI calculation gave abnormal results in 66 (83.5%) cases. The MESI ABI recognised 45 limbs (57.0%) with text or numerical data at an ABI cut-off level of 0.9 and 59 limbs (74.7%) at an ABI cut-off level of 1.0, respectively.
TBI was obtainable in 76 limbs. PeriFlux LD was abnormal in 72 (94.7%) cases, SysToe in 69 (90.8%) cases, and MESI TBI in 70 (92.1%) cases.
MESI ABI combined with TBI measurement recognised 73 of 79 affected limbs (92.4%), thereby 42 of 44 (95.5%) PAD patients. If an automatic ABI cut-off level of 1.0 was taken, the number of diagnosed limbs rose to 74 (93.7%) and thus, 43 of 44 (97.7%) of the PAD patients could be recognised by the device. MESI ecfPWV identified only 12 (27.3%) out of 44 PAD patients.

6. Discussion

Both tested automated devices work in a user-friendly way, the measurements are easy to perform and do not require a considerable learning curve. They work fully automated, allowing simultaneous blood pressure measurement on all four limbs, so blood pressure fluctuations between the measurements can be prevented. A noteworthy disadvantage of the MESI mTablet device is that it does not perform exact numerical ABI measurements in case of incompressible arteries or severe PAD. As described in the user manual, at an ABI value “around or lower than 0.5”, the text message of “abnormally weak pulse” is displayed. An analysis of the recorded oscillation graphs and pulse waveforms could provide valuable additional information about the possibility of the forementioned two conditions; however, it also requires expertise on the examiner’s part. The device provided a text message in about 10% of our ABI measurements. The ratio of measurements lacking numerical ABI values was about two times higher in diabetic patients. In our opinion, the fact that an exact ABI cannot be achieved in case of severe PAD limits the use of the device and does not allow a precise condition assessment of severe PAD patients and a post-interventional follow-up. However, in all cases of lacking numerical data, severe PAD lesions were detected using the vascular imaging techniques, which supports the role of the device in PAD screening.

The ratio of high and very high CV risk patients screened positive for PAD in our study population is in good agreement with previous studies. Based on our sample, the diagnostic efficacy of all three ABI measurement methods was non-inferior in patients with high or very high CV risk compared to the subgroup of subjects with previously confirmed PAD.
In a 2012 meta-analysis, a significant absolute difference (0.048 ± 0.009) was found between ABI values assessed by the oscillometric vs. Doppler-method, which indicated that oscillometric devices measure slightly higher ABI values. Our study with the MESI mTablet device revealed a mean difference of 0.038 ± 0.226 in favour of the oscillometric MESI readings. In contrast to that, in our study with the BOSO device, we found a mean difference of 0.075 ± 0.652 in favour of the Doppler method. In the meta-analysis, the average correlation between the Doppler and oscillometric ABI values was reported to be 0.71 ± 0.05. The lower correlation coefficients of our studies may be explained by the fact that we did not exclude patients with incompressible ankle arteries, while some studies involved in the meta-analysis did.
The detailed comparison of the two methods revealed two drawbacks of the oscillometric ABI assessment. The measurement range of the BOSO device covers 60-240 mmHg, thus it is unable to detect low ankle pressures, which are reported as "0" mmHg. The MESI mTablet device does not provide accurate numerical measurements in case of severe PAD (usually ABI ≤0.5). Although these "0" readings hindered exact PAD diagnostics, they did not affect the potential role of the tested devices in screening. Consistent with prior observations, we also found that *erroneous* oscillometric ABI measurements (results of "0 mmHg") indicate the presence of PAD in the affected leg confirmed by vascular imaging. The other drawback of the oscillometric measurement compared to the Doppler method affecting both tested devices (also demonstrated using the Bland-Altman plots) is their failure to detect high ankle pressures indicating media sclerosis.

To determine the sensitivity and specificity of the automatic oscillometric devices, Doppler ABI values were used as a reference in most studies; hence, a sensitivity of 69 ± 6% and a specificity of 96 ± 1% were found. Our study did not evaluate only the Doppler ABI but also the modified Doppler ABI, which revealed a substantially higher sensitivity for modified Doppler ABI vs. Doppler ABI (84.0% vs. 70.6%). The use of modified Doppler ABI for more appropriate PAD diagnostics was also supported by other studies.

Thus far, a limited number of other studies are available based on the results of vascular imaging. These studies suggested that rather than using the cut-off value of 0.9 generally accepted for the Doppler method, a higher oscillometric ABI cut-off level would be more appropriate to increase sensitivity. We also highlighted that increasing the oscillometric ABI cut-off level from 0.9 to 1.0 would increase the sensitivity of the tested devices in detecting an at least 50% lower limb stenosis (for the BOSO device, from 61.5% to 80.7%; for the MESI device, from 57.0% to 74.7%), with an acceptable decrease of specificity, thereby resulting in

a more balanced ratio of the sensitivity and specificity. The calculated optimal cut-off values (0.96 of the BOSO, 0.99 of the MESI device) would also make the clinical use of the automated ABI cut-off level "1.0" reasonable. This could be an important message for vascular screening done by non-specialists using automated devices.

Another important cornerstone of our study was to investigate the role of the additional ecfPWV function in screening for atherosclerosis and definitive PAD. In a review an association has been shown between cfPWV and coronary or cerebral atherosclerosis; in a meta-analysis, cfPWV was described as an independent predictor of adverse CV events and all-cause mortality. However, the association between cfPWV and atherosclerosis of the extremity arteries is less well documented. Moreover, the existing literature presents controversial data regarding the connection between ABI and PWV. We found that the BOSO device was not able to perform an exact ecfPWV measurement in almost half of the confirmed PAD patients; therefore it is not possible to demonstrate any correlation between the ABI and ecfPWV values based on these data. We saw that the device displayed an erroneous ecfPWV measurement when the higher ABI value of the two lower limbs measured by the device was below 0.9. This may support the potential role of the BOSO device in PAD screening since 100% of patients with non-measurable ecfPWV were diagnosed with PAD of at least one limb by vascular imaging. However, the BOSO device can only perform the ecfPWV measurement sequential to the measurement of ABI, these patients have already been screened out by the ABI measurement.
The ROC analysis of the numerically measurable BOSO ecfPWV values showed only moderate diagnostic efficacy in predicting stenotic PAD. At the same time, BOSO ecfPWV proved to be a reliable tool in predicting lower limb atherosclerotic lesions. The cut-off value of 10.0 m/s coincided the optimal cut-off level established by the ROC analysis and showed an acceptable sensitivity of 63.2% and a specificity of 100% in detecting atherosclerotic plaques, which practically meant that every patient with an ecfPWV greater than or equal to 10.0 m/s was diagnosed with atherosclerotic lesions by the vascular imaging. Therefore, it may contribute to selecting patients at very high CV risk who would benefit most from the optimal antiatherosclerotic medical treatment. Polyvascular artery disease is a common finding in PAD patients; accordingly, half of our PAD patients had atherosclerotic disease at another vascular bed. On the other hand, PAD screening could reveal more multivascular diseases among coronary and cerebrovascular patients who may benefit from the dual-pathway (acetylsalicylic acid and low dose rivaroxaban) antithrombotic therapy, besides those who have undergone lower extremity revascularization.
In contrast to that, the MESI ecfPWV measurement revealed only a moderate efficiency in detecting lower limb atherosclerosis. Moreover, the ecfPWV values measured in PAD were inconsistent; therefore, the MESI ecfPWV measurement failed to predict lower limb PAD lesions. In contrast to the BOSO device, to our knowledge, no study comparing the MESI ecfPWV measurement with applanation tonometry has been published so far.

The moderate sensitivity of either Doppler-based or oscillometric ABI measurements in diabetic patients emphasise the importance of toe pressure measurement in detecting PAD. Since toe arteries are usually not affected by MAC, the measurement of systolic toe pressure helps overcome the limitations resulting from falsely elevated ankle pressure values due to media sclerosis. The two most common measurement methods of toe pressure, LD flowmetry and photoplethysmography, have been validated in some studies and are considered a reliable alternative for each other. Although some portable, battery-powered, partly or fully automated devices are already available, their widespread use in primary care has not been realised due to unawareness, cost or personnel factors. Unfortunately, even among medical personnel, the importance of toe pressure measurement is not emphasised enough. Despite the fact that it can eliminate the limitations of ABI measurement, for PAD screening, TBI is almost never measured routinely. A meta-analysis published in 2020 concluded that the measurement of TBI is more sensitive [81% (95% CI: 70–94)] than the measurement of ABI [61% (95% CI: 55–69)] at the cost of lower specificity [92% (95% CI: 89–95) for ABI and 77% (95% CI: 66–90) for TBI]. Moreover, partly because it can also diagnose PAD in the case of MAC, this meta-analysis considered it a better screening tool than the measurement of ABI. A previous study conducted in our department highlighted the importance of determining not only the resting but also the post-exercise TBI, which was the most efficient of the tested parameters to recognise severe limb ischaemia.

Since the MESI mTablet unites the ABI and TBI measurements in one, easily operated device, the possibility of sequential measurements could facilitate more widespread use. Based on our data, no significant differences could be found between the three types of measurement techniques. The Bland-Altman analysis revealed good intermodality agreement with the results of LD flowmetry, and the ROC curves showed an excellent diagnostic efficiency for all three methods. However, two pitfalls of the automatic MESI TBI measurement should be noted. On one hand, the measurement range covers 20 to 250 mmHg, so in contrast to the LD fluxmetry, no accurate measurement can be carried out in very low range of toe pressures, which affected 4.8% of our measurements. It should also be noted that an operator cannot completely rely on automated toe pressure measurement since the perfusion curve has to be manually adjusted in most cases due to movement artifacts. Despite these disadvantages, toe pressure measurement provides a very valuable addition to ABI measurements. When the standard Doppler and MESI ABI readings were compared for screening purposes, MESI was underpowered compared to the Doppler method (57.0% vs. 70.9% of all limbs affected by PAD as recognised by MESI and Doppler ABI). If MESI ABI was combined with TBI measurement, the proportion of limbs recognised as pathological rose to 92.4%.

By analysing the contribution of the various methods to PAD screening, detecting TBI by LD or PPG method proved to be the most sensitive. The BOSO ABI measurement alone showed a moderate sensitivity with nearly 100% specificity in detecting at least 50% arterial stenosis of the lower limbs. Using an automatic ABI cut-off level of 1.0 resulted in an increased balanced

ratio of sensitivity and specificity. The moderate sensitivity of the MESI ABI readings could also be substantially improved by taking an automated ABI cut-off level of 1.0.; by adding the TBI, MESI's power increased substantially reaching an excellent sensitivity of 93.7%.

Study limitations

Our study with the MESI mTablet device involved a relatively small number of previously confirmed PAD patients. All measurements of our study were performed by one independent operator. Our study did not aim to test interobserver or intrapatient variability of the various ABI and TBI measurement methods. As a limitation, the use of three different vascular imaging techniques, the subjective evaluation by the colour-coded duplex ultrasound examination and the difficulties in assessing vascular lesions in the iliac and calf arteries by ultrasound also bear mentioning. The heterogeneity of the "confirmed PAD" group, also including patients with critical limb ischaemia or previous amputations, may also limit the investigation.

7. Conclusions

Our studies concluded that with additional functions, the BOSO ABI-system 100 PWV and the MESI mTablet automatic oscillometric devices could be efficiently applied for PAD screening. In case of both devices, using an ABI cut-off level of 1.0 resulted in a more balanced ratio of sensitivity and specificity.

The additional ecfPWV measurement function of the BOSO device may significantly contribute to the screening of PAD by selecting patients with atherosclerosis who should undergo further non-invasive PAD evaluation.

The sequential TBI measurement of the MESI mTablet device improves the sensitivity in detecting PAD significantly.

The quick and user-friendly implementation of the measurements may contribute to the widespread use of the automated devices in primary care and screening programmes.

However, based on the drawbacks resulting from the technical specifications, the use of both devices could be limited regarding precise PAD classification.

8. Summary of the new scientific findings

1. Our study was the first to obtain the sensitivity and specificity values of the ABI measurement using the automated BOSO ABI-system 100 PWV and MESI mTablet devices and the TBI measurement using the MESI mTablet device based on results of various vascular imaging methods. Our study was also the first to investigate the role of the automated, oscillometric BOSO and MESI ecfPWV measurement in predicting lower limb atherosclerotic and definitive PAD lesions.
2. In 100% of cases where the BOSO device measured an ABI of "0", significant PAD lesions were detected by vascular imaging. Also 100% of the limbs where the MESI device provided

a text signal could be diagnosed with PAD lesions. The ratio of the "0" measurements was higher in diabetic patients in case of both devices.

3. None of the tested automatic devices was able to detect an ABI >1.4 indicating media sclerosis.
4. At an ABI cut-off level of 0.9, both tested automatic devices showed a moderate sensitivity with nearly 100% or 100% specificity. The use of an automated ABI cut-off level of 1.0 resulted in a more balanced ratio of the sensitivity and specificity values for both tested devices.
5. The calculated optimal cut-off values based on our studies (0.96 of the BOSO, 0.99 of the MESI device) would make the clinical use of the automated ABI cut-off level "1.0" reasonable, which has already been supported by other studies.
6. We highlighted the importance of PAD screening in risk groups. Based on our sample, the diagnostic efficacy of the Doppler, modified Doppler and oscillometric measurement methods was non-inferior in patients with high or very high CV risk compared to the subgroup of subjects with previously confirmed PAD.
7. Consistent with previous studies, our investigations also emphasised the substantially higher sensitivity of the modified Doppler ABI calculation compared to the Doppler ABI in PAD diagnostics.
8. Our study was the first to evaluate the toe pressure measurement function of the MESI mTablet device. Comparing the TBI measurement using the PeriFlux 5000 device (LD flowmetry), using the SysToe device (PPG) and the MESI mTablet (PPG), no significant differencies could be found.
9. The MESI TBI measurement revealed an excellent diagnostic efficacy. Combining the MESI ABI and TBI measurements recognised more than 90% of all examined PAD limbs.
10. The BOSO ABI-system 100 PWV device was not able to perform an ecfPWV measurement when the higher BOSO ABI value of the patient's two lower limbs was below 0.9. PAD lesions were confirmed in 100% of these cases.
11. The MESI ecfPWV measurement revealed a moderate efficiency in detecting lower limb atherosclerotic lesions, and based on our data, it proved to be an insufficient tool to predict lower limb PAD.
12. The BOSO ecfPWV measurement showed 100% specificity and an acceptable sensitivity in predicting lower limb atherosclerotic lesions at the cut-off value of 10.0 m/s. Therefore, it may contribute to selecting patients at very high CV risk who would benefit from the optimal antiatherosclerotic medical treatment.

    The BOSO ecfPWV measurement showed a moderate diagnostic efficacy in predicting PAD lesions.

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10. Publications of the Author

10.1. Topic related journal articles

- **Fendrik K**, Biró K, Endrei D, Koltai K, Sándor B, Tóth K, Késmárky G. Screening for Peripheral Artery Disease Using an Automated Four-Limb Blood Pressure Monitor Equipped with Toe-Brachial Index Measurement. *J Clin Med* 2023 Oct 15; 12(20):6539. doi: 10.3390/jcm12206539. (Q1)
  Impact Factor: 3.9
- **Fendrik K**, Biró K, Endrei D, Koltai K, Sándor B, Tóth K, Késmárky G. Oscillometric measurement of the ankle-brachial index and the estimated carotid-femoral pulse wave velocity improves the sensitivity of an automated device in screening peripheral artery disease. *Front Cardiovasc Med* 2023 Dec 12; 10:1275856. doi: 10.3389/fcvm.2023.1275856. (Q2)
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10.2. Other journal articles

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