

A systematic review and meta-analysis of the diagnostic accuracy of point-of-care tests used to establish the presence of peripheral arterial disease in people with diabetes

Pasha Normahani, BSc, MBBS, MSc, MRCS (Eng),^{a,b} Chira Mustafa, BSc, MBBS, MRCP,^c Joseph Shalhoub, BSc, MBBS, FHEA, PhD, MEd, FRCS, FEBVS,^{a,b} Alun H. Davies, MA, DM, DSc, FRCS, FHEA, FACPh, FLSW,^{a,b} John Norrie, BSc, MSc (Statistics), FFPH,^d Viknesh Sounderajah, BSc, MBBS, MSc, MRCS (Eng),^{a,b} Sasha Smith, BSc,^b and Usman Jaffer, BSc, MSc (Ultrasound), MSc (Surgery), PhD, FRCS,^{a,b} *London and Edinburgh, United Kingdom*

ABSTRACT

Objective: No agreement has been reached regarding which bedside test is the most useful for the diagnosis of peripheral arterial disease (PAD) in patients with diabetes. The aim of the present systematic review and meta-analysis was to evaluate the performance of bedside tests for the detection of PAD in individuals with diabetes.

Methods: MEDLINE and EMBASE databases were systematically searched for studies providing data on the diagnostic performance of bedside tests used for the detection of PAD in those with diabetes. A meta-analysis was performed to obtain pooled estimates of sensitivity and specificity for the diagnosis of PAD.

Results: A total of 18 studies, reporting on a total of 3016 limbs of diabetic patients, were included in our qualitative review. Of these, 11 studies (1543 limbs) were included in the meta-analysis of diagnostic accuracy: ankle-brachial pressure index (9 studies and 1368 limbs; sensitivity, 63.5% [95% confidence interval (CI), 51.7%-73.9%]; specificity, 89.3% [95% CI, 81.1%-94.2%]); toe-brachial pressure index (3 studies and 221 limbs; sensitivity, 83.0% [95% CI, 59.1-94.3%]; specificity, 66.3% [95% CI, 41.3%-84.6%]); and tibial waveform assessment (4 studies and 397 limbs; sensitivity, 82.8% [95% CI, 73.3%-89.4%], specificity, 86.8% [95% CI, 75.5%-93.3%]). Overall, we found a high risk of bias across the studies, most frequently relating to patient selection and the lack of blinding.

Conclusions: The toe-brachial pressure index, pulse oximetry, and tibial arterial waveform assessment demonstrated some promise, warranting further investigation. (*J Vasc Surg* 2021;73:1811-20.)

Key words: Diabetes; Diabetic foot; Diagnosis; Foot ulcer; Peripheral arterial disease

Diabetes is a major global healthcare issue with an estimated prevalence of 9.3%.¹ More than 6% of those with diabetes will develop diabetic foot ulcers (DFUs).² DFUs are slow to heal and impose a significant economic burden on healthcare systems.³ The annual costs of

DFUs in the United Kingdom and United States have been estimated at £1 billion⁴ and \$9.1 to \$13.2 billion,⁵ respectively.

Peripheral arterial disease (PAD) is a key risk factor for the development of DFU⁶ and has been estimated to be present in one half of patients presenting with DFUs in western populations.^{7,8} The presence of PAD is also associated with delayed healing and an increased risk of major lower limb amputation and mortality.^{3,9} Therefore, the prompt and accurate diagnosis of PAD is important to allow for rapid revascularization, which, in some patients, has been shown to improve the chance of ulcer healing.¹⁰ However, the detection of PAD in those with diabetes can be challenging owing to the confounding effects of neuropathy and medial arterial calcification. Although a variety of bedside tests are available for the diagnosis of PAD, no agreement has been reached regarding which is most useful. These tests must be evidence based and must demonstrate robust diagnostic accuracy, because false-negative results can lead to missed cases of PAD in an ulcerated foot, which, if left untreated, could result in lower limb amputation.

From the Imperial Vascular Unit,^a and Department of Haematology,^c Imperial College Healthcare NHS Trust, London; the Department of Surgery and Cancer, Imperial College London, London^b; and the Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh.^d

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Correspondence: Pasha Normahani, BSc, MBBS, MSc, MRCS (Eng), Department of Surgery and Cancer, Imperial College London, 2nd Floor, Patterson Bldg, St Mary's Hospital, Paddington, London W2 1NY, UK (e-mail: p.normahani@imperial.ac.uk).

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The aim of the present systematic review and meta-analysis was to evaluate the sensitivity and specificity of bedside tests for the detection of PAD in people with diabetes.

METHODS

Search strategy. The present systematic review was undertaken in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines (Supplementary Fig, online only) and was prospectively registered on the PROSPERO registry (identification no. 186651).

The MEDLINE and Embase databases were searched using Ovid online for all available records from January 1, 1980 to May 12, 2020 written in English. The search string is provided in the Supplementary Table (online only). The search was complemented by a search of the reference lists of the included studies. Two reviewers (P.N. and C.M.) independently screened all abstracts and full-text articles. Disagreement was resolved by a third author (U.J.). Full text articles of the selected abstracts were assessed for inclusion, and the data were extracted.

Selection of studies. Prospective or retrospective cohort, cross-sectional and case control studies providing data on the performance of any bedside test used to detect the presence of PAD in patients with diabetes were included. Diagnostic tests were considered as any specific evaluation that sought to identify the presence of PAD at the point of care. Clinical examination and serum markers of PAD were excluded as index tests. We included studies that had evaluated bedside tests in any clinical setting, including primary, secondary, and community care. To be eligible for inclusion, the studies were required to evaluate index tests against a reference standard of full lower limb duplex ultrasonography (DUS), computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA). DSA has long been considered the reference standard for the diagnosis of PAD. However, it is invasive and carries risk. DUS,¹¹ MRA,¹² and CTA¹³ have all been shown to have excellent accuracy compared with DSA. Studies that had adopted a focused DUS technique as a reference standard, compared two reference tests, or reported insufficient data to allow for calculations of the sensitivity and specificity were excluded. Additionally, mixed population studies were only included if data had been separately reported for patients with diabetes (with ≥ 10 patients with diabetes).

The primary outcomes of interest for the present review of diagnostic performance were the sensitivity and specificity of the diagnostic tests.

Data extraction. Data extraction was undertaken and independently verified by two of authors (P.N. and C.M.). Data extraction forms were used to collect

information on the study design, patient characteristics (including the presence of neuropathy or active foot ulceration), diagnostic tests (technique and cutoff values), reference tests (technique and cutoff values), and outcome measures (sensitivity and specificity).

Quality assessment. The risk of bias was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool,¹⁴ a consensus quality assessment tool designed specifically for diagnostic accuracy studies.

Statistical analysis. For each study, a 2×2 contingency table consisting of true-positive, false-positive, false-negative, and true-negative values, based on the concordance between the reference and index tests, was constructed. If a 2×2 contingency table was either not reported or could not be constructed (using the reported sensitivity, specificity, and total number of diabetic patients with and without PAD), the study was excluded from the meta-analysis. Study investigators were not contacted regarding missing data. A separate meta-analysis was performed for each index test identified in the review process. Given the high risk of bias in the included studies, a meta-analysis was not performed for index tests reported in fewer than three studies. If a single study had reported on multiple index test diagnostic cut-off values, the single most widely used cutoff definition across all studies was adopted.

The summary estimates of sensitivity and specificity and their 95% confidence intervals (CIs) were modeled based on bivariate analysis. It was assumed that the test performance would vary across studies because of differences in study populations, sampling error, and differences in diagnostic thresholds for PAD. Therefore, a random effects model was applied to account for between-study heterogeneity. The summary receiver operating characteristic curve was plotted from this procedure. All analyses were performed using R, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria; available at: <https://www.r-project.org>), with the package "mada."¹⁵

RESULTS

Search results. A total of 5362 articles were identified in the literature search. Of these, 45 were selected for full-text screening, and 18 (reporting on a total of 3016 limbs of diabetic patients) were eligible for inclusion¹⁶⁻³⁴ (Fig 1). Of the 18 studies, 12 had evaluated the diagnostic performance of multiple index tests and 6 had evaluated a single index test (Table 1). The ankle-brachial pressure index (ABPI) was the most commonly evaluated test, with the diagnostic performance reported in 14 studies. Other index tests included the toe-brachial pressure index (TBPI; $n = 5$), qualitative analysis of visually displayed tibial arterial waveforms ($n = 4$), toe pressure ($n = 2$), ankle pressure ($n = 2$), transcutaneous pressure of oxygen

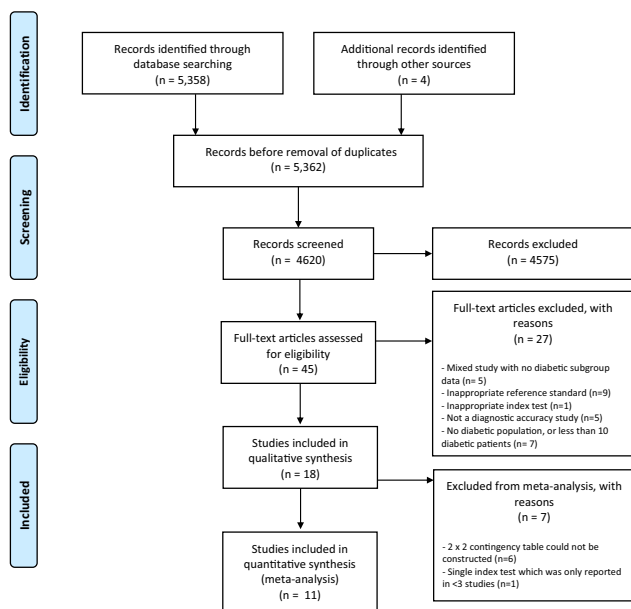


Fig 1. PRISMA (preferred reporting items for systematic reviews and meta-analysis) flow diagram: search and study selection process for the present review.

(TcPO₂; n = 2), pulse oximetry (n = 2), exercise ABPI (n = 1), pole test (n = 1), quantitative analysis of tibial arterial waveforms (n = 1), pulse reappearance time (n = 1), and pulse volume waveform (n = 1). Two studies reported the diagnostic performance of combining tests. In one study, the effect of combining ABPI and pulse oximetry was reported,³⁴ and in the other, the performance of ABPI and TBPI was reported.²⁹

Risk of bias and quality assessment. All studies were single-center studies. Of the 18 studies, 13 were prospective and 5 were retrospective case series. The risk of bias assessment for the included studies in the analysis of diagnostic performance for PAD in those with diabetes is presented in Table II. Overall, the risk of bias across studies was high. The most common sources of bias were related to patient selection (Fig 2). In most studies, the sampled population was often not representative of the full spectrum of the diabetic population seen in primary, secondary, and community care. Some studies had exclusively recruited patients with active ulceration or infection, and others had excluded those with active foot ulceration all together. Furthermore, the reporting of patient demographics was often incomplete, including the presence of neuropathy or active ulceration. We also found much variation in the prevalence of PAD in the included studies (mean ± standard deviation, 50.9% ± 29.1%). Some studies had recruited patients already admitted or referred for clinical suspicion of PAD according to the signs and symptoms (selection bias).

In the 12 studies providing a head-to-head comparison of tests, no formal analysis was performed to determine the statistical significance of the differences in

performance. The reference standard and index tests were not blinded in most of the included studies. Most studies had provided an insufficient overview of the technical success associated with index and reference tests. Additionally, clear statements regarding the management of missing or indeterminate results were not provided.

Reference tests to confirm PAD. DUS was used as the reference test for confirming PAD in 17 of the included studies, and DSA was used by 1 study. Most of the studies had described a DUS cutoff of >50% stenosis for the detection of PAD according to the velocity measurements. Across the studies, insufficient information was reported on the reference tests and lack of clarity regarding possible indeterminate results.

Index tests and cutoff values used to diagnose PAD. In the 14 studies evaluating the diagnostic performance of ABPI, a number of different techniques were used: Doppler (n = 13),^{16,17,19,22-26,28-30,32,34} plethysmography (n = 3),^{16,30,32} and ultrasound-derived (n = 1).³¹ The most commonly used ABPI cutoff for the diagnosis of PAD was <0.9 or ≤0.9. Three studies had used both a lower and upper threshold for diagnosis (eg, <0.9 or >1.3).^{22,24,29} One study compared the diagnostic performance of using a single lower threshold vs a combined lower and upper threshold, demonstrating an improvement in sensitivity but a reduction in specificity.³² Two studies evaluated the performance of systolic ankle pressure for the diagnosis of PAD with a defined cutoff value of <70 mm Hg.^{24,27}

TBPI was performed using plethysmography in four studies^{22,24,29,35} and a Doppler method in one study.³⁰ The TBPI cutoffs used for the diagnosis of PAD were <0.7 (n = 2),²² <0.75 (n = 1),²⁵ ≤0.75 (n = 1),²⁴ and <0.64 (n = 1).³⁰ Of the two studies that had investigated the systolic toe pressures, one had used a prespecified cutoff of <50 mm Hg,²⁰ and the other study had used an optimized threshold (based on the post-data collection analysis of receiver operating characteristic curve) of <97 mm Hg.²⁴

The visual tibial arterial waveform assessment for the diagnosis of PAD was most commonly performed using a handheld continuous wave Doppler device.^{21,22,25} One study used a duplex ultrasound machine for the assessment of waveforms.²⁴ One study did not specify the threshold used for qualitative waveform assessment.²⁴ Two studies defined a monophasic waveform cutoff,^{21,22} and another defined a biphasic waveform as the threshold for diagnosis of PAD.³⁵

Meta-analysis of performance of ABPI, TBPI, and tibial waveform analysis for diagnosis of PAD. Eleven studies (with a total of 1543 limbs in diabetic patients) were

Table I. Characteristics and diagnostic results of included studies

Investigator	Country	Study design and setting	Population (sex; active foot ulceration; neuropathy)	Index test and cutoff value
Clairotte et al, ⁶ 2009	France	Cohort; outpatient	83 DM; active foot ulceration, NS; neuropathy, 48% ⁷	Oscillometric ABPI ≤ 0.9 ; Doppler ABPI ≤ 0.9
Dhanowar et al, ¹⁷ 2016	India	Cohort; hospital inpatient	80 DM; active foot ulceration, NS; neuropathy, NS	Doppler ABPI < 0.9
Faglia et al, ²⁷ 2010	Italy	Cohort; hospital inpatient	261 DM; active foot ulceration, 94%; neuropathy, 82%	TcPO ₂ < 50 mm Hg; ankle pressure < 70 mm Hg
Kumar et al, 2016	India	Cross-sectional study; hospital outpatient	120 DM; active foot ulceration, 0%; neuropathy, NS	Doppler ABPI < 0.9 ; pulse oximetry (SpO ₂); toe saturation 2% less than finger saturation or 2% decrease in toe saturation after leg elevation
Premalatha, 2002	India	Cohort; hospital inpatient	100 DM; active foot ulceration, NS; neuropathy, NS	Doppler ABPI < 0.9
Tehan et al, ²⁰ 2017	Australia	Retrospective case-control; private outpatient vascular laboratory	176 DM; active foot ulceration, NS; neuropathy NS	Toe pressure: cutoff not prespecified; optimum threshold of < 97 mm Hg used based on AUC analysis
Tehan et al, ¹⁸ 2018	Australia	Retrospective case-control; private outpatient vascular clinic	176 DM; active ulceration, 3%; neuropathy, NS	Tibial waveforms (visual continuous wave Doppler assessment): monophasic or absent signal
Tehan et al, ²² 2016	Australia	Cross-sectional case-control; private outpatient vascular clinic	72 DM; active ulceration, NS; neuropathy, NS	ABPI ≤ 0.9 or ≥ 1.4 ; TBPI < 0.7 ; tibial waveforms (visual continuous-wave Doppler assessment): loss of multiphasic pattern
Vogelberg et al, ²³ 1988	Germany	Cross-sectional; hospital (inpatient vs outpatient not specified)	20 DM; active foot ulceration, NS; neuropathy, NS	PRT after 3 minutes of thigh compression (measured with Doppler probe); ABPI; cutoffs for both PRT and ABPI not prespecified
Vriens et al, ²⁴ 2018	UK	Observational cohort; hospital inpatient and outpatient	60 DM; active foot ulceration, 100%; neuropathy, 85%	ABPI < 0.9 or > 1.3 ; ankle pressure, < 70 mm Hg; toe pressure, < 50 mm Hg; TBPI, ≤ 0.75 ; TcPO ₂ , < 60 mm Hg; pole test (using handheld Doppler), NS; tibial waveforms (visual waveform analysis using PW DUS machine), NS
Williams et al, ^{25,35} 2005	UK	Cross-sectional; hospital outpatient	89 limbs in patient with DM; active foot ulcer, 0%; neuropathy, 72%	ABPI (PPG) < 0.9 ; TBPI, < 0.75 ; tibial waveforms (visual continuous-wave Doppler assessment): loss of triphasic signal
Zhang et al, ²⁶ 2010	China	Retrospective case series; hospital outpatient	92 DM; active foot ulceration, NS; neuropathy, NS	ABPI < 0.9
Tehan et al, ²¹ 2018	Australia	Retrospective case-control; private outpatient vascular clinic	107 Limbs of people with DM; active ulceration, NS; neuropathy, NS	Postexercise ABPI: $> 20\%$ reduction compared with resting ABPI; postexercise ABPI ≤ 0.9 ; > 30 mm Hg reduction in systolic ankle pressure
AbuRahma et al, ²⁹ 2019	USA	Retrospective case series; hospital (inpatient or outpatient not specified)	537 DM; active ulceration, NS; neuropathy, NS; not all patients had undergone all index and reference tests	ABPI, ≤ 0.9 + > 1.3 ; TBPI, < 0.7 ; ABPI and TBPI combined
Babaei et al, ³⁰ 2019	Iran	Cross-sectional study; hospital (inpatient or outpatient not specified)	303 DM (606 limbs); active foot ulceration, 6.6%; neuropathy, NS	Plethysmography ABPI, ≤ 0.9 ; Doppler ABPI, ≤ 0.9 ; Doppler TBPI, < 0.64 ; PVWs: loss of normal PVWs according to a prespecified grading system
Siao et al, ³⁴ 2018	Philippines	Cross-sectional; hospital (outpatient and inpatient)	78 DM (155 limbs); active foot ulceration, NS; neuropathy, NS	Pulse oximetry: SpO ₂ of big toe 2% different than index finger, either at rest or after 12-in. leg elevation; ABPI, ≤ 0.9 ; combination of ABPI and pulse oximetry
Homza et al, ³² 2019	Czech Republic	Cross-sectional; hospital outpatient	62 DM (124 limbs); active foot ulceration, NS; neuropathy, 32%	Oscillometric ABPI, < 0.9 or > 1.4 ; Doppler hABPI, < 0.9 or > 1.4 ; IABPI, < 0.9 or > 1.4
Buschmann et al, ³¹ 2018	Germany	Cross-sectional study; hospital outpatient	76 DM (158 limbs); neuropathy, NS; active foot ulceration, NS	Ultrasound-derived ABPI, 0.88; quantitative ultrasound Doppler waveform analysis using systolic ACCmax, 498 cm/s ² ; RPSI, 45 s ⁻¹ ; no predefined cutoffs for any test; optimized cutoff values used

Reference test and cutoff value	Index test performance	Comment
DUS (stenosis with PSVR >2)	Oscillometric ABPI: sensitivity, 29.4%; specificity, 95.9%; Doppler ABPI: sensitivity, 54%; specificity, 97%	Patients referred for vascular investigations; unblinded; incompressible ABPI or values >1.3 not considered diagnostic
DUS (atherosclerotic plaques)	Doppler ABPI: sensitivity, 71.4%; specificity, 97%	Unblinded; reference test cutoff not specific; no definition of significant plaque
DSA (stenosis causing >50% reduction in vessel diameter)	TcPO ₂ : sensitivity, 100%; specificity, NA; ankle pressure: sensitivity, 61%; specificity, NA	Only included patients with rest pain or tissue loss; reference test only performed in those with ankle pressure <70 mm Hg or TcPO ₂ <50 mm Hg; unblinded study; all patients had positive reference test results; no specificity data can be calculated
DUS (presence of monophasic waveform in any one of the arteries)	ABPI: sensitivity, 70.3%; specificity, 87.1%; pulse oximetry: sensitivity, 74.1%; specificity, 95.7%; combination of both tests: sensitivity, 92.3%; specificity, 83.3%	Lesion and lesion severity not considered in reference test cutoff definition; large proportion of screened patients excluded from study
DUS (stenosis >50% or occlusion)	ABPI: sensitivity, 71%; specificity, 89%	Only included patients diagnosed with active foot infection; 6 patients with incompressible vessels excluded from analysis; unclear whether tests were blinded
CDUS (>50% stenosis)	Toe pressure: sensitivity, 73.7%; specificity, 72.4%	Patients referred for suspected PAD; unblinded study
CDUS (>50% stenosis)	Tibial waveform: sensitivity, 82.8%; specificity, 88.3%	Patients referred for suspected PAD; unblinded study
CDUS (>50% stenosis)	ABPI: sensitivity, 45.2%; specificity, 92.7%; TBPI: sensitivity, 63.6%; specificity, 82.1%; visual Doppler: sensitivity, 74.2%; specificity, 92.9%	Assessor blinded to reference test
DSA (>50% stenosis)	PRT: sensitivity, 41%; specificity, 92%; ABPI: sensitivity, 36%; specificity, 93%	Only patients with PAD found on DSA were included
DUS (PSVR >2, representing >50% stenosis)	ABPI: sensitivity, 68%; specificity, 59%; ankle pressure: sensitivity, 47%; specificity, 79%; toe pressure: sensitivity, 45%; specificity, 97%; TBPI: sensitivity, 89%; specificity, 45%; TcPO ₂ : sensitivity, 28%; specificity, 66%; pole test: sensitivity, 28%; specificity, 97%; tibial waveform: sensitivity, 85%; specificity, 100%	Tibial waveforms not blinded to results of reference test; other tests blinded
DUS (occlusions, single or multiple stenoses, or diffuse stenotic disease in femoropopliteal segments, individually or collectively, causing significant velocity change and flow disturbance locally and resulting in loss of reverse flow distally)	DM, no neuropathy: ABPI: sensitivity, 100%; specificity, 88%; TBPI: sensitivity, 91%; specificity, 65%; tibial waveforms: sensitivity, 100%; specificity, 92%; diabetic neuropathy: ABPI: sensitivity, 53%; specificity, 95%; TBPI: sensitivity, 100%; specificity, 61%; tibial waveforms: sensitivity, 94%; specificity, 66%	Tibial vessels only assessed for occlusion and not stenosis on reference scan; patients with active foot ulceration or signs/symptoms of PAD excluded; unblinded study; performance of tests across all diabetic patients (neuropathy vs no neuropathy) NR; calculated separately for meta-analysis of waveform assessment and TBPI (not possible for ABPI); bilateral scans for most patients; analysis by limb
DUS (plaque associated with 100% increased PSV, concomitant with loss of flow reversal)	ABPI: sensitivity, 94%; specificity, 82%	Unblinded study
DUS (>50% stenosis)	Performance for three different thresholds: 1) sensitivity, 60.9%; specificity, 64.4%; 2) sensitivity, 70.8%; specificity, 71.4%; 3) sensitivity, 50.3%; specificity, 43.8%	Unblinded study; bilateral scans for most patients; analysis by limb
DUS (>50% stenosis)	ABPI: sensitivity, 51%; specificity, 89%; TBPI: sensitivity, 84%; specificity, 58%; ABPI and TBPI: sensitivity, 64%; specificity, 78%	Only included patients with symptomatic PAD; not clear what proportion of DM patients had both index and reference tests
DUS (≥50% stenosis)	Plethysmography ABPI: sensitivity, 20%; specificity, 95.6%; Doppler ABPI: sensitivity, 72.7%; specificity, 95.8%; PVW: sensitivity, 81.8%; specificity, 93.2%; TBPI: results for prespecified cutoff not presented owing to poor performance	Patients with active wounds precluding measurements excluded; included patients at high risk of PAD or with signs/symptoms of PAD; only 2.2% of patients had PAD on reference test; bilateral scans for all patients; analysis by limb; index and reference tests blinded
DUS (>50% stenosis)	Pulse oximetry: sensitivity, 76.7%; specificity, 85.3%; ABPI: sensitivity, 40.7%; specificity, 88.2%; combination of ABPI and pulse oximetry: sensitivity, 88.1%; specificity, 74.2%	Index and reference tests blinded; patients with severe ulceration excluded
DUS (>50% stenosis)	Oscillometric ABPI: sensitivity, 60.7%; specificity, 93.7%; hABPI: sensitivity, 67.2%; specificity, 74.6%; IABPI: sensitivity, 86.9%; specificity, 76.2%	Unblinded study; patients referred to cardiovascular outpatient clinic; bilateral scans for all patients; analysis by limb
DSA (>50% stenosis)	ABPI (ultrasound): sensitivity, 56%; specificity, 98%; systolic ACCmax: sensitivity, 57%; specificity, 98%; RPSI: sensitivity, 57%; specificity, 95%	Profunda femoris not considered in reference scan; ABPI >1.3 not considered indicative of PAD; unblinded study

ABPI, Ankle-brachial pressure index; ACCmax, maximum acceleration time; CDUS, color Doppler ultrasonography; DM, diabetes mellitus; DSA, digital subtraction angiography; DUS, duplex ultrasonography; hABPI, ankle-brachial pressure index using highest ankle pressure; IABPI, Doppler ankle-brachial pressure index using lowest ankle pressure; NA, not available; NR, not reported; NS, not specified; PAD, peripheral arterial disease; PPG, photoplethysmography; PRT, pulse reappearance time; PSV, peak systolic velocity; PSVR, peak systolic velocity ratio; PVW, pulse volume waveform; RPSI, relative pulse slope index; SpO₂, oxygen saturation (pulse oximetry); TBPI, toe-brachial pressure index; TcPO₂, transcutaneous pressure of oxygen.

Table II. Quality assessment of diagnostic accuracy studies-2 quality assessment

Investigator	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Clairrotte et al, ¹⁶ 2009	+	-	-	+	+	+	+
Dhanowar et al, ¹⁷ 2016	?	-	-	?	+	+	-
Faglia et al, ²⁷ 2010	-	-	-	+	-	-	-
Kumar et al, ²⁸ 2016	?	+	+	+	+	+	-
Premalatha et al, ¹⁹ 2002	?	?	?	+	?	+	+
Tehan et al, ²⁰ 2017	-	-	?	+	+	?	+
Tehan et al, ¹⁸ 2018	-	?	?	+	+	+	+
Tehan et al, ²² 2016	+	+	+	+	+	+	+
Vogelberg et al, ²³ 1988	-	-	?	?	-	-	-
Vriens et al, ²⁴ 2018	?	+	+	?	+	+	+
Williams et al, ^{25,35} 2005	-	?	?	+	-	?	?
Zhang et al, ²⁶ 2010	-	?	?	+	+	?	?
Tehan et al, ²¹ 2018	?	?	?	+	+	+	+
AbuRahma et al, ²⁹ 2019	-	-	-	-	-	+	+
Babaei et al, ³⁰ 2019	-	+	+	+	-	+	+
Siao et al, ³⁴ 2018	?	+	+	?	+	+	+
Homza et al, ³² 2019	-	?	?	?	+	+	+
Buschmann et al, ³¹ 2018	?	-	?	?	+	-	?

+, Low risk; -, high risk; ?, unclear.

included in the meta-analysis of the diagnostic performance for ABPI (n = 9 studies; 1368 limbs), TBPI (n = 3 studies; 221 limbs), and qualitative tibial waveform assessment (n = 4 studies; 397 limbs).^{16,17,19,21,22,24,26,28,30,34,35}

For the meta-analysis of ABPI data, plethysmography and ultrasonography were excluded owing to their particularly poor performance across a small number of studies. Additionally, four ABPI^{23,29,32,35} and two TBPI^{29,30} studies were excluded because 2 × 2 contingency tables could not be constructed owing to incomplete reporting.

Comparative summary receiver operating characteristic curve plots for ABPI, TBPI, and tibial waveform assessment are shown in Fig 3. The meta-analysis for the studies evaluating ABPI for the detection of PAD in those with diabetes showed a sensitivity of 63.5% (95% CI, 51.7%-73.9%) and a specificity of 89.3% (95% CI, 81.1%-94.2%). For TBPI, the analysis showed a sensitivity of 83.0% (95% CI, 59.1%-94.3%) and a specificity of 66.3% (95% CI, 41.3%-84.6%). For the visual tibial arterial waveform assessment, the analysis showed a sensitivity of 82.8% (95% CI, 73.3%-89.4%) and specificity of 86.8% (95% CI, 75.5%-93.3%).

DISCUSSION

To the best of our knowledge, the present study is the first systematic review to include a meta-analysis of

studies on the diagnostic performance of bedside tests for the detection of PAD in people with diabetes. We identified a number of studies^{18,29-34} that had not been previously included in the recent systematic review by Forsythe et al.³⁶ Additionally, a number of studies included in their review did not meet our stricter reference test inclusion criteria.³⁷⁻³⁹ We believe that despite the inevitable heterogeneity in the reported studies, from both methodologic and clinical diversity, a meta-analysis provided valuable estimates that might be used to guide future research and clinical practice.

The National Institute for Health and Care Excellence in the United Kingdom has recommended that adults with diabetes should undergo a formal foot risk assessment at diagnosis, annually after the diagnosis, on admission to the hospital, and if any foot problems arise.⁴⁰ An important part of this assessment is testing for PAD. In the non-ulcerated foot, the detection of PAD will place patients in the "moderate risk" category and should initiate referral to foot protection services, who will take measures to reduce the risk of foot ulceration and optimize diabetes and cardiovascular risk management. Patients at moderate risk will also require more regular foot evaluations (eg, every 3-6 months). The timely detection of PAD in the presence of active foot ulceration is critical to allow for rapid restoration of the blood supply to the foot, which has been shown to improve the chances of ulcer

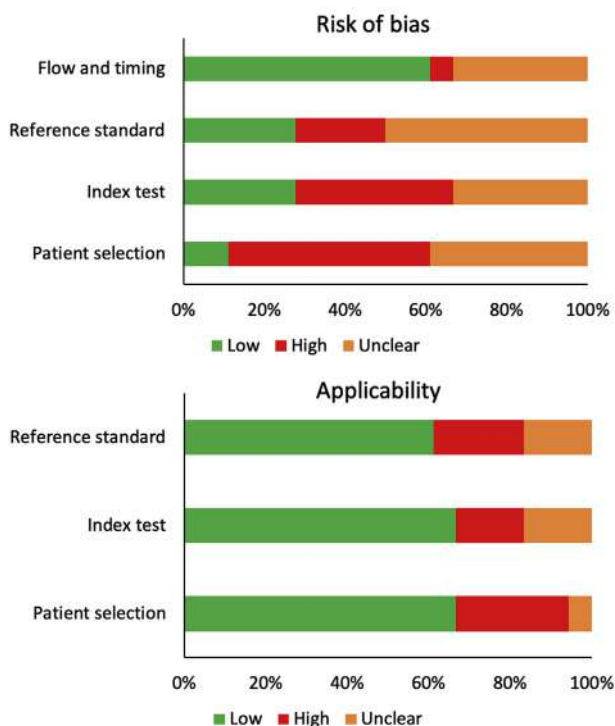


Fig 2. Graph showing QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) results. “Flow and timing” domain refers to any potential source of bias that might have been introduced by the patient flow in the study (eg, an inappropriate interval between the index tests and reference standard, not all patients receiving the same reference test, and not including all patients in the analysis). By convention, this domain was not assessed for applicability judgments.

healing.¹⁰ New guidelines in the United Kingdom now advocate for revascularization within 2 weeks of presentation in the presence of PAD.⁴¹ Although this might not be practical or necessary for all patients, the recommendations do highlight the importance of accurate PAD testing at the initial presentation in individuals with diabetes.

The results from our analysis suggest that, although ABPI has a high specificity (89.3%; 95% CI, 81.1%-94.2%), its sensitivity (63.5%; 95% CI, 51.7%-73.9%), even at the upper end of the 95% CI, is insufficiently low to be used alone for the screening of PAD in people with diabetes. We found insufficient evidence to support the routine use of exercise ABPI because only one study evaluated its diagnostic performance.

Across the studies, the tibial arterial waveform assessment and TBPI measurements appeared the most promising modalities for the diagnosis of PAD in diabetes. In our meta-analysis, we found very wide CIs for the sensitivity and specificity of TBPI, reflecting the small number of studies included in our analysis. However, three of the included studies achieved some of the lowest risk of bias scores in our review but showed quite different results relating to the diagnostic performance

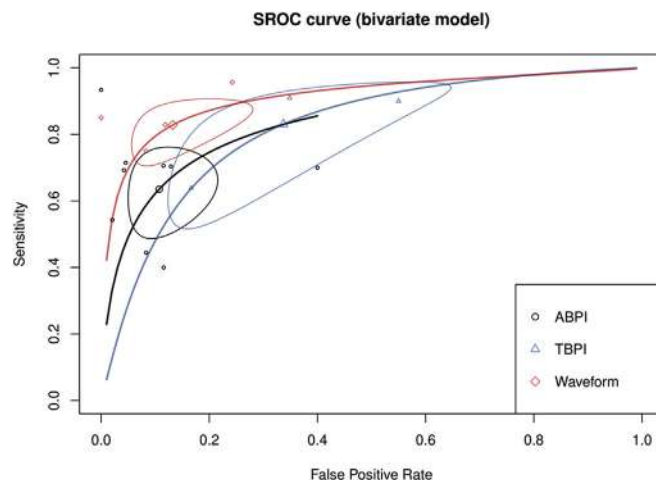


Fig 3. Summary receiver operating characteristic curve (SROC) for ankle-brachial pressure index (ABPI), toe-brachial pressure index (TBPI), and tibial waveform assessment. Size of ellipse indicates the 95% confidence interval (CI). Waveform, Tibial waveform assessment.

of TBPI. This might have resulted from differences in the study populations. In contrast, tibial arterial waveform assessment performed more consistently across the studies with a narrower CI for sensitivity and specificity.

We found that although the cutoff values for TBPI studies were very similar, significant variation was present in the diagnostic cutoff values used for tibial waveform assessment, with both monophasic and biphasic waveforms described as the diagnostic threshold for the diagnosis of PAD. At present, no threshold has been accepted for qualitative tibial waveform assessment. Reaching consensus on this might further improve the diagnostic performance of this promising testing modality. Furthermore, the best method for qualitative waveform assessment has not yet been established. Visual waveforms can be detected using a handheld continuous-wave device (three of four studies) or a duplex ultrasound machine (one of four studies). The potential advantage of DUS is that it allows for direct visualization of the blood vessel and blood flow (in color) allowing for sampling of the waveforms from a specific region of interest and reducing the risk of mistaken sampling from a nearby collateral branch. Additionally, DUS allows for visualization of more detailed waveforms for more precise waveform interpretation. However, a learning curve is involved for the operator and it necessitates the provision of a portable ultrasound machine.

In our review, we found no studies evaluating the diagnostic performance of audible Doppler assessment. Although this is the most widely used test for the detection of PAD in diabetes,⁴² it is limited by significant inter-observer variation.⁴³ Visually displayed waveforms allow for greater objectivity in assessment and should be the preferred method for tibial waveform assessment.

We found little evidence supporting the use of systolic ankle or toe pressures for the diagnosis of PAD in diabetes. Vriens et al²⁴ reported corresponding sensitivities of 47% and 45% for these modalities. Another study evaluating ankle pressures (and TcPO₂) was rated as at high risk of bias for patient selection and reference and index tests.²⁷ Another study, evaluating toe pressure, used an optimized cutoff value to determine diagnostic performance.²⁰ This approach, especially in small studies, has been shown to overestimate test performance.⁴⁴ Finding robust estimates of cutoff values requires a large sample size. The only reliable study evaluating TcPO₂ measurements in our review demonstrated a low sensitivity of 28%.²⁴ Considering these values and that measurement of the TcPO₂ is challenging and time consuming to perform, it is unlikely to be a useful modality for PAD screening.

Pulse oximetry was investigated in two studies.^{28,34} Although some uncertainty was present regarding patient selection bias (one study did not report the presence of foot ulceration and the other had not included patients with foot ulceration), the estimated sensitivity was 74.1% and 76.7%. Siao et al³⁴ also reported that parallel testing using a combination of ABPI and pulse oximetry might yield a sensitivity as high as 88.1%. Given that both methods are inexpensive and readily available, this is an attractive finding that warrants further investigation to confirm these observations in a suitably representative population of patients with diabetes. Their study also highlights the need for further investigation of parallel testing strategies that might improve sensitivity, although often at the expense of specificity.

After the initial detection of PAD using a noninvasive bedside test, patients will be referred for specialist assessment and anatomic imaging studies. Determining the severity of PAD at the initial presentation might help inform the urgency of the referral to specialist services. The severity of PAD can be determined from clinical (eg, rest pain, ulcer severity), anatomic (eg, severity and/or location of the arterial lesion), and/or functional (eg, foot perfusion deficit) parameters. However, each of these parameters poses unique challenges. Clinical severity can be difficult to determine from the symptoms alone because patients with diabetes are more likely to present with atypical symptoms owing to the presence of neuropathy.⁴⁵ Furthermore, ulcer severity is multifactorial (eg, neuropathy and the presence of infection) and might not be reflective of the severity of PAD. Anatomic severity might not be representative of the degree of foot perfusion, which could require additional testing. Therefore, studies evaluating the value of diagnostic bedside tests for predicting foot outcomes, such as ulcer healing and amputation, would be of particular interest in establishing the severity and prognosis at the initial patient presentation.

The results of the present review coincide with the recent completion of the TrEAD (testing for arterial disease in diabetes) study⁴⁶ ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04058626) identifier, NCT04058626) by our group, which will be presented in another report.

Study limitations. In our meta-analysis, we did not explicitly control for study quality and design owing to the small number of available studies. However, this was indirectly achieved by the exclusion of those studies with inadequate reporting. Owing to the limited number of studies and inadequate reporting of diabetic subgroups (eg, those with neuropathy and active ulceration), we could not control for the patient population in our meta-analysis. Disease prevalence was also variable across the studies, and the results should be viewed in this context. Similarly, our analysis did not control for differences in diagnostic cutoffs (for both index and reference tests) because this would have meant the exclusion of a number of good quality studies. Defining PAD for diagnostic accuracy studies is challenging. Any evidence of atherosclerotic disease might be considered positive for PAD. However, from a clinical perspective, a more useful definition would be a hemodynamically significant lesion (ie, stenosis of >50%), which would trigger intervention. Although this definition was used by most studies, clarification was lacking regarding the management of clinically relevant indeterminate results such as hemodynamically significant tandem lesions.

Additionally, a large proportion of studies in our analysis evaluated the diagnostic performance of tests by performing bilateral scans and interpreting the results in each limb independently ("analysis by limb"). This was a potential source of bias because the presence of PAD in one limb increases the probability of the presence of PAD in the other. However, owing to inadequate reporting, we could not control for this in our analysis. Furthermore, despite our efforts to standardize the outcome definitions and measurements, clinical and methodologic heterogeneity was inevitable.

Another potential limitation of the present review was that most studies had used DUS as the reference test. DUS is inexpensive and noninvasive and has been shown to have good agreement with intra-arterial DSA.¹¹ However, DUS might be less reliable in identifying significant PAD in the crural vessels,¹¹ which are more likely to be affected by atherosclerosis in people with diabetes,⁴⁷ especially in the presence of significant calcification. Alternative noninvasive methods that could be used as reference tests include CTA and MRA.

CONCLUSIONS

TBPI, pulse oximetry, and ankle arterial waveform assessment have demonstrated some promising results that warrant further investigation in a robust prospective diagnostic accuracy study. Given the disappointingly

poor sensitivity of ABPI and the lack of evidence for its performance when used in combination with other tests, we cannot at present recommend it as a rule out test for PAD in people with diabetes. Although further evidence is awaited, we recommend that all patients with active diabetic foot ulceration undergo full lower limb DUS for the assessment of PAD.

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AUTHOR CONTRIBUTIONS

Conception and design: PN, JS, AD, SS, UJ

Analysis and interpretation: PN, JS, AD, JN, VS, UJ

Data collection: PN, CM

Writing the article: PN, UJ

Critical revision of the article: PN, CM, JS, AD, JN, VS, SS, UJ

Final approval of the article: PN, CM, JS, AD, JN, VS, SS, UJ

Statistical analysis: PN, JN

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