Received: 1 June 2019 | Revised: 25 September 2019 | Accepted: 2 October 2019

DOI: 10.1002/dmrr.3277

SUPPLEMENT ARTICLE

WILEY

Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: A systematic review

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Abstract

The accurate identification of peripheral artery disease (PAD) in patients with diabetes and foot ulceration is important, in order to inform timely management and to plan intervention including revascularisation. A variety of non-invasive tests are available to diagnose PAD at the bedside, but there is no consensus as to the most useful test, or the accuracy of these bedside investigations when compared to reference imaging tests such as magnetic resonance angiography, computed tomography angiography, digital subtraction angiography or colour duplex ultrasound. Members of the International Working Group of the Diabetic Foot updated our previous systematic review, to include all eligible studies published between 1980 and 2018. Some 15 380 titles were screened, resulting in 15 eligible studies (comprising 1563 patients, of which >80% in each study had diabetes) that evaluated an index bedside test for PAD against a reference imaging test. The primary endpoints were positive likelihood ratio (PLR) and negative likelihood ratio (NLR). We found that the most commonly evaluated test parameter was ankle brachial index (ABI) <0.9, which may

be useful to suggest the presence of PAD (PLR 6.5) but an ABI value between 0.9 and 1.3 does not rule out PAD (NLR 0.31). A toe brachial index >0.75 makes the diagnosis of PAD less likely (NLR 0.14-0.24), whereas pulse oximetry may be used to suggest the presence of PAD (if toe saturation < 2% lower than finger saturation; PLR 17.23-30) or render PAD less likely (NLR 0.2-0.27). We found that the presence of triphasic tibial waveforms has the best performance value for excluding a diagnosis of PAD (NLR 0.09-0.28), but was evaluated in only two studies. In addition, we found that beside clinical examination (including palpation of foot pulses) cannot reliably exclude PAD (NLR 0.75), as evaluated in one study. Overall, the quality of data is generally poor and there is insufficient evidence to recommend one bedside test over another. While there have been six additional publications in the last 4 years that met our inclusion criteria, more robust evidence is required to achieve consensus on the most useful non-invasive bedside test to diagnose PAD.

KEYWORDS

amputation, diabetes, diabetic foot, diagnosis, foot ulcer, peripheral artery disease

1 | INTRODUCTION

The estimated pooled worldwide global prevalence of foot ulceration among people with diabetes is 3%,[1] of which up to 50% may have underlying peripheral artery disease (PAD).[2] Diabetes is strongly associated with the presence of PAD; among individuals with diabetes in the US National Health and Nutrition Examination Survey in 2004; 9.6% had PAD as defined by ankle brachial index (ABI) <0.9 in either leg, compared with 4% of individuals without diabetes (age and gender standardised).[3] In diabetic subjects older than 60 years, the prevalence of PAD was 25%.[4] Evidence suggests that PAD is causally related to the development of a Diabetic foot ulcer (DFU), thereby leading to a higher prevalence of PAD in diabetic patients with DFU than in those without a DFU. A prospective study of 749 patients without diabetic foot ulcer identified a significant association between lower ABI and higher foot ulcer risk.[5]

The combination of diabetes and PAD substantially increases the risk of amputation or non-healing and of cardiovascular mortality.[6-8] In the Eurodiale study, patients with a foot ulcer and PAD, when compared with ulcer patients without PAD, had healing rates of 69% vs 84% and major amputation rates of 8% vs 2%, respectively.[2] Not only is PAD an independent risk factor for developing foot ulceration and limb loss, it is also associated with a higher risk of incident cardiovascular disease and of overall mortality, irrespective of symptoms or the populations studied.[9] PAD is therefore clearly associated with poorer lower extremity and cardiovascular outcomes in patients with diabetes. It is important for healthcare professionals to recognise it promptly, and accurately, and to risk stratify patients and take steps to minimise its deleterious effects. However, many patients with diabetes and co-existing PAD present late with foot ulceration[10] and with few or no preceding symptoms of PAD, probably due to the masking of typical symptoms (such as claudication and ischaemic rest pain) by peripheral neuropathy. In addition, physical examination in these patients may not reliably exclude a diagnosis of PAD, or assess its severity. Bedside tests that are useful to diagnose PAD in a population of patients without diabetes may be rendered less accurate in patients with diabetes due to the distal distribution of the peripheral arterial disease, co-existing neuropathy, peripheral oedema and infection. Moreover, in patients with diabetes the lower leg or pedal arteries can be less compressible on cuff inflation during external arterial pressure measurements due to medial sclerosis (medial arterial calcification) which can render tests, such as the ABI or toe brachial index (TBI) less reliable.[11] These tests can play a central role in diagnosing or excluding PAD,[12] and their advantage over reference imaging tests (such as magnetic resonance angiography [MRA], computed tomography angiography [CTA], digital subtraction angiography [DSA] and colour duplex ultrasound [CDUS]) is that they are quick, cheap, non-invasive, may be performed at the bedside and can be used as initial screening tests in order to identify those patients who should go on to have formal vascular imaging tests.

The aim of this systematic review was to evaluate the performance of index non-invasive diagnostic tests against reference standard imaging techniques for the detection of PAD among patients with diabetes and is an update of our previous review.[13] This systematic review forms the basis for developing the IWGDF Guideline on diagnosis, prognosis, and management of PAD in patients with a foot ulcer and diabetes.[14]

2 | METHODS

2.1 | Search methods

Using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance,[15] we updated our previous systematic

review,[13] guided by a recent consensus document on updating systematic reviews[16] and the IWGDF methodology document.[17]

As a start, the population of interest (P), interventions (I), comparators (C) and outcomes (O) were defined, and clinical questions (PICOs) were formulated accordingly. These definitions and PICOs were reviewed for their clinical relevance by the IWGDF Editorial Board and external experts worldwide, from various geographical regions (see acknowledgements). Final definitions and PICOs are integrated within this paper.

We searched the MEDLINE and EMBASE databases for studies relating to the diagnosis of PAD among patients with diabetes, updating the previous search and therefore capturing any new records published between 14 June 2014 and 14 September 2018. The search string can be found in Data S1. Two reviewers independently screened the abstracts for inclusion and a third reviewer adjudicated any conflicts. Full-text articles of included abstracts were accessed and assessed for inclusion and data were then extracted and verified by members of the IWGDF PAD working group.

2.2 | Inclusion/exclusion criteria

We sought to evaluate the performance and reliability of bedside tests for PAD in diabetic patients with and without a foot ulcer. We evaluated any bedside test that aimed to detect the presence of PAD in patients with diabetes. Diagnostic tests were considered as any specific evaluation that sought to identify the presence of PAD. To be eligible for inclusion, all studies were required to meet the following criteria: (a) evaluated a potential index diagnostic test for PAD against a standard reference test (including DSA, CTA, MRA or CDUS); (b) reported separately on at least 10 patients with diabetes or, in mixed studies, more than 80% of the cohort were patients with diabetes. We included studies that reported on patients with or without a foot ulcer. Studies were excluded if the comparison was between two reference tests, or if there was insufficient data with which to calculate the sensitivity/specificity values. Unlike our previous review, we did not include serum markers as an expression of possible PAD as it was concluded that such tests would have little added value in diagnosing PAD.

2.3 | Primary endpoints

The positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were the primary endpoints for this systematic review. In order to assess the usefulness of bedside tests, we have used likelihood ratios, which reflect a diagnostic test's ability to rule in or rule out disease.[18] Likelihood ratios were used to express a change in odds of reaching an outcome, in the context of a known pre-test probability of disease (ie, knowledge or estimation of the prevalence of disease in the studied population). The PLR gives the change in odds of experiencing an outcome if the test is positive, whereas the NLR expresses a change in odds of experiencing an outcome if the test is negative. PLR is calculated as follows: PLR = sensitivity/(1 − specificity); NLR is calculated as follows: NLR = (1 − sensitivity)/specificity. A PLR or NLR of 1.0 means that the test does not change the probability of the outcome over and above the pre-test probability and therefore is not a useful diagnostic test. As a general rule of thumb, a test is considered to have very good performance if PLR ≥10 (representing an increased probability of the specified outcome by around 45% in the presence of a positive test result) and NLR≤0.1 (representing a decrease in the probability of the specified outcome of around 45% in the presence of a negative test result).[19-21] Generally, minimal change in disease probability can occur when a test is used with a PLR between 1 and 2 or a NLR between 0.5 and 1. The PLR and NLR therefore provide a more meaningful assessment of diagnostic utility than sensitivity or specificity when used with the aim of disease-probability revision (Table 1).

2.4 | Data extraction and quality assessment

Data extraction was undertaken and independently verified by two investigators. Methodological quality was assessed using the QUADAS tool, a consensus quality assessment tool designed specifically for diagnostic accuracy studies.[22] There was a wide range of heterogeneity in the populations evaluated, outcomes reported and diagnostic tests used, and it was therefore not possible to conduct a meta-analysis. Instead, measures of test performance were presented for each diagnostic test used and summarised within and across studies. Where not explicitly reported, sensitivity/specificity, PLR and NLR were calculated from the available data and reported in our evidence table (Table 2).

2.5 | Evidence statements

Finally, two investigators drew conclusions for each intervention based on the strength of the available evidence, formulated as evidence statements and accompanying assessment of the quality of the evidence, according to GRADE.[23]

3 | RESULTS

3.1 | Search results

In the search performed for our previous systematic review, 6629 studies were screened (published between 1980 and 2014), which

TABLE 1 Interpretation of likelihood ratios and their effect on probability of disease[46]

High likelihood ratios	Low likelihood ratios	Interpretation—affect on ability to rule in/rule out disease
>10	<0.1	Large
5-10	0.1-0.2	Moderate
2-5	0.2-0.5	Small
1	1	No change

TABLE 2 Evidence table of all papers included in systematic review

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
Clairotte et al[25]	Cohort Secondary care outpatient clinic	83 DM; mean duration DM 12 ± 11; y, HbA1c 8.4% ± 2.1%; presence foot ulcers NS; 60% with "normal clinical foot examination" & presence 2 pedal pulses; 48% neuropathy Mean age 63 ± 11 y; 71% male; CAD 26.5%; CVD 6%; smoking 27%	Automated oscillometric ABI <0.9 & Doppler ABI <0.9 Technical success DopABI 97%; Osc-ABI 96%	DUS (Max systolic velocity ratio ≥2)	Dop ABI (<0.9): Sensitivity 54%; Specificity 97%; PLR 17.0; NLR 0.28 Osc ABI (<0.9): Sensitivity 29.4%; Specificity 95.9%; PLR 7.9; NLR 0.50 Analysis by patient	+	Incompressible ABI (>1.3 included in study but not considered an indicator of PAD) ABI measurement not blinded but was obtained by automated device
Zhang et al, 2009[47]	Retrospective case series Secondary care outpatient clinic	92 DM; mean HbA1c 8.09%-8.78%; mean duration DM ranged from 8.9 to 16.7 y between groups; presence foot ulceration NS; presence neuropathy NS Mean age 63 ± 14 y; 78% male CAD 26%, CVD not reported	ABI <0.9	CDUS (Large plaque >10 mm^2 with 100% increase in peak systolic velocity)	Sensitivity 95%; Specificity 86%; PLR 6.8; NLR 0.06 Analysis by patient	+	Those with unobtainable ABIs categorised as high Exclusively Chinese population may differ from other populations
Premalatha et al[29]	Cohort Secondary care inpatients	100 T2DM; mean duration DM 11.7 ± 8.1 y; HbA1c 9.5% ± 2.0%; admitted to hospital; presence severe foot infection 100%; presence neuropathy NS Mean age 59.5 ± 10.1 y; CAD/CVD not reported	ABI <0.9	CDUS (Stenosis >50% or occlusion)	Sensitivity 71%; specificity 89%; PLR 6.5, NLR 0.33 Analysis by patient	+	6 patients with arterial calcification excluded from analyses. Overall agreement poor 42.6%—kappa = 0.2
Parameswaran et al[39]	Cross-sectional Primary care outpatient clinic	57 T2DM; mean duration DM 9 y; presence foot ulceration NS; presence neuropathy NS	ABI & pulse oximetry (technical success unreported)	Doppler waveform analysis Lower extremity arterial disease (LEAD) defined as monophasic waveform at any lower limb artery)	ABI (<0.9): Sensitivity 63%; Specificity 97%; PLR 24.8; NLR 0.38 Pulse oximetry (2% lower than finger value/	+	Combination of ABI & pulse oximetry (either test abnormal)—sensitivity 86%; specificity 92%; PLR 11.29; NLR 0.15

(Continues)

TABLE 2 (Continued)

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
		Mean age 63 y; male 47%; CAD 18%; carotid disease 2%; HTN 66%; hyperlipidaemia 29%; current smoker 30%			elevation of leg): Sensitivity 77%; Specificity 97%; PLR 30.0; NLR 0.23 Analysis by limb		No incompressible ABIs reported Patients with known LEAD/symptoms of LEAD excluded Assessor of index test blinded to results reference test
Lewis et al[30]	Cross-sectional Population sample	205 DM; T1DM 23; T2DM 182; duration DM NS; presence foot ulceration 0%; presence neuropathy NS Mean age 62.8 ± 12.9 y; male 105/205; CAD/CVD not reported	ABI <0.9 OR > 1.3 measured using photoplethysmography	Colour spectral waveform (monophasic)	Sensitivity 91%; Specificity 67%; PLR 4.0; NLR 0.12 Analysis by limb	+	Patients with foot ulcers or previous major amputation excluded Incompressible ABI included in index test definition Unblinded study
Williams et al[26]	Cross-sectional Secondary care outpatient clinic	79 limbs with DM; patients with DM NS; 85% T2DM; 74% male; mean age 63-69 y; mean duration DM ranged from 11 to 24 y between groups; presence foot ulceration 0%; 72% neuropathy CAD/ CVD not reported	ABI, TBI, Doppler waveform	CDUS (definition significant PAD if stenosis in fem-pop segments causing significant velocity change and loss of reverse flow distally)	Diabetes, no neuropathy: ABI (<0.9): Sensitivity 100%; Specificity 88%; PLR 8.0; NLR N/A TBI (<0.75): Sensitivity 91%; Specificity 65%; PLR 3.0; NLR 0.1.Wave (loss of triphasic signal): Sensitivity 100%; Specificity 92%; PLR 13.0; NLR N/A Diabetic neuropathy: ABI: Sensitivity 53%; Specificity 95%; PLR 11.0; NLR 0.49 TBI: Sensitivity 100%; Specificity 61%; PLR 3.0; NLR N/A	+	Exclusions: active foot disease; signs or symptoms suggestive CLI Incompressible ABI (>1.3 included in study but not considered an indicator of PAD) Unblinded study

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TABLE 2 (Continued)

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
					Wave: Sensitivity 94%; Specificity 66%; PLR 3.0; NLR 0.09 Analysis by limb		
Aboyans et al[44]	Cross-sectional Secondary care outpatient clnic	158 DM; mean duration DM 16.1 y; 67% insulin therapy; 82.9% oral medication; presence foot ulceration NS; presence neuropathy NS Mean age 68 y (range30-100); 88% males CVD/CAD not reported	ABI ≤0.9	Peak tibial flow velocity (≤10 cm/s)	Sensitivity 99%; Specificity 58%; PLR 2.4; NLR 0.02 Analysis by patient	+	7.6% of DM patients had an ABI ≥1.4 Unblinded study
Ezio et al[27]	Cohort Secondary care inpatients	261 CLI and DM; mean duration DM 18 ± 12 y; 60.9% insulin therapy; 39.1% oral therapy; presence of foot ulceration 94%; 82% neuropathy Mean age 76 ± 8 y (females), 71.6 ± 8.7 y (males); males 66.5%, HTN 46.0%; CAD 20.3%; CVD 24.5% CLI definition: ankle pressure < 70 mm Hg and $TcPo_2$ at dorsum of foot <50 mm Hg	Ankle pressure < 70 mm Hg and $TcPO_2$ < 30 mm Hg Technical success: ankle pressure 58.2%; $TcPO_2$ 100%	DSA (stenosis causing >50% reduction in vessel diameter) Technical success: 100%	Ankle pressure: Sensitivity 67%; Specificity N/A $TcPO_2$: Sensitivity 82%; Specificity N/A Analysis by patient	+	Cohort of patients with DM and rest pain/ft lesions. Unrecordable ankle pressures due to arterial calcification or absent foot pulses were not excluded 100% of patients had a stenosis >50% of lumen on DSA therefore no specificity data can be calculated Unblinded study
Vogelberg and stork[31]	Cross-sectional Secondary care patients (inpatients/ outpatients NS)	20 DM; 30% NIDDM; mean duration DM 15 ± 10 y Mean age 61 ± 9; 65% male; with angiographically confirmed PAD were	Pulse reappearance time (measured with Doppler probe) & ABI	DSA (pathological angiographic findings defined as stenosis >50%)	PRT: Sensitivity 41%; Specificity 92%; PLR 5.1; NLR 0.64	+	No definition provided for cut-offs for pathological PRT or ABI Only patients with PAD included

(Continues)

TABLE 2 (Continued)

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
		selected; gangrene 47%, CAD/CVD not reported; gangrene of the foot in 47%; presence neuropathy NS			ABI: Sensitivity 36%; Specificity 93%; PLR 5.1; NLR 0.69 Analysis by arterial segments		
Dhanowar et al, 2016[38]	Case series Tertiary care hospital inpatients	80 with Type 2 DM; no further info given. No follow up data reported.	ABI <0.9	CDU: presence of atherosclerotic plaques or arterial calcification	ABI <0.9 sensitivity 71.4%; specificity 97%; PPV 83.3%; NPV 94.1%; PLR 23.80; NLR 0.29. Analysis by patient		Minimal clinical information Blinding—not specified.
Tehan et al[32] [b]	Retrospective case-control Private outpatient clinic	Sub-group analysis of 176 patients with DM. Age 74.65 y; male 65%, ever smoked 58%; active ulceration 3%; claudication 9%. CAD/CVD/neuropathy not reported. No follow up data reported.	CWD: multiphasic waveform = non-pathological/no significant PAD; monophasic or absent waveform = pathological/ significant PAD	CDU: presence of PAD = one or more arteries with ≥50% luminal stenosis. Presence of MAC also documented.	CWD sensitivity 82.76%; specificity 88.33%; PLR 7.09; NLR 0.19. Analysis by patient		Sub-group analysis of DM patients is clearly reported therefore this study is included despite overall <80% DM. Sensitivity best in patients with occlusive disease (85.26%) and worst in patients with >75% stenosis (54.55%). In patients with MAC (n = 45), sensitivity 87.5%; specificity 69.23%; PLR 2.84; NLR 0.18.
Tehan et al[36] [b]	Retrospective case-control Private outpatient clinic	Sub-group analysis of 176 with DM. Age 74.60 y; male 65%; history of foot complications 7%; ever smoked 58%. CAD/CVD/neuropathy not reported. No follow up data reported.	Resting systolic toe pressure < 97 mm Hg	CDU: presence of PAD = at least one arterial stenosis >50%. Stenosis graded as >50% (50%-75% stenosis, focal increase in velocities 250 cm/s-350 cm/s, greater than 3-fold increase in velocities); >75% (75%-99% stenosis, focal increase in velocities >350 cm/s, 4-fold increase in velocities);	Toe pressure sensitivity 73.73%; specificity 72.41%; PLR 2.67; NLR 0.36. Analysis by patient		Also analysed sensitivity of toe pressure by anatomical location and stenosis severity. Best sensitivity in patients (n = 39; 22.16%) with proximal and distal disease (79.49%) and those (n = 11; 6.25%) with 50-75% stenosis (81.82%).

(Continues)

TABLE 2 (Continued)

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
				occlusion (vessel wall visualised, no colour or Doppler flow seen)			
Tehan et al[37]	Cross-sectional case-control Private outpatient clinic	Sub-group analysis of 72 with DM. Age 73 y; male 65%; neuropathy 12%; ever smoked 58%; cardiovascular disease 31%. Neuropathy or ulceration not reported. Follow up not reported.	ABI ≤0.9 or ≥1.4 CWD: presence of PAD = loss of multi-phasic patterns in DP or PT demonstrated by low-resistance, slow systolic acceleration and no diastolic flow reversal TBI <0.7	CDU: presence of PAD = one or more arteries with ≥50% stenosis	ABI: sensitivity 45.16%; specificity 92.68%; PLR 6.17; NLR 0.59; PPV 82.35; NPV 69.09. CWD: sensitivity 74.19%; specificity 92.86%; PLR 10.29; NLR 0.28; PPV 88.46; NPV 82.98. TBI: sensitivity 63.63%; specificity 82.05%; PLR 3.55; NLR 0.44; PPV 75.00; NPV 72.73. Analysis by patient		Assessor blinded to reference test
Kumar et al[33]	Cross-sectional Tertiary hospital outpatients	120 patients with Type 2 DM; asymptomatic PAD; 0% ulceration. No further clinical information given. Follow up not reported.	ABI: <0.9 Pulse oximetry (SpO2): presence of PAD = toe saturation less than finger saturation by <2% or if foot saturation decreased by >2% when elevated.	CDU: presence of PAD = monophasic waveforms in any one artery	ABI: sensitivity 70.3%; specificity 87.2%; PPV 61.3%; NPV 91.0%; PLR 5.49; NLR 0.34. Pulse oximetry: sensitivity 74.1%; specificity 95.7%; PPV 83.3%; NPV 92.7%; PLR 17.23; NLR 0.27 Parallel testing (ABI + SpO2 combined): sensitivity 92.3%; specificity 83.3%; PLR 5.53; NLR 0.09 Analysis by patient		Assessor of index test blinded to results reference test
Vriens et al[28]	Observational cohort	60 patients with DM and new onset foot ulceration; 25% inpatients. Age 66 y; male 75%; duration of	Clinical examination: hair loss, muscle atrophy, dependent rubor, cool skin, blue/purple skin,	CDU: presence of PAD = PSV ratio >2, representing >50% stenosis;	Clinical examination: Pedal pulse assessment: sensitivity 0.55, specificity 0.60; PPV 0.41, NPV		Assessor blinded to results reference test

(Continues)

TABLE 2 (Continued)

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
	Tertiary hospital outpatients and inpatients	diabetes 2 y; current smokers 7%, hypertension 73%; CVD 7%; CAD 16%; CKD 23%; neuropathy 85%; active infection 32%	capillary refill time, venous filling time, palpation of peripheral pulses, presence of neuropathy. ABI <0.9 or >1.3; ankle pressure < 70 mm Hg; toe pressure < 50 mm Hg; TBI ≤0.75; TcPO2 < 60 mm Hg; Pole test Tibial waveforms: not specified	Flow velocity waveforms: presence of PAD = monophasic flow beneath a calcified segment	0.73; PLR 1.38, NLR 0.75. Hair loss: sensitivity 0.8, specificity 0.44; PPV 0.42, NPV 0.81; PLR 1.42, NLR 0.46. Atrophy: sensitivity 0.5, specificity 0.87; PPV 0.67, NPV 0.77; PLR 3.9, NLR 0.57. Dependent rubor: not discriminatory. Cool skin: sensitivity 0.3, specificity 0.9; PPV 0.6, NPV 0.71; PLR 2.93, NLR 0.78. Blue/purple skin: not discriminatory. Capillary refill: sensitivity 0.42, specificity 0.63; PPV 0.36, NPV 0.69; PLR1.14, NLR 0.92. Venous filling: not discriminatory. Ankle pressure: sensitivity 0.47, specificity 0.79; PPV 0.53, NPV 0.75; PLR 2.25, NLR 0.67. Toe pressure: sensitivity 0.45, specificity 0.97; PPV 0.90, NPV 0.78; PLR 17.55, NLR 0.56. TBI: sensitivity 0.89, specificity 0.45; PPV 0.45, NPV 0.89; PLR 1.63, NLR 0.24. ABI: sensitivity 0.68, specificity 0.59; PPV 0.46, NPV 0.79; PLR 1.69, NLR 0.53. Pole test: sensitivity 0.28, specificity 0.97; PPV 0.83, NPV 0.73; PLR 10.29, NLR 0.74.		

(Continues)

TABLE 2 (Continued)

Source, year, ref	Study design & setting	Population (age, sex, comorbidity, proportion with DM, number ulcerated etc)	Index test; definition of PAD	Reference test; definition of PAD	Index test performance (sensitivity, specificity, PLR, NLR)	Quality assessment[a]	Comment/opinion
					TcPO2: sensitivity 0.28, specificity 0.66; PPV 0.28, NPV 0.66; PLR 0.81, NLR 1.10. Tibial waveforms: sensitivity 0.85, specificity 1; PPV 1, NPV 0.93; PLR diagnostic; NLR 0.15 (the definition of PAD included monophasic waveforms therefore specificity/PPV are 1 and PLR is infinite and diagnostic. Analysis by patient.		

[a]QUADAS quality assessment: High quality (++): majority of criteria met; Acceptable (+): most criteria met; Low quality (0): Either most criteria not met, or significant flaws relating to key aspects of study design.
[b]Same patient set used in two different papers - only included once in the total number of patients presented in the manuscript.
Abbreviations: ABI, ankle brachial index; CAD, coronary artery disease; CDU, colour duplex ultrasonography; CHD, coronary heart disease; CLI, critical limb ischaemia; CVA, cerebrovascular accident; CWaD, colour wave Doppler; CWD, continuous-wave Doppler; DM, diabetes mellitus; Dop-ABI, Doppler ABI; DP, dorsalis pedis artery; DSA, digital subtraction angiography; DUS, duplex ultrasound; HbA1c, glycosylated haemoglobin; HTN, hypertension; LEAD, lower extremity arterial disease; LLI, lower limb ischaemia; MAC, medial arterial calcification; NA, not applicable (cannot be calculated); NLR, negative likelihood ratio; NPV, negative predictive value; NS, not stated; Osc-ABI, oscillatory ABI; PAD, peripheral artery disease; PLR, positive likelihood ratio; PPV, positive predictive value; PN+, with peripheral neuropathy; PN-, without peripheral neuropathy; PSV, peak systolic velocity; PT, posterior tibial artery; ROC, receiver operator characteristic; SpO2, peripheral arterial oxygen saturation; TBI, toe brachial index; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

resulted in total of 10 observational studies reporting data from 2585 patients with diabetes. Our updated search included papers published between June 2014 and June 2018; this search yielded 8751 titles, of which six observational studies ultimately met the inclusion criteria. After including nine studies from the 2016 systematic review (having excluded one paper investigating a serum biomarker of PAD[24]), a total of 15 studies (comprising 1563 patients) were included in the qualitative data table for this updated systematic review (Table 2). The total numbers of identified, screened, eligible and finally included publications in both the original and the updated search are given in the PRISMA flowchart in Figure 1.

3.2 | Patient demographics

The mean or median age of participants was reported as 66 years, with most study cohorts consisting primarily of men (range 47%-88%). The reporting of patient demographics was variable and surprisingly sparse, but, where reported, comorbidities were as expected—coronary artery disease in 22.9%, cerebrovascular disease in 10% and 40% of patients were current or ex-smokers (Table 2). Few studies reported the presence or absence of neuropathy and ulceration, despite the importance of both of these clinical features on subsequent outcome. Only four studies reported on the

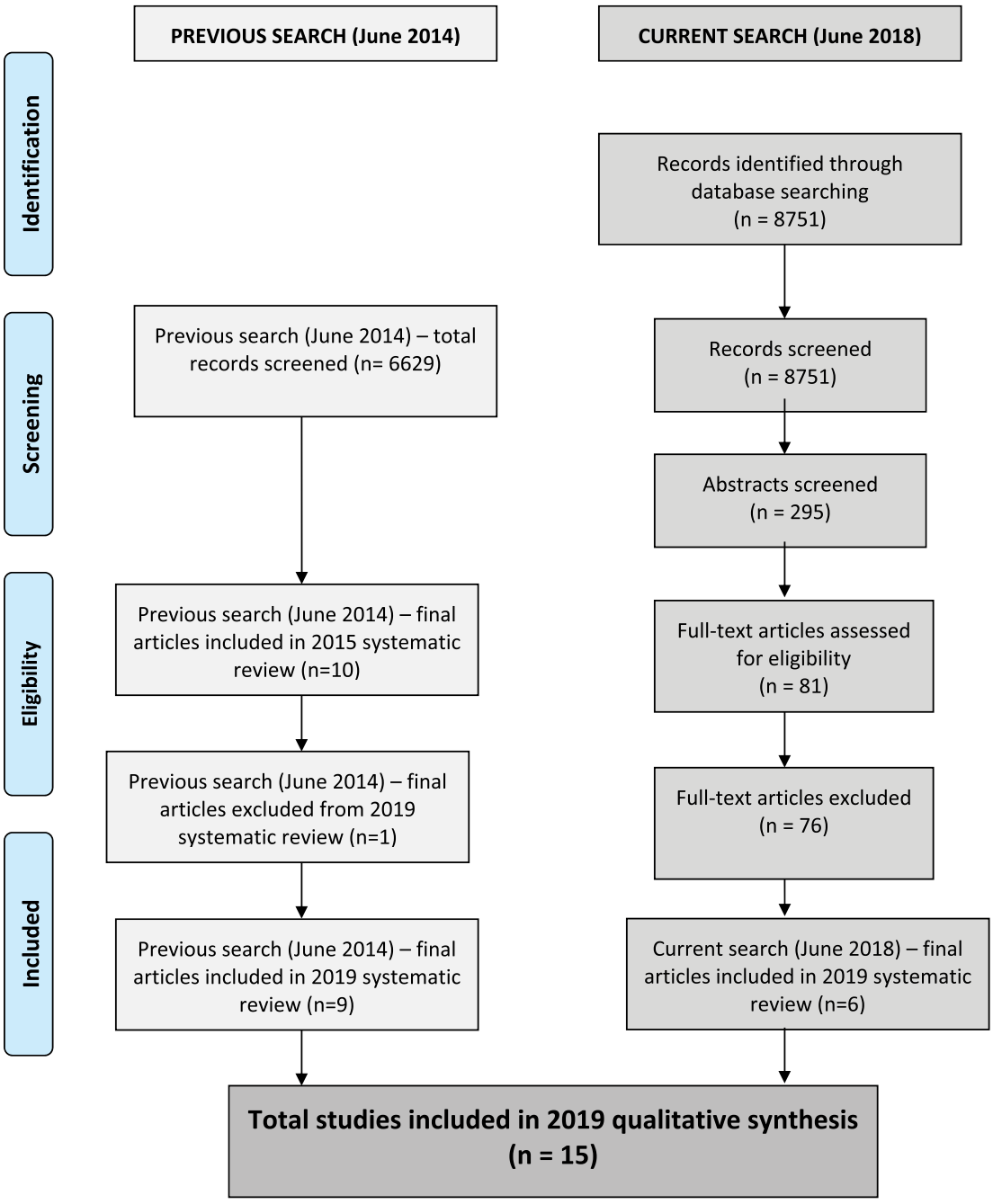

FIGURE 1 PRISMA Flow Diagram

presence of neuropathy[25-28] with a mean prevalence of 72%. The median prevalence of foot ulcers was 7% among those studies reporting it[26-33] —two of these studies included a population of patients of which all had a foot ulcer.[28,29] The mean duration of diabetes was 13.6 years among those studies in which it was reported.

3.3 | Reference tests to confirm PAD

CDUS was used as the reference test for confirming PAD in 13 of the observational studies, while DSA was used in the other two studies. A variety of PAD definitions were used in the CDUS studies (Table 2), with some studies measuring change in velocity and others the degree of stenosis. The two studies with DSA as a reference test used a cut-off of >50% reduction in vessel diameter to diagnose PAD.

3.4 | Index beside tests and threshold values used to diagnose PAD

It is important to note that recent international guidelines abandon the idea of fixed threshold values for PAD, particularly in patients with diabetes,[34] and instead champion the use of classification systems to categorise patients into clinical stages correlating with outcomes. This is an important approach that also takes factors such as the severity of the perfusion deficit, wound characteristics and infection into account, when assessing the likely *prognosis* of a patient with DFU and PAD. This topic, in particular the WIfI system, is covered in the IWGDF systematic review of diabetic foot classifications, also published in this journal.[35] However, in this present review, we focus on the use of bedside tests for the *diagnosis* of PAD in the ulcerated or intact foot and present the available literature to date, with a caveat that we must accept that there is no "one-fits-all" threshold value for objective bedside testing that can be used in isolation to make the diagnosis of PAD.

Among the studies identified, the most commonly evaluated bedside test was the ABI, which was reported in 13 of the studies. Two studies that did not use ABI[32,36] were written by authors who previously reported on the use of ABI in a smaller cohort of patients[37] and a further study reported ankle pressure without correcting for brachial pressure.[27] The threshold value for diagnosis of PAD was defined as <0.9 or ≤0.9 in most studies; however, three studies used both a lower and upper threshold for diagnosis (<0.9 or >1.3[28,30] and ≤0.9 or ≥1.4.[37] Three studies used TBI with a threshold for diagnosis of <0.7[37] or ≤ 0.75.[26,28] Systolic toe pressure was reported by two studies (using <97 mm Hg[36] or <50 mm Hg[28] as thresholds). Other tests used included $TcPO_2$[27,28] altered waveforms on colour wave Doppler[26,28,32,37] audible Doppler waveforms,[26] pulse reappearance time (PRT),[31] change in pulse oximetry[33] and pole test.[28] One study looked at a wide variety of subjective clinical examination tests.[28]

3.5 | Data synthesis and analysis

3.5.1 | PICO 1

In a person with diabetes and an intact foot, which symptoms and signs (clinical examination) should clinicians examine in order to identify or exclude PAD?

3.5.2 | PICO 2

In a person with diabetes and a foot ulcer, which symptoms and signs (clinical examination) should clinicians examine in order to identify or exclude PAD?

3.5.3 | Summary of the literature

We found no eligible studies reporting the symptoms and signs that may identify or exclude PAD in patients with diabetes and an intact foot.

We found only one eligible recent study investigating basic clinical examination in patients with diabetes with foot ulceration,[28] which was a prospective observational case series of 60 out-patients and in-patients with diabetes and new onset foot ulceration at a tertiary hospital. This study evaluated a number of tests, including clinical signs (hair loss, muscle atrophy, dependent rubor, cool skin, purple/blue skin, capillary refill time, venous filling time, presence of neuropathy and palpation of foot pulses). Using CDU or flow velocity waveforms as the reference tests in order to confirm/define the presence of PAD, the study found that 33% of participants had PAD on diagnostic ultrasound. Palpation of foot pulses had a sensitivity of 55% and a specificity of 60% for diagnosing PAD, with a PLR of 1.38 and a NLR of 0.75, meaning that this clinical examination would not accurately rule in or exclude presence of PAD.

Pulse palpation should therefore not be used to rule out a diagnosis of PAD. None of the other clinical features investigated were found to accurately exclude the diagnosis of PAD.

3.5.4 | Evidence statement

In patients with diabetes (with an intact or ulcerated foot), there are no clinical signs or symptoms that can accurately exclude PAD.

3.5.5 | Quality of the evidence

Low: based on one observational study of 60 patients.

3.5.6 | PICO 3

In a person with diabetes, which "bedside" diagnostic procedure, alone or in combination, has the best performance in ruling in or excluding PAD?

3.5.7 | Summary of the literature

3.5.7.1 | ABI or systolic ankle pressure

Nine observational studies investigated the use of Doppler ABI (most commonly considered diagnostic if ABI < 0.9) compared to CDUS, with a variety of definitions, to diagnose PAD based on CDUS. Eight of these studies used peak systolic velocity—maximum systolic velocity ratio >2, corresponding to ≥50% stenosis, or monophasic waveforms in any artery, while one had a less well defined parameter—"presence of atherosclerotic plaques or arterial calcification".[38] These studies reported a sensitivity of the ABI between 45% and 100% and specificity between 58% and 97%, with corresponding PLR of 1.69 to 23.8 and NLR of 0.02 to 0.59. One study also looked at oscillatory ABI, which had a PLR of 7.9 and a NLR of 0.5.[25]

Of the other observational studies reporting on ABI, two studies used either Doppler waveform[39] or colour spectral waveform[30] as reference tests. These studies reported markedly different PLR (24.8 and 4.0) and NLR (0.38 and 0.12), while one study using DSA as the reference test[31] gave a PLR of 5.1 and NLR of 0.69.

One small study compared the use of ABI in patients with (n = 57) or without (n = 32) neuropathy.[26] The authors found that neuropathy does not seem to have a particularly adverse effect on PLR (11 in patients with neuropathy vs 8 in patients with no neuropathy); however, the NLR was significantly poorer in those patients with neuropathy (0.5 vs 0.1), suggesting that it is a less useful test to exclude PAD in patients with neuropathy. No significant improvement in PLR or NLR was observed when studies used thresholds to account for the presence of incompressible vessels (ie, abnormally raised ABI).

When comparing the four studies comprising patients with intact feet vs the two studies including only those with a foot ulcer, the ABI was found to produce sensitivity 80.7% vs 69.5%; specificity 91.5% vs 74%, PLR 6.74 vs 4.10 and NLR 0.12 vs 0.43 (median values of the combined studies), respectively.

Overall, of the 12 studies that used ABI as an index test (regardless of reference test used), the median PLR was 6.5 and the median NLR was 0.31. ABI <0.9 can therefore be considered helpful to rule in the diagnosis of PAD, but less effectively rules out PAD if the ABI is within the normal range (0.9-1.3). Moreover, the ABI may be more useful to rule in the diagnosis of PAD in patients with intact feet, but is a less useful test to exclude PAD in patients with neuropathy or foot ulceration.

Ankle pressure <70 mm Hg (vs DSA[27] or CDUS[28]) did not appear to be accurate for the detection or exclusion of PAD (PLR 2.25, NLR 0.67).

3.5.7.2 | TBI or systolic toe pressure

Of the three observational studies that evaluated TBI, all used CDUS as the reference test, with a diagnostic threshold of either <0.7[37] or <0.75.[26,28] Two studies presented data on groups with a high prevalence of neuropathy (>70%), finding that TBI >0.7 or > 0.75 is useful to exclude PAD, while TBI <0.7 or <0.75 is less useful to diagnose PAD (PLR 1-3; NLR 0.14 to 0.24).[26,28] The third study[37] did not report on the prevalence of neuropathy, but found broadly similar outcomes (PLR 3.55; NLR 0.44).

In a study of 60 patients with a foot ulcer, toe pressure <50 mm Hg was found to have a much better diagnostic performance (PLR 17.55) than TBI (PLR 1.63)[28] but this was at the expense of poorer NLR (0.56 vs 0.24) and sensitivity (0.45 vs 0.89). However, when the diagnostic threshold for toe pressure was increased to <97 mm Hg in another study,[36] the performance of the test reduced markedly (PLR 2.67).

3.5.7.3 | Transcutaneous oxygen pressure

Two studies that reported on transcutaneous oxygen pressure ($TcPO_2$)[27,28] used different diagnostic thresholds ($TcPO_2$ < 50 mm Hg and < 60 mm Hg) and compared this with an ankle pressure of <70 mm Hg, with either DSA or CDUS as reference. One study provided only enough data to suggest that the sensitivity of $TcPO_2$ was better than ankle pressure (82% vs 67%).[27] However, another study of patients with foot ulcers showed much lower sensitivities for TcPO2 and ankle pressure (28% vs 47%), with overall minimal diagnostic value for $TcPO_2$ (PLR 0.81, NLR 1.1).[28]

3.5.7.4 | Pulse oximetry

Two studies compared pulse oximetry with ABI, using Doppler waveform or CDUS as the reference test.[33,39] Both studies used the same definition ("toe saturation <2% lower than finger saturation or increased by >2% when the leg is elevated to 12 in. higher than the horizontal plane"). They found that pulse oximetry was a more useful diagnostic test than ABI, with PLR and NLR of pulse oximetry of 17.23 to 30 and 0.2 to 0.27, respectively, when compared to PLR and NLR of ABI of 5.49 to 24.8 and 0.09 to 0.37, respectively.[33,39]

3.5.7.5 | Doppler waveform analysis

Four studies used Doppler waveform analysis, recording abnormal waveform at the tibial arteries or ankles as suggestive of PAD.[26,28,32,37] In all studies, waveform analysis performed very well with respect to NLR (0.09-0.28), although the PLR were less consistent and varied between 3 and 13. Abnormal waveform was variably defined.

3.5.7.6 | Pulse reappearance time

One study looked at PRT after compression of the thigh for 3 minutes, and compared this with ABI at a threshold of <0.9.[31] DSA was used as the reference test. PRT and ABI had identical PLR and very similar

NLR when compared to DSA (PLR 5 vs 5; NLR 0.6 vs 0.7). However, PRT correlated with the severity of stenosis seen on DSA, whereas ABI did not, although this property of PRT did not translate into improved ability to detect PAD compared to ABI.

3.5.7.7 | Pole test

In this test, the leg is elevated passively, with the patient supine, while the Doppler signal is continuously monitored and the height at which the Doppler signal is lost is determined. The pole test was used in one study of patients with ulcerated feet.[28] The PLR was found to be 10.29 and of potentially high diagnostic value but the NLR was of minimal value at 0.74.

3.5.7.8 | Evidence statements

1. An ABI < 0.9 may be useful to suggest the diagnosis of PAD, but a value between 0.9 and 1.3 does not rule out PAD, in particular in patients with neuropathy and/or a foot ulcer.
2. A TBI >0.75 makes the diagnosis of PAD less likely.
3. Pulse oximetry (if toe saturation <2% lower than finger saturation or increased by >2% when the leg is elevated to 12 in. higher than the horizontal plane) may be useful to suggest the diagnosis of PAD and to render PAD less likely.
4. The presence of triphasic tibial waveforms demonstrated small to large value for ruling in or ruling out PAD depending on the study, and hence may be useful in diagnosis.

3.5.7.9 | Quality of the evidence

1. Low: based on 12 studies on ABI using different definitions of PAD with inconsistent results, with one study on the effect of neuropathy and four studies that included patients with a foot ulcer, with the majority having a high risk of bias.
2. Moderate: based on three observational studies, one with low and two with moderate to high risk of bias.
3. Low: based on two observational studies with limited number of patients with diabetes and PAD.
4. Low: based on four observational studies with variable definitions of an abnormal waveform and two with low and two with moderate to high risk of bias.

4 | DISCUSSION

Despite increasing knowledge and understanding of the deleterious effect of PAD on DFU outcomes, there were limited new data regarding diagnosis of the presence of PAD since our previous review.[13] Previous studies have reported on the use of bedside tests to identify PAD in mixed cohorts of patients with and without diabetes; however, there are few studies dedicated to the assessment of patients with diabetes, and even fewer examining patients with diabetes and a foot ulcer. However, it should be noted that in the period 1980 to 2014 we found nine eligible studies while in the last 4 years, six new studies were identified, indicating that this important topic is beginning to garner more interest, but certainly needs more sustained attention.

In patients with diabetes and a foot ulcer and features suggestive of PAD, it is important for early referral to a specialist foot team, as the combination of these pathologies is associated with poorer outcomes than either in isolation.[2] But to what extent can the clinician rely on clinical examination to rule out PAD in this context? The study of Vriens et al that was included in this review was the only study to evaluate the diagnostic performance of clinical examination and concluded that the negative and PLRs of pedal pulse assessment (0.75, 1.38) and other aspects of clinical examination were poor,[28] in line with other publications on this topic.[40,41] Clinical examination alone is therefore an insufficient assessment of patients with diabetes and a foot ulcer. These data stress the importance of non-invasive diagnostic tests, irrespective of the presence of foot pulses. In addition, we have not assessed the usefulness of symptoms to suggest the diagnosis of PAD. Cohort studies suggest that patients with diabetes and PAD, compared to PAD patients without diabetes, are less likely to report classical intermittent claudication, but have more frequently atypical symptoms that may be related to co-morbidities such as neuropathy.[42]

Given the high impact on outcome and the relatively high prevalence in many circumstances, the best method of assessing the utility of a diagnostic test for PAD in patients with a DFU is the NLR, which expresses a change in odds of experiencing an outcome if the test is negative (ie, a test that is effective in ruling out PAD). For a test to be considered useful, the NLR should be low and NLR≤0.1 is considered to have very good performance (representing a decrease in the probability of the specified outcome of around 45% in the presence of a negative test result).[19,20] If, for example, we assume that a prevalence of PAD is 50% in patients treated in a diabetic foot ulcer clinic, an ABI < 0.9 is measured in a patient and a PLR of 6.5 is assumed, the probability of PAD would be increased to approximately 87%. Vice versa if a normal Doppler waveform is found in this patient, for which an NLR of 0.2 is assumed, the probability of PAD is reduced to approximately 17%.

In this context, it is less important for the initial test to reliably diagnose PAD, as the consequences of a false positive result would be less than the consequences of a false negative test result, that is, in which the diagnosis may be missed. Those patients in whom a positive result is obtained should proceed for further investigations in order to confirm the presence of PAD. The next step is to establish the extent of the perfusion deficit and its likely impact on ulcer healing and amputation risk, as discussed in our IWGDF systematic review on prognosis.[43] The final step is the identification of patients who may require revascularization to promote healing and prevent amputation. This decision is based not only on the severity of the perfusion deficit but also on wound and patient related factors. Once a revascularization

procedure is considered, establishing the anatomical distribution of disease may be achieved using CDUS, CTA, MRA or DSA.

The most commonly used bedside test to diagnose PAD is the ABI, which was assessed in the majority of studies included in this review. In this review, we found that the presence of a normal ABI (0.9-1.3) was too inaccurate to exclude PAD in patients with foot ulcers (NLR >0.3); however, ABI <0.9 appeared useful to suggest the diagnosis of PAD (PLR >5 in most research). Moreover, in patients with neuropathy, a normal ABI could not, in one study, effectively rule out PAD (NLR 0.5).[26] As the vast majority of DFU patients have neuropathy, this could therefore contribute to the poorer performance of the ABI in patients with a foot ulcer. Up to a third of DFU patients have incompressible lower leg arteries resulting in abnormally high ABI[2,11] and an elevated ABI increased the probability of PAD in patients with diabetes, but we could not calculate the PLR or NLR.[44,45] In conclusion, a normal ABI cannot accurately rule out PAD, although an ABI < 0.9 or also an elevated ABI are suggestive of the diagnosis of PAD. We suggest that ABI should not be used in isolation to exclude PAD in patients with a diabetic foot ulcer.

The digital arteries are relatively spared from calcification and the measurement of toe pressure (and TBI) may therefore be a more reliable alternative to ABI in the diagnosis of PAD. Unfortunately, in patients with digital ulceration or a toe amputation it may not be possible to perform this examination. Four studies investigated the use of toe pressure[28,36] or TBI[26,28,37] but only one study examined the use of these tests in a population of patients with foot ulcers. A negative test result seems somewhat more accurate to exclude PAD (NLR 0.14-0.44), whereas a positive test result (TBI <0.75 or <0.7) appeared to be less accurate to rule in PAD (PLR 1.63-3.55). A toe pressure of <50 mm Hg appeared to have very good diagnostic ability in patients with foot ulcers (PLR 17.55) but a normal toe pressure was not considered accurate enough to exclude the diagnosis (NLR 0.56).[28]

A number of studies investigated other index bedside tests, the most accurate was CWD with triphasic Doppler waveforms (NLR <0.2 in most cases). Pulse oximetry was tested in two studies[33,39] with NLR of 0.2 and 0.27, although it was unclear if any patient had a foot ulcer, and the sensitivity estimates were only 77% and 74%.

In one study of patients with intact feet, parallel testing using ABI and pulse oximetry improved the NLR from their individual values of 0.34 and 0.27 to 0.09 when used in a parallel combination strategy,[33] suggesting that a combination of tests is potentially most useful to exclude PAD. This was the only study to present a parallel testing approach and further similar studies are warranted. Pulse oximetry is an attractive technique because it requires equipment that is relatively inexpensive and available in most healthcare environments, but further studies are necessary to define its role in diagnosing PAD in patients with a foot ulcer. In addition, in the experience of some of the authors who have used this technique, it can be difficult to obtain a reliable measurement due to practical issues. It is certainly important to consider the technical aspects and potential inter-observer variability when conducting any bedside test; however, these aspects are out of the scope of our review. Ankle pressure, $TcPO_2$, PRT and pole test all had limited diagnostic utility (NLR >0.6 in most cases).

No study included satisfied the QUADAS criteria for an overall "high quality" rating. The studies were generally of poor or moderate quality, with substantial heterogeneity of patient characteristics and outcome reporting. The presentation of data was frequently also poor, with a number of studies failing to report on the presence of important features such as ulceration and neuropathy. This precluded the production of a valid meta-analysis.

In addition to the eligible observational studies included in our review, we came across an informative systematic review/meta-analysis of 31 studies that reported the use of clinical examination, as well as a number of bedside tests, to diagnose PAD in patients with diabetes (the majority of which did not have foot ulcers).[41] It did not meet the inclusion criteria for our review, as some of the studies used ABI or "complete wound healing" as reference tests, rather than the standard vascular imaging tests specified in our inclusion criteria. In addition, the studies included were widely heterogeneous. Nonetheless, it provided some interesting comparisons. Barshes and colleagues found the presence of palpable foot pulses to have poor diagnostic reliability (PLR 3.06, NLR 0.57),[41] which corresponds to the findings of Vriens and colleagues included in our review,[28] and suggested that strategies using non-invasive bedside tests to investigate only those patients with abnormal pulses had too low overall diagnostic sensitivity. In addition, they reported on the use of ABI, TBI, $TcP0_2$ and skin perfusion pressure, all of which performed poorly when evaluating a patient with diabetes for the presence of PAD (NLR >0.2 in all cases).

A limitation of this review is that the majority of studies used CDUS as the reference test; however, this has its drawbacks. CDUS may be less reliable in identifying significant arterial disease in the crural vessels, particularly in the presence of significant calcification and if doubt exists then an alternative method of imaging should be considered. There is also a potential role for dynamic testing, such as pre- and post-exercise ABI or TBI, but these tests were not reported in the studies we included in our review.

It seems remiss that there continues to be such a dearth of evidence in this area, but it is important to note the current trend away from simply diagnosing PAD. As discussed above, determining the presence of PAD is only the first step in evaluating the vascular assessment of a person with diabetes and a foot ulcer. Not only should we assess the presence and severity of ischaemia but also we must simultaneously assess the presence of neuropathy, wound characteristics, infection and other mitigating clinical characteristics, as discussed elsewhere in this issue.[14,35]

5 | CONCLUSIONS

Among the studies included in our review, an ABI <0.9 or >1.3 appears to be a useful test for the detection of PAD, although it has variable performance among the populations studied. Although widely used to assess PAD at the bedside, palpation of peripheral pulses showed disappointingly poor performance in either ruling in or ruling out PAD. Alternative bedside tests that appear accurate are CWD with absence of triphasic waveforms and perhaps pulse oximetry with

toe saturation < 2% lower than finger saturation or increased by >2% when the leg is elevated to 12 in. higher than the horizontal plane. Overall, there was insufficient evidence to recommend a single bedside test to reliably rule out PAD in a patient with a foot ulcer. In such a patient, a normal ABI (or palpable pulses) cannot reliably rule out PAD. A second test should be performed such as assessment of Doppler waveforms, possibly in combination with toe pressure/TBI measurements. Pulse oximetry could become an attractive alternative if confirmed in future studies. There is clearly a need for improved reporting and for more informative studies of diagnostic tests for PAD in patients with diabetes in order to reach more robust conclusions in the future.

ACKNOWLEDGEMENTS

We would like to thank the following external experts for their review of our PICOs for clinical relevance: Stephan Morbach (Germany), Heidi Corcoran (Hongkong), Vilma Urbančič (Slovenia), Rica Tanaka (Japan), Florian Dick (Switzerland), Taha Wassila (Egypt), Abdul Basit (Pakistan), Yamile Jubiz (Colombia), Sriram Narayanan (Singapore), Eduardo Alvarez (Cuba). We would like to thank Jaap J. Van Netten (on behalf of the IWGDF editorial board) and Neal Barshes (independent external expert) for their peer review of the manuscript. In addition, we would like to thank Jack Brownrigg for his input into the previous version of this systematic review.

CONFLICT OF INTEREST

Production of the 2019 IWGDF Guidelines was supported by unrestricted grants from: Molnlycke Healthcare, Acelity, ConvaTec, Urgo Medical, Edixomed, Klaveness, Reapplix, Podartis, Aurealis, SoftOx, Woundcare Circle, and Essity. These sponsors did not have any communication related to the systematic reviews of the literature or related to the guidelines with working group members during the writing of the guidelines, and have not seen any guideline or guideline-related document before publication. All individual conflict of interest statement of authors of this guideline can be found at: https://iwgdfguidelines.org/about-iwgdf-guidelines/biographies/.

AUTHOR CONTRIBUTIONS

R.O.F. performed the literature search, screened the titles, abstracts and full papers, assessed the literature, extracted data, drew conclusions for the PICOs, completed the evidence table, and wrote the manuscript. J.A. checked the evidence table and reviewed the manuscript. E.J.B. assessed the literature, extracted data, checked and revised the evidence table, reviewed and critically revised the manuscript. R.F. screened the abstracts, assessed the literature, extracted data, checked and revised the evidence table, and reviewed the manuscript. J.P.H. checked the evidence table and reviewed the manuscript. K.K. checked the evidence table and reviewed the manuscript. J.L.M. extracted data, checked the evidence table and reviewed the manuscript. S.N. checked the evidence table and reviewed the manuscript. J.R. checked the evidence table and reviewed the manuscript. M.V. checked the evidence table and reviewed the manuscript. R.E.Z. extracted data, checked the evidence table and reviewed the manuscript. N.C.S. assessed the literature, drew conclusions for the PICOs, checked and revised the evidence table, reviewed and critically revised the manuscript. R.J.H. reviewed and provided final consensus for the data extraction, drew conclusions for the PICOs, reviewed and critically revised the manuscript. R.O.F. acted as secretary of the working group, R.J.H. as chair of the working group. All authors take full responsibility for the content of the publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Forsythe RO, Apelqvist J, Boyko EJ, et al. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: A systematic review. *Diabetes Metab Res Rev*. 2020;36(S1):e3277. https://doi.org/10.1002/dmrr.3277