National Institute for Health and Care Excellence

Consultation

Peripheral Arterial Disease: Diagnosis and Management

[A] Evidence review for determining diagnosis and severity of PAD in people with diabetes

NICE guideline <number>

Evidence reviews

[Month Year]

Draft for Consultation

This evidence review was developed by the NICE Guideline Updates Team

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Determining diagnosis and severity of PAD in people with diabetes

Review question

In people with diabetes who have suspected Peripheral Arterial Disease (PAD), is ankle brachial pressure index (ABPI) as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, in determining diagnosis and severity of PAD?

It became apparent during the development of the update that the above review question carried forward from the original guideline should include other non-invasive diagnostic tests along with ABPI, ABPI as an adjunct to clinical assessment and clinical assessment alone. This decision was made based on the findings identified by the surveillance team along with committee input during the development of the review protocol. Hence, the review question answered in the update (and to be carried forward in any future updates) was:

- In people with diabetes who have suspected PAD, what are the most accurate non-invasive diagnostic tests in determining diagnosis and severity of PAD?

Based on this question, a search strategy was used which explored non-invasive diagnostic tools such as toe brachial index, Doppler waveform analysis and pulse oximetry along with ABPI alone, ABPI as an adjunct to clinical assessment and clinical assessment alone.

Introduction

Peripheral arterial disease (PAD) is a cardiovascular disease that commonly affects the arteries in the legs. Characterised by the narrowing of the arteries, PAD results in reduced blood flow to the limbs.

Diagnosis of PAD is based on clinical assessment and diagnostic tests. The most widely used diagnostic test for PAD is the ankle brachial pressure index (ABPI) test, which allows the blood flow to the limbs to be evaluated. However, assessment of PAD using ABPI among people with diabetes may be challenging due to medial sclerosis, which is the hardening of the arteries. As the arteries become incompressible, a falsely elevated ABPI may be obtained.

The 2012 NICE guideline on the diagnosis and management of PAD recommended the use of ABPI in people with suspected PAD, but did not explicitly consider people with diabetes. This topic was reviewed in 2017 by the NICE surveillance team and new evidence was identified which examined the diagnosis of PAD in people with diabetes. This evidence suggested that other forms of assessment may be superior to ABPI for diagnosing PAD in people with diabetes, and thus prompted a partial update of the guideline to review the new evidence. This review aims to determine the most accurate tools for diagnosis and assessment of severity of PAD among people with diabetes who have suspected PAD.

Table 1 Review summary table

Population	Adults (≥ 18 years old) with diabetes with suspected PAD (symptoms - intermittent claudication, leg ulcers, foot ulcers, common foot problems or cardiovascular risk factors).
Index Tests(s)	Any relevant index non-invasive diagnostic test including: • Resting Ankle brachial pressure index (ABPI) as an adjunct to clinical assessment. • Resting ABPI alone. • Post exercise ABPI

	• Clinical assessment alone (minimum within assessment to include physical assessment, observation of limb, palpation of foot pulses (10g Monofilament test) and validated claudication questionnaires for example The Edinburgh Claudication Questionnaire) • Toe brachial index • Doppler Wave form analysis • Pulse oximetry
Reference Standard(s)	Imaging: • Magnetic resonance imaging (MRI) • Computed tomography angiography (CTA) In the event of less than 5 studies being identified, for each assessment tool, using preferred reference standard, studies using following imaging techniques as reference standard will be included: • Digital subtraction angiography (DSA) • Duplex ultrasound (DUS)
Outcomes	Diagnosis of PAD: • Specificity • Sensitivity • Positive likelihood ratio • Negative likelihood ratio • Inter- and intra-operative reliability Severity of PAD: • Logistic regression model fit • Area under the curve • Critical limb ischemia

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). The review protocol for this review question is described in appendix A. Methods specific to this review question are described in appendix B.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

A search strategy was used to identify all studies that examined the diagnostic test accuracy and reliability of diagnostic tools (outlined in Table 1) which are used in the assessment of PAD in people with diabetes. Cohort studies, cross-sectional studies and systematic reviews of these study designs, examining diagnostic test accuracy using sensitivity, specificity and likelihood ratios and inter- and intra-operator reliability were considered for inclusion. Studies examining severity of PAD using logistic regression models, area under the curve and presence of critical limb ischaemia were also considered.

Ideally, studies using imaging techniques such as magnetic resonance imaging (MRI) and computed tomography angiography (CTA) as the reference standard were included. However, in the event of fewer than 5 studies being identified using MRI and CTA as reference standards, studies utilising digital subtraction angiography (DSA) and duplex ultrasound (DUS) were included.

If studies did not report diagnostic test accuracy measures, 2x2 tables of true positives, false positives, true negative and false negatives were derived from raw data or calculated from the set of test accuracy statistics. These measures were then presented as calculated diagnostic test accuracy measures within the evidence review. Studies from which 2x2 tables could not be calculated were excluded.

Studies were also excluded if they were:

- not in English
- not full reports of the study (for example, published only as an abstract)
- not peer-reviewed.

Diagnostic accuracy of the tools was evaluated using positive and negative likelihood ratios. Positive likelihood ratios describe how many times more likely positive features are in people with the condition compared to people without the condition. Negative likelihood ratios describe how many times less likely negative features are in people with the condition compared to people without the condition. The schema for the interpretation of likelihood ratios is outlined in Appendix B.

Studies included in the review reported different cut-off points for the diagnostic tests. For ABPI, 3 studies reported a cut-off point of less than 0.9 while 1 study reported a cut-off point of less than 0.9 and greater than 1.4. 2 studies examining diagnostic accuracy of toe brachial index utilised cut-offs of less than 0.70 and less than 0.75. Studies examining diagnostic accuracy of Doppler waveform analysis defined the cut-offs as the loss of triphasic waveforms or the loss of multiphasic waveforms. Evidence statements were formed to reflect the different cut-off points.

Also, 1 study reported diagnostic accuracy of tests in people with diabetes presenting with and without neuropathy. Based on this, evidence statements were formed to reflect the findings for the whole diabetes population along with diabetes population without neuropathy and diabetes population with neuropathy.

Clinical evidence

Included studies

From a database of 795 studies, 85 studies were identified as being potentially relevant. 5 studies were identified as being potentially relevant from a systematic review [Brownrigg 2016]. 1 study was identified through citation searching, as being potentially relevant. Following full text review of the 91 studies, 7 studies of cross-sectional study design were included.

1 study was identified which examined the diagnostic test accuracy and presented ROC curves to examine severity of PAD defined by ≥ 50% stenosis. 3 studies were identified which examined the diagnostic test accuracy. 2 studies were identified which examined severity of PAD defined by ≥ 50% stenosis and ≥75% stenosis and presented ROC curves. One study was identified which examined inter and intra-rater reliability.

Overall, studies explored the diagnostic accuracy of ABPI, toe brachial index, Doppler waveform analysis and pulse oximetry. No studies were identified which examined diagnostic accuracy of ABPI as an adjunct to clinical assessment or clinical assessment alone.

Excluded studies

The list of papers excluded at full text review, with reasons, is given in Appendix H

Summary of clinical studies included in the evidence review

A summary of the included studies is provided in the Included Studies Table. See Appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

All studies included were prospective or retrospective cross sectional studies. The quality of the evidence was started at high for prospective studies and moderate for retrospective studies. Studies were further downgraded for risk of bias, mainly due to unclear blinding between index and reference test and time interval between the tests. Studies were also downgraded for indirectness if studies carried out sub-group analysis on patients with diabetes or if patients did not present characteristics listed in the review protocol (Appendix A). Only 1 study was identified which used CTA as a reference standard and no studies were identified which utilised MRI. Due to this, studies utilising DSA and DUS were included in the review. Studies utilising inadequate thresholds for reference standard and index test, were downgraded for very serious indirectness. Other areas of downgrading included serious imprecision.

Cross sectional reliability studies presenting inter- and intra-rater reliability as intra-class correlation (ICC) were included in this review. ICC was interpreted following the schema, adapted from the suggestions of Fleiss, shown in Appendix B. To assess risk of bias the QUADAS-2 tool was adapted to assess patient selection, index test and flow and timing.

See appendix G for full GRADE tables, and appendix F for forest plots in situations where data have been meta-analysed.

Economic evidence

No health economics work (either original modelling or a literature search for published economic evaluations) was undertaken for this guideline update, as it was decided when the protocol for this question was agreed that any recommendations made were highly unlikely to result in a substantial economic impact.

1 Included Studies Table

Study ID	Study	Aim	Study Population	Index Test(s)	Reference Test(s)
Ichihashi (2014)	Ichihashi S, Hashimoto T, Iwakoshi S, and Kichikawa K (2014) Validation study of automated oscillometric measurement of the ankle-brachial index for lower arterial occlusive disease by comparison with computed tomography angiography. Hypertension Research - Clinical & Experimental 37(6), 591-4	Evaluate the diagnostic accuracy and optimal threshold of oscilllometric ABPI for detecting PAD using CTA as gold standard.	Number of Patients: 108 patients with 216 limbs Study Location: Japan Setting: Department of Radiology Inclusion Criteria: • Patients suspected of PAD Exclusion Criteria: • History of vascular surgery or endovascular treatment for PAD.	ABPI	Computed tomography angiography (CTA)
Jeevanantham (2014)	Jeevanantham V, Chehab B, Austria E, Shrivastava R, Wiley M, Tadros P, Dawn B, Vacek J L, and Gupta K (2014) Comparison of accuracy of two different methods to determine ankle-brachial index to predict peripheral arterial disease severity confirmed by angiography. American Journal of	Study the diagnostic accuracy of LABI and HABI in the detection of PAD and total PAD burden Study the diagnostic accuracy in patients with diabetes in whom ABI determined by HABI method is often falsely elevated because of medial calcinosis Assess the diagnostic utility for detection below	Number of Patients: 130 patients (260 limbs) Study location: Kansas City, Kansas Study setting: Tertiary Referral Academic Medical Canter Inclusion Criteria: • Patients who had ABPI done within 6 months before the angiogram Exclusion Criteria:	ABPI	Digital subtraction angiography (DSA)

Study ID	Study	Aim	Study Population	Index Test(s)	Reference Test(s)
	Cardiology 114(7), 1105-10	the knee PAD that is unknown	• Previous limb amputations proximal to the heads of metatarsals or proximal to the elbow in the upper limbs • Previous bypass • Stenting or prosthetic vascular reconstruction to the lower limbs or of the arteries of lower limb/ abdominal aorta or subclavian or axillary arteries • An ABPI>1.3 in both lower limbs • Any abdominal or lower extremity vascular surgery or intervention between the time of having the ABI measurement and the first available angiography		
Kumar (2016)	Kumar M S, Lohiya A, Ramesh V, Behera P, Palepu S, and Rizwan S A (2016) Sensitivity and Specificity of Pulse Oximetry and Ankle-Brachial Index for Screening Asymptomatic Peripheral Vascular Diseases in Type 2 Diabetes Mellitus. Journal of the Association of Physicians of India 64(8), 38-43	To compare pulse oximetry and ABPI with duplex ultrasonography as reference standard to determine the diagnostic accuracy for screening asymptomatic PVD in type 2 diabetes mellitus.	Number of Patients: 120 patients Study Location: Madurai, India Setting: Tertiary care hospital Inclusion Criteria: • Adults pre-diagnosed type 2 diabetes mellitus, either physician diagnosed or based on blood glucose records as per American Association (ADA) criteria, irrespective of control of glucose sugar, duration of diagnosis, treatment and presence of other complications • Not previously investigated for or diagnosed as PAD and asymptomatic with regards of PAD such as pain, swelling, ulcers, previous amputation. Exclusion Criteria:	• ABPI • Pulse Oximetry	Duplex ultrasound (DUS)

Study ID	Study	Aim	Study Population	Index Test(s)	Reference Test(s)
			• Aged less than 40 years • Patients suffering from hypercoagulable states, congestive heart failure, valvular heart disease, suspected arteritis and collagen vascular disease • Patients who were unable to lie supine, for the period of testing • Extreme sick patients who required intensive care.		
Premalatha (2002)	Premalatha G, Ravikumar R, Sanjay R, Deepa R, and Mohan V (2002) Comparison of colour duplex ultrasound and ankle-brachial pressure index measurements in peripheral vascular disease in type 2 diabetic patients with foot infections. Journal of the Association of Physicians of India 50, 1240-4	Compare the specificity and sensitivity of ABPI measured by peripheral Doppler with the colour duplex ultrasound for diagnosis of PVD	Number of Patients : 100 Study Location: India Setting: Tertiary care specialised diabetes centre Inclusion Criteria: All patients admitted to the hospital with type 2 diabetes and severe foot infections Exclusion Criteria: None reported	ABPI	Duplex ultrasound (DUS)
Romanos (2010)	Romanos MT, Raspovic A, and Perrin BM (2010) The reliability of toe systolic pressure and the toe brachial index in patients with diabetes. Journal of	Determine the intra- and inter-rater reliability of the measurement of toe systolic pressure and the toe brachial index (TBI) in patients with diabetes using a manual measurement system	Number of patients: 30 Study Location: Victoria, Australia Setting: University Podiatry Clinic Inclusion Criteria:	TBI	-

Study ID	Study	Aim	Study Population	Index Test(s)	Reference Test(s)
	foot and ankle research 3, 31		• 21 years of age and older Exclusion Criteria: • Unable to lie supine for the duration of the tests • Presented with wounds or infection around the testing site • Individuals who has a vasometer condition such as Raynaud's disease		
Tehan (2016)	Tehan P E, Bray A, and Chuter V H (2016) Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. Journal of Diabetes & its Complications 30(1), 155-60	Determine the sensitivity and specificity of ABPI, Continuous Wave Doppler (CWD) and Toe Brachial Index (TBI) in a population with and without diabetes.	Number of Patients: 117 patients (Diabetes= 72, No Diabetes=45) Study Location: New South Wales, Australia Setting: Private vascular clinic Inclusion Criteria: • Aged over 65 years • or aged over 50 years with history of diabetes • or aged over 50 years currently smoking exertional leg pain or non-healing wounds Exclusion Criteria: • Known allergy to coupling gel • presence of a wound preventing Doppler probe or ankle cuff placement • Previous bilateral mastectomy preventing bilateral brachial blood pressure examination	• ABPI • TBI • Doppler Waveform analysis	Duplex ultrasound (DUS)

Study ID	Study	Aim	Study Population	Index Test(s)	Reference Test(s)
Williams (2005)	Williams D T, Harding K G, and Price P (2005) An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care 28(9), 2206-2210	Evaluate the efficacy of foot pulses, the ABPI, the TBI and Doppler Waveform analysis in screening for lower-limb arterial disease in diabetes, by comparison with the gold standard non-invasive assessment, colour duplex imaging.	Number of Patients: 130 limbs from 68 individuals Study Location: Wales, UK Setting: Diabetic foot clinics Inclusion Criteria: • None reported Exclusion Criteria: • Smoking and other causes of peripheral arterial disease • History of reconstructive vascular surgery • Other causes of peripheral vascular disease • Skin changes associated with venous disease • Pyrexia • Significant cardiorespiratory and/ or renal disease	• ABPI • TBI • Doppler Waveform analysis	Duplex ultrasound (DUS)

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Evidence statements

Diagnostic test accuracy

4 studies were identified which examined the diagnostic accuracy of different diagnostic tests (ABPI, TBI, Doppler waveform analysis and pulse oximetry). Diagnostic accuracy of the tools was evaluated using positive and negative likelihood ratios. The schema for the interpretation of likelihood ratios is outlined in Appendix B. Evidence statements were formed to reflect the different cut-off points utilised in the studies as well as the findings for the whole diabetes population along with diabetes population without neuropathy and diabetes population with neuropathy.

Diabetes Population

Diagnostic tools which increase the probability of diagnosing PAD:

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **very large**:

Doppler Waveform Analysis

- 1 study providing high-quality evidence, containing 72 participants, examining Doppler waveform analysis defined as the loss of multiphasic waveforms (LR 95% CI ranged from moderate to very large)

Pulse Oximetry

- 1 study of very low-quality, examining pulse oximetry, defined as toe saturation less than finger saturation >2% or if foot saturation decreased by >2% in elevated position (LR 95% CI ranged from large to very large)

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **large**:

Doppler ABPI

- 3 studies providing very low-quality evidence, containing 302 measurements, examining Doppler ABPI at a cut off at <0.9 (LR 95% CI ranged from moderate to large)
- 1 study providing moderate quality evidence, containing 72 participants, examining Doppler ABPI at a cut off at ≤0.9 or >1.4 (LR 95% CI ranged from slight to very large)

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **moderate**:

Toe Brachial Index

- 1 study providing moderate-quality evidence, containing 72 participants, examining TBI at a cut off at <0.7 (95% CI ranged from slight to large)

Diagnostic tools which decrease the probability of diagnosing PAD:

The following tools decrease the probability of diagnosing PAD (based on negative likelihood ratios) to a degree that is likely to be **moderate**:

Doppler ABPI

- 3 studies providing very low-quality evidence, containing 302 measurements, examining Doppler ABPI at a cut off at ≥0.9

Toe Brachial Index

- 1 study providing moderate-quality evidence, containing 72 participants, examining TBI at a cut off at ≥0.7 (LR 95% CI ranged from slight to moderate)

Doppler Waveform Analysis

- 1 study providing moderate-quality evidence, containing 72 participants, examining Doppler waveform analysis defined as the loss of multiphasic waveforms (LR 95% CI ranged from slight to large)

Pulse Oximetry

- 1 study of very low-quality, examining pulse oximetry, defined as toe saturation less than finger saturation >2% or if foot saturation decreased by >2% in elevated position (LR 95% CI ranged from slight to large)

The following tools decrease the probability of diagnosing PAD (based on negative likelihood ratios) to a degree that is likely to be **slight**:

Doppler ABPI

- 1 study providing moderate-quality evidence, containing 72 participants, examining Doppler ABPI at a cut off at >0.9 or ≤1.4 (LR 95% CI ranged from slight to moderate)

Diabetes Population without neuropathy

Diagnostic tools which increase the probability of diagnosing PAD:

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **large**:

Doppler ABPI

- 1 study providing very low-quality evidence, containing 32 limbs, examining Doppler ABPI at a cut off at <0.9 in patients with diabetes without neuropathy (LR 95% CI ranged from moderate to very large)

Doppler Waveform Analysis

- 1 study providing very low-quality evidence, containing 32 limbs, examining Doppler waveform analysis defined as the loss of triphasic waveforms in patients with diabetes without neuropathy (LR 95% CI ranged from moderate to very large)

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **moderate**:

Toe Brachial Index

- 1 study providing very low-quality, containing 32 limbs, examining TBI at a cut off at <0.75 in patients with diabetes without neuropathy (LR 95% CI ranged from slight to moderate)

Diagnostic tools which decrease the probability of diagnosing PAD:

The following results were **not significantly different** from random chance:

Doppler ABPI

- 1 study of very low-quality, containing 32 limbs examining, Doppler ABPI at cut-off at ≥0.9 in patients with diabetes without neuropathy (LR 95% CI ranged from very large decrease to slight increase)

Toe Brachial Index

- 1 study providing very low-quality, containing 32 participants, examining TBI at a cut off at ≥0.75 in patients with diabetes without neuropathy (LR 95% CI ranged from very large decrease to slight increase)

Doppler Waveform Analysis

- 1 study providing very low-quality evidence, containing 32 limbs, examining Doppler waveform analysis defined as the loss of triphasic waveforms in patients with diabetes without neuropathy (LR 95% CI ranged from very large decrease to slight increase)

Diabetes Population with neuropathy

Diagnostic tools which increase the probability of diagnosing PAD:

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **very large**:

Doppler ABPI

- 1 study providing very low-quality evidence, containing 56 limbs, examining Doppler ABPI at a cut off at <0.9 in patients with diabetes with neuropathy (LR 95% CI ranged from moderate to very large)

The following tools increase the probability of diagnosing PAD (based on positive likelihood ratios) to a degree that is likely to be **moderate**:

Toe Brachial Index

- 1 study providing very low-quality, containing 56 limbs, examining TBI at a cut off at <0.75 in patients with diabetes with neuropathy (LR 95% CI ranged from slight to moderate)

Doppler Waveform Analysis

- 1 study providing very low-quality evidence, containing 57 limbs, examining Doppler waveform analysis defined as the loss of triphasic waveforms in patients with diabetes with neuropathy (LR 95% CI ranged from slight to moderate)

Diagnostic tools which decrease the probability of diagnosing PAD:

The following tools decrease the probability of diagnosing PAD (based on negative likelihood ratios) to a degree that is likely to be PAD **very large**:

Toe Brachial Index

- 1 study providing very low-quality, containing 56 limbs, examining TBI at a cut off at ≥0.75 in patients with diabetes with neuropathy (LR 95% CI ranged from slight to very large)

Doppler Waveform Analysis

- 1 study providing very low-quality evidence, containing 57 limbs, examining Doppler waveform analysis defined as the loss of triphasic waveforms in patients with diabetes with neuropathy (LR 95% CI ranged from slight to very large)

The following tools decrease the probability of diagnosing PAD based on negative likelihood ratios) to a degree that is likely to be **moderate**:

Doppler ABPI

- 1 study providing very low-quality evidence, containing 56 participants, examining Doppler ABPI at a cut off at ≥0.9 in patients with diabetes with neuropathy (LR 95% CI ranged from slight to moderate)

Intra- and Inter-operative reliability

Toe Brachial Index

A single prospective study examining the reliability of TBI was identified. This study was downgraded for serious indirectness as patients were not accurately measured for PAD.

Low-quality evidence from 1 prospective study, including 30 participants, examined inter-rater agreement between 3 raters during 2 session and reported excellent agreement (95% CI ranging from good to excellent agreement).

Very low-quality evidence from 1 prospective study, including 30 participants, examined the mean intra-rater agreement among 3 raters and reported excellent agreement (95% CI ranging from good to excellent agreement)

Severity of PAD

3 studies of very low to moderate quality were identified which evaluated different diagnostic tools for estimating the severity of PAD defined by ≥ 50% stenosis and ≥ 75% stenosis.

≥ 50% Stenosis

- Doppler ABPI:
  - Low-quality evidence from 1 cross sectional study, including 72 patients with diabetes and using DUS as reference standard, did not find an acceptable level of model discrimination (95% not reported)
  - Very low-quality evidence from 1 cross sectional study, which calculated ABPI using the low ankle brachial index method and using DSA as reference standard, did not find an acceptable level of model discrimination (95% CI not reported)
  - Very low-quality evidence from 1 cross sectional study, which calculated ABPI using the high ankle brachial index method and using DSA as reference standard, did not find an acceptable level of model discrimination (95% CI not reported)

- TBI: Low-quality evidence from 1 cross sectional study, including 72 patients with diabetes and using DUS as reference standard, found an acceptable level of model discrimination (95% not reported)

≥75% Stenosis

- Oscillometric ABPI: Very low-quality evidence from 1 cross sectional study, including 58 patients and using CTA as reference standard, found an excellent level of model discrimination (95% CI excellent to outstanding)
- Doppler ABPI:
  - Very low-quality evidence from 1 cross sectional study, which calculated ABPI using the low ankle brachial index method and using DSA as reference standard, found an acceptable level of model discrimination (95% CI not reported)
  - Very low-quality evidence from 1 cross sectional study, which calculated ABPI using the high ankle brachial index method and using DSA as reference standard, did not find an acceptable level of model discrimination (95% CI not reported)

Recommendations

A1. Do not use pulse oximetry for diagnosing peripheral arterial disease in people with diabetes

A2. Do not exclude a diagnosis of peripheral arterial disease in people with diabetes based on a normal or raised ankle brachial pressure index alone

Research recommendations

A3. What is the most clinically and cost-effective diagnostic tool to establish the presence of PAD in people with diabetes?

A4. What is the most clinically and cost-effective diagnostic tool to establish the severity of PAD and the impact of mortality, morbidity and limb amputation in people with diabetes?

A5. What is the inter- and intra-rater reliability of assessment tools for the diagnosis of PAD in people with diabetes?

Rationale and impact

Why the committee made the recommendations

Evidence showed that Doppler ankle brachial pressure index below an agreed cut-off increased the probability of diagnosing peripheral arterial disease. However, people with diabetes and peripheral arterial disease may have a normal or raised index because of hardening of the arteries. The committee agreed that it was important to highlight this so that healthcare professionals do not exclude peripheral arterial disease in people with diabetes based on a normal or raised ankle brachial index alone.

There was a lack of evidence on the use of pulse oximetry for diagnosing peripheral arterial disease in people with diabetes. The committee noted that a universal cut-off point for the presence of peripheral arterial disease had not been established. This could lead to variation in the interpretation of results. Furthermore, it was noted that pulse oximetry is rarely used in clinical practice for the assessment of peripheral arterial disease and there was general clinical agreement that it is not a useful test in this context. Therefore, the committee recommended against the use of pulse oximetry for this purpose.

There was not enough evidence on the use of other tests (Doppler waveform analysis and toe brachial pressure index) for diagnosing peripheral arterial disease in people with diabetes. However, the committee agreed it was not appropriate to make recommendations against the use of these tests, as there were good theoretical arguments as to why these tests might provide useful diagnostic value. The committee therefore agreed to make a number of research recommendations to inform future practice and any further update of this guidance.

Impact of the recommendations on practice

The new recommendations should improve the holistic assessment of peripheral arterial disease in people with diabetes. This is important because this group has a higher risk of cardiovascular events and foot problems such as diabetic neuropathy, foot ulcer and limb loss. The recommendation clarifies the use of ankle brachial index and highlights the importance of interpreting pulse measurements in relation to clinical context, including symptoms.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that likelihood ratios would be considered in the guideline update as the use of a number of different diagnostic tools in a range of settings was being explored. Inter- and intra-rater reliability were also identified as important outcomes due the range of healthcare professionals who undertake the test in different settings. These outcomes were included in the research recommendations.

The quality of the evidence

Overall, the committee noted that the studies ranged from very low to moderate quality and contained small sample sizes. Also, it was identified that studies were in different countries, with only 1 study conducted in the UK. The studies were also conducted in specialised settings.

Studies were mostly downgraded for the risk of bias due to unclear blinding between index test and reference standards. In terms of reference standards, MRI and CTA were identified as the preferred gold standards. However, as fewer than 5 studies were identified for each assessment tool using this preferred reference standard, studies using digital subtraction angiography (DSA) and duplex ultrasound (DUS) were included. Overall, only one study was identified using CTA as reference standard. Studies using DUS or DSA were not downgraded for indirectness, but thresholds used within these studies were further examined. The committee raised concerns about the quality of 2 studies [Williams 2005 and Kumar 2016].

In the Williams 2005 study it was identified that, while DUS was used as a gold standard, arterial disease was only considered to be present if detected from the common femoral artery to the popliteal artery. The committee considered this to be an inappropriate and indirect measurement as the most common distribution of peripheral arterial disease in people with diabetes is in the arteries below the knees. This raised concerns about the reliability of the study and the study was downgraded for serious indirectness. Similarly, in the Kumar 2016 study, DUS was listed as the gold standard but the presence of PAD was identified through monophasic waveforms. The committee noted that such waveforms are an inappropriate threshold, as these do not show arterial disease. Due to this reason, it was agreed that the study would be downgraded for very serious indirectness.

The committee also noted that the thresholds used for index tests varied among studies. It identified that an ABPI threshold of less than 0.9 is commonly accepted, but an elevated ABPI of more than 1.4 can be seen in people with diabetes due to incompressible arteries caused by calcification. Through committee discussion, an ABPI of over 1.4 was identified as an important indicator for the presence of PAD among people with diabetes. In the evidence review, 4 studies [Premalatha 2002, Williams 2005, Tehan 2016 and Kumar 2016] examined the diagnostic test accuracy of ABPI. Among the 4 studies, an ABPI threshold of less 0.9 was used to determine presence of PAD. The committee noted that only 1 study [Tehan 2016] of moderate quality, took into account ABPI measurements of over 1.4.

For TBI, the committee identified that a universally accepted threshold had not been established. This was reflected in the evidence review as the 2 studies which examined the diagnostic accuracy of TBI [Williams 2005 and Tehan 2016] utilised cut-offs of less than 0.75 and less than 0.7 respectively. Furthermore, only 1 study [Kumar 2016] examined the diagnostic accuracy of pulse oximetry. This study stated a cut-off of toe saturation less than finger saturation >2% or if foot saturation decreased by >2% in elevated position. The committee did not consider this as an appropriate threshold and the study was downgraded.

For Doppler waveform analysis, 2 studies were identified which examined the diagnostic test accuracy of the tool. In the William 2005 study, the presence of PAD was defined as the loss of triphasic waveforms, while in the Tehan 2016 study the presence of PAD was defined by the loss of multiphasic (triphasic and biphasic) waveforms. The committee noted that data from both studies demonstrated Doppler waveform analysis to be an effective method for identifying the presence of PAD in people with diabetes, including those who are also exhibiting neuropathy. However, the committee queried the directness of the Williams study due to the threshold utilised for the reference standard, The committee also agreed that while Tehan 2016 was of moderate quality, the sample size (n=72) was too small to draw valid conclusions.

Two studies included within the evidence review [Ichihashi 2014 and Jeevanantham 2014] were downgraded for indirectness due to sub-group analysis being carried out in patients with diabetes. These studies did not actively identify a diabetic population through their inclusion criteria and it was further noted that in the Jeevanantham 2014 study, patients exhibiting an ABPI of over 1.3 were excluded. This could have potentially excluded diabetics with falsely elevated ABPI.

Additionally, studies included in the review were downgraded for unsuitable time intervals between index and reference test. In the Ichihashi 2014 study, diagnostic test accuracy of oscillometric ABPI was retrospectively reviewed, however the reference test was conducted within 1 month before or after the ABPI measurement. Similarly, in the Jeevanantham 2014 study, which retrospectively assessed the diagnostic accuracy of 2 different methods of determining ABPI, intra-arterial DSA was performed within a 6-month period from the ABPI. The committee identified these time intervals as methodological concerns. With Kumar 2016 study, DUS was conducted within 1 week of ABPI and pulse oximetry. The committee noted that a period of 1 week between ABPI and DUS would not affect overall diagnosis of PAD, but an effect would be noted for pulse oximetry.

With regards to operative reliability of diagnostic tools, only 1 study [Romanos 2010] of low quality was identified. The committee agreed that while the study explored the prioritised outcomes, the study did not focus on accurately assessing for the presence of PAD, making the data indirect to the research question.

Benefits and harms

The committee agreed on the importance of the timeliness of diagnosis of PAD in this population. However it was identified that the challenges associated with the interpretation of ankle brachial pressure index has an impact on diagnosis, particularly as falsely elevated results can be interpreted as showing no disease. This is a concern as this could lead to patients presenting with severe disease, leading to foot problems such as foot ulcer and limb loss.

Based on these issues and the evidence identified with regards to Doppler ABPI, recommendations were made with the aim to provide further clarification to the current guideline. The committee highlighted that the new recommendation would influence healthcare professionals to be cautious of normal and elevated measurements in the diabetes population and allow false negatives to be identified. This could result in symptoms being reported earlier and protection against amputation.

The committee also recommended against the use of pulse oximetry among patients with diabetes, suspected of PAD. The committee took into consideration the quality of evidence and the lack of a universally accepted threshold for the diagnosis of peripheral arterial disease. The committee also noted that pulse oximetry is not a recognised assessment tool and without acceptable thresholds, results could vary and be misinterpreted. In addition, there was general clinical agreement that it is not a useful test in this context. Furthermore, without evidence on operator reliability, the overall utility of the diagnostic tool could not be determined.

The committee agreed it was not appropriate to make similar recommendations against the use of the other diagnostics tests looked at in this review. The committee noted that tests such as toe brachial index are utilised in specialised settings. The committee also thought that Doppler waveform analysis could be a useful test in people presenting with critical limb ischemia. This demonstrated that these tests might provide useful diagnostic value, which does not apply to pulse oximetry.

Cost effectiveness and resource use

No health economics work was undertaken for this guideline update, as it was agreed that any recommendations made were highly unlikely to result in a substantial economic impact. It was noted that due to the lack of reliability of ABPI as a test in people with diabetes, additional investigations may need to be carried out to confirm a diagnosis. The committee agreed that investigations such as examination of lower limb pulses are already being carried out so these recommendations should not lead to any substantial change in practice. It was further noted that in clinical settings such as vascular units, radiological imaging is used to allow confirmation of diagnosis. The committee agreed that the recommendations provide further clarification to the current guideline and should allow healthcare professionals to be vigilant of ABPI test in people with diabetes.

Other factors the committee took into account

During committee discussion, no equality issues were identified with regards to the accuracy of diagnostic tools. Furthermore, a number of different factors were taken into account when making recommendations. In the evidence review, 1 study of very low quality presented data for the diagnostic test accuracy of ABPI, TBI and Doppler waveform analysis in patients with diabetes also presenting with neuropathy, which can cause pain, numbness or muscle weakness among patients. While the committee noted that this study presented serious methodological issues, neuropathy was a problem among people with diabetes and further research in this population was required.

The committee also highlighted that within the population affected by PAD, asymptomatic patients presented similar morbidity as symptomatic patients, meaning that quicker diagnosis was essential. Keeping these factors in mind, along with the possible presence of calcification among patients with diabetes, the committee agreed that normal or elevated ABPI measurements should be further examined along with any symptoms, to allow an effective diagnosis of PAD.

The committee also identified a number of issues with regards to competency, availability and accessibility of diagnostic tests. With regards to availability, the committee highlighted that majority of measurements are conducted using a sphygmomanometer and handheld Doppler. However, there are national variations in relation to services and practice. In some clinical settings, ABPI is not being conducted as part of standard work, unless structured protocols have been established. Other diagnostic measures, such as toe pressures and Doppler waveform analysis along with pulse palpation are mainly used in specialised settings. In settings where vascular radiology services are available, imaging procedures such as magnetic resonance angiography (MRA) and arterial duplex ultrasound are utilised.

Furthermore, ankle brachial pressure index is not widely used in GP practices. In some regions, GP practices tend to refer people with suspected peripheral arterial disease to podiatrist or nurse led clinics. Where such services are not available, patients are referred to vascular teams based on symptoms alone, where ankle brachial pressure index or a full assessment is conducted. This raised questions about the usage and reliability of Doppler ABPI particularly in community settings. However the committee identified that the ABPI is used as a tool in other conditions such as in the management of venous leg ulcers, meaning that most clinical settings should include professionals trained to use the ABPI. Taking these factors into account, recommendations were made to add further clarifications to the current

PAD guideline. The committee noted that more research is needed in relation to operative reliability of diagnostic tools.

The recommendations included in the current PAD guideline were also taken into consideration when evaluating the review evidence. When evaluating severity of PAD, defined as ≥75% stenosis, Ichihashi 2014 study found oscillometric ABPI to show excellent model discrimination. However, it was noted that the current guideline recommends measurements to be taken using a Doppler probe in preference to an automated system. The committee also discussed that while oscillometric ABPI provides a quick measure of ABPI, the machines are expensive, difficult to use and are subjective to variation. Oscillometric ABPI was identified to be better suited to specialised clinics rather than community settings. This means that cost implications would need to be considered alongside diagnostic test accuracy when determining effectiveness of this tool.

Similarly, the Jeevanantham 2014 study found that ABPI calculated using the low ankle brachial index method showed an acceptable level of model discrimination. The current guideline recommends index to be calculated in each leg by dividing the highest ankle pressure by the highest arm pressure. Within the clinical setting, ABPI is also commonly measured using the highest readings obtained. While it was identified that using low ankle brachial index method could help with early diagnosis of arterial disease, overall insufficient evidence was identified to support the use of low ankle brachial pressure for the calculation of ABPI.

Appendices

Appendix A – Review protocol

Review protocol for diagnosis and severity of PAD in people with diabetes

ID	Field (based on PRISMA-P)	Content
I	Review question	In people with diabetes who have suspected PAD, what are the most accurate non-invasive diagnostic tests in determining diagnosis and severity of PAD?
II	Type of review question	Diagnostic
III	Objective of the review	Among patients with diabetes who have suspected PAD, what are the most accurate tools for diagnosis and assessment of severity of peripheral arterial disease
IV	Eligibility criteria – Population	Adults (≥ 18 years old) with diabetes with suspected PAD (symptoms - intermittent claudication , leg ulcers, foot ulcers, common foot problems or cardiovascular risk factors).
V	Eligibility criteria – Assessment Tool	Any relevant index non-invasive diagnostic test including: • Resting Ankle brachial pressure index (ABPI) as an adjunct to clinical assessment.

		• Resting ABPI alone. • Post exercise ABPI • Clinical assessment alone (minimum within assessment to include physical assessment, observation of limb, palpation of foot pulses (10g Monofilament test) and validated claudication questionnaires for example The Edinburgh Claudication Questionnaire) • Toe brachial index • Doppler Wave form analysis • Pulse oximetry
VI	Eligibility criteria – Reference standard	Imaging: • Magnetic resonance imaging (MRI) • Computed tomography angiography (CTA) In the event of less than 5 studies being identified , for each assessment tool, using preferred reference standard, studies using following imaging techniques as reference standard will be included: • Digital subtraction angiography (DSA)

		• Duplex ultrasound (DUS)
VII	Outcomes and prioritisation	<u>Diagnosis of PAD</u> • Specificity • Sensitivity • Positive likelihood ratio • Negative likelihood ratio • Inter- and intra-operative reliability <u>Severity of PAD</u> • Logistic regression model fit • Area under the curve • Critical limb ischemia
VIII	Eligibility criteria – study design	• Cohort studies • Cross-sectional studies • Systematic reviews of the above study designs No limitations on sample size
IX	Other exclusion criteria	• Non-English language publications • Abstract/non-published
X	Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups: • Patients with diabetes also presenting with renal disease • Patients with diabetes aged 85 and over

XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
XII	Data management (software)	See Appendix B
XIII	Information sources – databases and dates	See Appendix C
XIV	Identify if an update	Update of 2012 Peripheral Arterial Disease: Diagnosis and Management: In people with suspected peripheral arterial disease (PAD) is ankle brachial pressure index (ABPI) as an adjunct to clinical assessment better than clinical assessment alone or ABPI alone, in determining diagnosis and severity of PAD?

		New update would look specifically at people with diabetes.
XV	Author contacts	Guideline Update
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix C
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables).
XX	Methods for assessing bias at outcome/study level	See Appendix B
XXI	Criteria for quantitative synthesis	See Appendix B
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B

XXIV	Confidence in cumulative evidence	See Appendix B
XXV	Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Susan Bewley in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

XXX	PROSPERO registration number	N/A

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Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, the number of included studies was recorded after every 1,000 records were screened. If, assuming studies were to be found in the remainder of the dataset at the same rate as in that 1,000 records (for example, if 5 includes were found, every subsequent 1,000 records would contain 5 includes), it was estimated that at least 95% of the included studies (at title and abstract level) in the database had been identified, the screening was stopped.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search. If a meaningful number of studies were found that had been eliminated by the priority screening feature, the full original database was then screened.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline.
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table . When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 2: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of

interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 3: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following two groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).
- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the `mada` package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table below.

Table 4: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for a positive likelihood ratio spanned 2, the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratios that spanned 0.5 led to downgrading for serious imprecision. Any likelihood ratios that spanned both 0.5 and 2 were downgraded twice, as suffering from very serious imprecision. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Methods for combining inter-rater agreement evidence

The reliability of agreement for diagnostic data between observers was evaluated using the kappa coefficient. The measure calculates the level of agreement in classification. The general rule of thumb to follow is: if there is no agreement among the classification, then kappa ≤0; if there is complete agreement then kappa=1 (Fleiss 1971). The following schema (see Table), adapted from the suggestions of Fleiss, was used to interpret the level of agreement in diagnostic classification. Random-effects models (der Simonian and Laird) were fitted for all syntheses in R v3.4.0.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Table 5: Interpretation of kappa coefficient

Value of kappa coefficients	Interpretation
$\kappa < 0$	No agreement
$0 < \kappa \leq 0.2$	Poor agreement
$0.2 < \kappa \leq 0.4$	Fair agreement
$0.4 < \kappa \leq 0.7$	Good agreement
$0.7 < \kappa < 1.0$	Excellent agreement
$\kappa = 1.0$	Complete agreement

Modified GRADE for inter-rater agreement evidence

GRADE has not been developed for use with inter-rater agreement; therefore a modified approach was applied using the GRADE framework. Data from all study types was initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

Table 6: Rationale for downgrading evidence for inter-rater agreement

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Inconsistency	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Indirectness	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for the kappa coefficient spanned two or three of the categories in Table , it was downgraded one level. If the 95% confidence interval for the kappa coefficient spanned four or more of the categories in Table , it was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Severity assessment evidence

Area under the curve (AUC)

Studies including ROC curves were also included in this evidence review, if they looked at assessing the severity of PAD. A ROC curve plots the sensitivity of a model against its specificity across the full range of possible thresholds scores. Accuracy, in terms of being able to discriminate between cases and non-cases, is measured by the area under the ROC curve (AUC). An area of 1 represents a perfect prediction; an area of 0.5 represents a worthless prediction (equivalent to ‘random chance’). An area under the curve (AUC) value of 0.7 to 0.8 was defined in this guideline as indicating acceptable model discrimination; values of 0.8 to 0.9 were defined as indicating excellent discrimination, and values greater than 0.9 were defined as indicating outstanding discrimination (following Hosmer 2000).

Studies reporting area under ROC curve (AUC) were included in this review. The GRADE working group has not published criteria for assessing imprecision in relation to AUC statistics. For the current review, the AUC classification categories referred to above were used. Arbitrary minimal important difference levels of 0.7 and 0.8 were chosen for the assessment of imprecision, to be applied to the range of AUC scores reported across contributing studies (or to the 95% confidence interval where a model was evaluated by a single study). If 95% CIs around AUC for a single study crossed one MID (0.7 or 0.8) –

downgrade one level (serious imprecision). If 95% CIs around AUC for a single study crossed both MIDs (0.7 and 0.8) – downgrade two levels (very serious imprecision). These data are shown in the GRADE profiles in Appendix K.

Appendix C – Literature search strategies

C.1 Clinical search summary

Databases	Date searched	Version/files	No. retrieved	EndNote data
Cochrane Central Register of Controlled Trials (CENTRAL)	04/10/2017	Cochrane Central Register of Controlled Trials : Issue 8 of 12, August 2017	65	31
Cochrane Database of Systematic Reviews (CDSR)	04/10/2017	Cochrane Database of Systematic Reviews : Issue 9 of 12, September 2017	10	9
Database of Abstracts of Reviews of Effect (DARE)	04/10/2017	Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015	1	0
Embase (Ovid)	04/10/2017	Embase 1974 to 2017 Week 36	440	248
MEDLINE (Ovid)	04/10/2017	Ovid MEDLINE(R) 1946 to August Week 4 2017	487	445
MEDLINE In-Process (Ovid)	04/10/2017	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations September 01, 2017	18	17
CINAHL	04/10/2017	-	84	45
Health Technology Assessment (HTA Database)	04/10/2017	Issue 4 of 4, October 2016	1	0

C.2 Clinical search terms (Medline)

Database: Medline

Strategy used:

1 Peripheral Arterial Disease/ (5105)
2 Peripheral Vascular Diseases/ (12777)
3 (peripheral adj4 (arter* or vascular*) adj4 (obstruct* or occlus* or disease*)).tw. (22151)
4 (PAD or PVD or PVOD or PAOD or POAD).tw. (20834)
5 (peripheral adj4 angiopath*).tw. (84)
6 ((arter* or ather* or vascular*) adj4 oblit*).tw. (4776)
7 (atherosclero* adj4 (oblit* or occlusion* or peripheral)).tw. (2542)
8 Intermittent Claudication/ (7968)
9 (intermitten* adj4 claudica*).tw. (4780)
10 (critical adj4 isch?emia*).tw. (4739)
11 (fontaine adj4 stag*).tw. (517)
12 or/1-11 (60963)
13 exp Diabetes Mellitus/ (386536)
14 diabet*.tw. (483365)
15 (NIDDM or IDDM or MODY or LADA or DKA).tw. (15258)
16 (DM adj1 ("1" or "2")).tw. (3737)
17 (DM1 or DM2 or T1D or T2D).tw. (10974)
18 or/13-17 (545990)

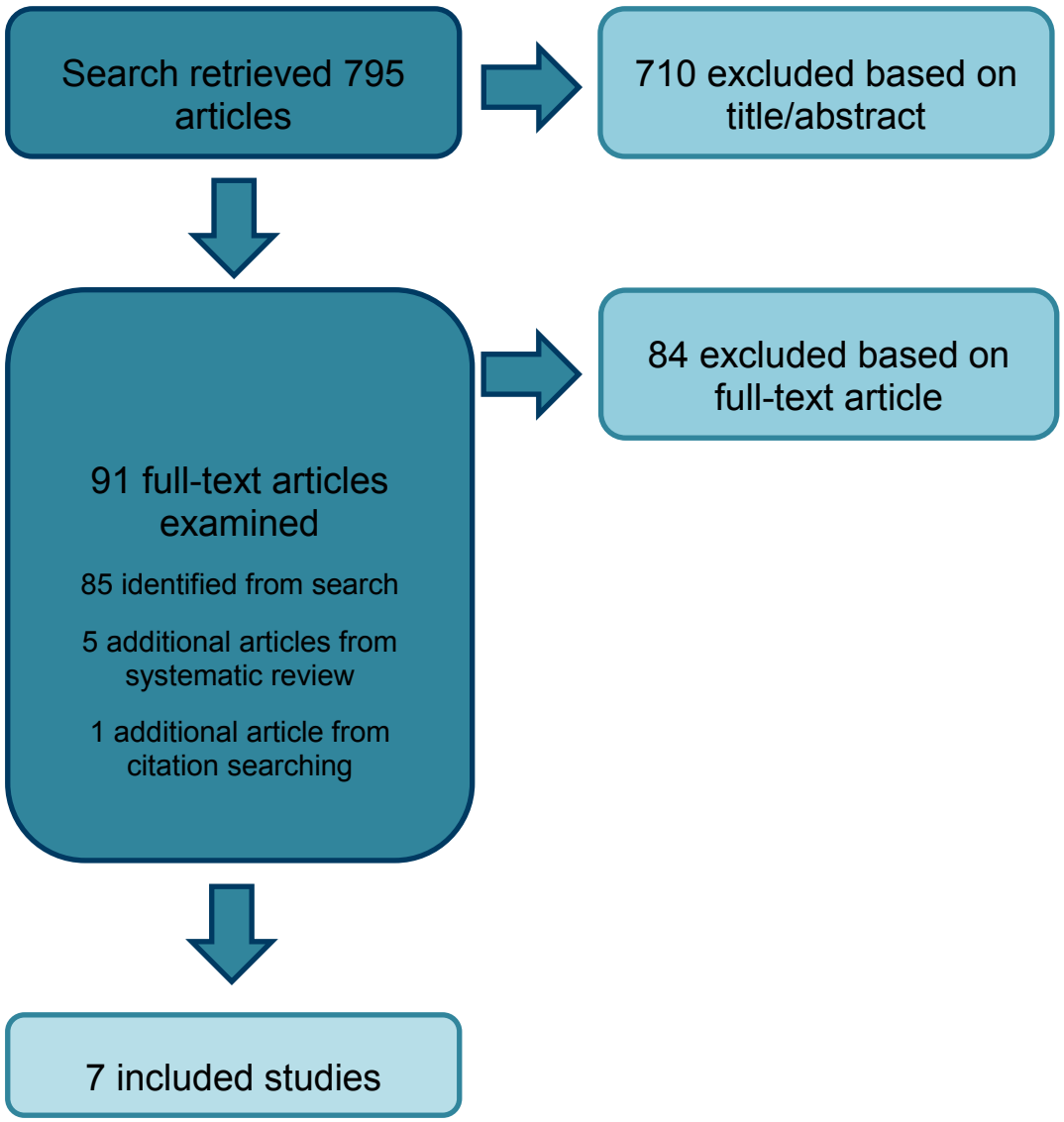
Database: Medline

19 Ankle Brachial Index/ (2487)
20 Blood Pressure Determination/ (26163)
21 (ankle adj2 brachial adj3 (index* or indices or ratio*)).tw. (4855)
22 (ABPI or ABI).tw. (5568)
23 Brachial artery/ (9817)
24 Tibial arteries/ (1513)
25 Ankle/bs [Blood Supply] (1257)
26 Leg/bs [Blood Supply] (26023)
27 ((Ankle or brachial or posterior or anterior or tibial) adj4 pressure*).tw. (6228)
28 or/19-27 (72959)
29 exp Physical Examination/ (1272699)
30 Point-of-Care Testing/ (604)
31 Medical History Taking/ (18485)
32 ((medical or clinical or patient* or client*) adj4 histor*).tw. (117598)
33 ((clinic* or physic* or peripheral vascular*) adj4 (exam* or assess*)).tw. (261005)
34 ((foot or feet or limb* or extremit*) adj4 (puls* or exam* or assess* or observ* or inspect* or recogni* or scrutin*)).tw. (13772)
35 (10g adj4 monofilament*).tw. (9)
36 exp Surveys/ and Questionnaires/ (393842)
37 ((validat* or Edinburgh or claudicat*) adj4 (questionnaire* or survey*)).tw. (14147)
38 or/29-37 (1954271)
39 28 or 38 (1991208)
40 ((toe* or hallux*) adj2 brachial adj3 (index* or indices)).tw. (135)
41 (TBPI or TBI).tw. (16426)
42 exp Toes/bs [Blood Supply] (1077)
43 Metatarsus/bs [Blood Supply] (70)
44 ((toe* or hallux* or metatars*) adj4 pressure*).tw. (760)
45 (metatars* adj4 arter*).tw. (177)
46 Pulse Wave Analysis/ (2506)
47 (puls* adj4 (wave* or transit* or velocit* or curv*)).tw. (17537)
48 Laser-Doppler Flowmetry/ (8118)
49 exp Ultrasonography, Doppler/ (66636)
50 Doppler Effect/ (1508)
51 ((doppler* or wave form* or waveform*) adj4 (imag* or laser* or ultra* or assess* or exam* or analys* or flow* or pulse* or echo* or veloc* or anemom*)).tw. (74996)
52 (doppler* adj4 (wave* or effect*)).tw. (6346)
53 exp Oximetry/ (14128)
54 (oximetr* or oximeter*).tw. (10772)
55 (blood adj1 (gas or oxygen) adj1 (monitor* or measur*)).tw. (1149)
56 or/40-55 (161660)
57 39 or 56 (2115432)
58 12 and 18 and 57 (4078)
59 Animals/ not Humans/ (4495993)
60 58 not 59 (3960)
61 limit 60 to english language (3385)
62 Observational Studies as Topic/ (2512)
63 Observational Study/ (41898)
64 Epidemiologic Studies/ (7789)
65 exp Case-Control Studies/ (903805)
66 exp Cohort Studies/ (1738487)
67 Cross-Sectional Studies/ (257124)

Database: Medline	
68	Controlled Before-After Studies/ (271)
69	Historically Controlled Study/ (129)
70	Interrupted Time Series Analysis/ (324)
71	Comparative Study.pt. (1843662)
72	case control$.tw. (97555)
73	case series.tw. (46714)
74	(cohort adj (study or studies)).tw. (124186)
75	cohort analy$.tw. (5135)
76	(follow up adj (study or studies)).tw. (42225)
77	(observational adj (study or studies)).tw. (63674)
78	longitudinal.tw. (170695)
79	prospective.tw. (429637)
80	retrospective.tw. (353259)
81	cross sectional.tw. (220619)
82	or/62-81 (3955508)
83	Meta-Analysis.pt. (85003)
84	Network Meta-Analysis/ (163)
85	Meta-Analysis as Topic/ (16341)
86	Review.pt. (2247427)
87	exp Review Literature as Topic/ (9698)
88	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (99657)
89	(review$ or overview$).ti. (347622)
90	(systematic$ adj5 (review$ or overview$)).tw. (95234)
91	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (6395)
92	((studies or trial$) adj2 (review$ or overview$)).tw. (32887)
93	(integrat$ adj3 (research or review$ or literature)).tw. (7741)
94	(pool$ adj2 (analy$ or data)).tw. (20751)
95	(handsearch$ or (hand adj3 search$)).tw. (7002)
96	(manual$ adj3 search$).tw. (4257)
97	or/83-96 (2446810)
98	animals/ not humans/ (4495993)
99	97 not 98 (2296995)
100	82 or 99 (6030448)
101	61 and 100 (2283)
102	(sensitiv: or specificit: or predictive value: or likelihood ratio:).mp. or accurac:.tw. (2188647)
103	exp Reproducibility of Results/ (355533)
104	(reliab* or valid* or concord*).tw. (810426)
105	(interrat* or intrarat*).tw. (6982)
106	((intra* or inter*) adj1 rat*).tw. (25150)
107	or/102-106 (2890565)
108	101 and 107 (487)

1
2

Appendix D – Clinical evidence study selection



1 Appendix E – Clinical evidence tables

2 E.1 Ichihashi (2014)

<table>
<tr><th colspan="2">Ichihashi S, Hashimoto T, Iwakoshi S, and Kichikawa K (2014) Validation study of automated oscillometric measurement of the ankle-brachial index for lower arterial occlusive disease by comparison with computed tomography angiography. Hypertension Research - Clinical & Experimental 37(6), 591-4</th></tr>
<tr><td>Study type</td><td>Cross-sectional study</td></tr>
<tr><td>Aim</td><td>Evaluate the diagnostic accuracy and optimal threshold of oscilllometric ABPI for detecting PAD using CTA as gold standard.</td></tr>
<tr><td>Patient Characteristics</td><td>Inclusion criteria
• Patients suspected of PAD
Exclusion criteria
• History of vascular surgery or endovascular treatment for PAD.

<table>
<tr><th colspan="2">Study Characteristics</th></tr>
<tr><td>Female (%)</td><td>13</td></tr>
<tr><td>Mean age (SD)</td><td>71.2 ± 8.1</td></tr>
<tr><td>Diabetes (%)</td><td>54</td></tr>
<tr><td>Known CVD (%)</td><td>39</td></tr>
<tr><td>Cerebrovascular disease (%):</td><td>26</td></tr>
<tr><td>Hypertension (%)</td><td>95</td></tr>
<tr><td>Arterial Fibrillation (%)</td><td>10</td></tr>
<tr><td>Hemodialysis (%)</td><td>16</td></tr>
<tr><td colspan="2">Symptoms (207 limbs):</td></tr>
<tr><td>No symptom:</td><td>22</td></tr>
<tr><td>Intermittent Claudication</td><td>74</td></tr>
<tr><td>Critical Limb Ischemia</td><td>4</td></tr>
</table></td></tr>
<tr><td>Sample Size</td><td>108 patients with 216 limbs</td></tr>
</table>

Ichihashi S, Hashimoto T, Iwakoshi S, and Kichikawa K (2014) Validation study of automated oscillometric measurement of the ankle-brachial index for lower arterial occlusive disease by comparison with computed tomography angiography. Hypertension Research - Clinical & Experimental 37(6), 591-4	
Index test(s)	ABPI ABPI measurements were obtained after the patients had rested for 15 minutes in the supine position in a room with a comfortable temperature (19-20C) and refrained from smoking, heavy exercise and drinking alcohol or caffeinated beverages for at least 2 hours before the examination. ABI was measured in all patients using an automated oscillometric device. The highest ankle pressure was used for calculating the ABI. All measurements using the oscillometric method were performed by the same investigator with 10 years of experience in ABI measurements.
Reference standard(s)	CTA The CTA protocol consisted of plain, arterial and venous phases encompassing the abdomen and lower extremity. A single radiologist with 10 years' experience in vascular imaging, performed analyses of the contrast-enhanced CT images and was blinded to the patient's clinical symptom or ABI value. Stenosis of arteries were graded with a four-point scale (grade 1, 0-50%; grade 2, 50-75%; grade 3, 75-99%; grade 4, 100%) in each of the following arterial segments: aortoiliac, femoropoplital and below the knee. The artery with the least stenosis was used to grade below the knee arteries together, according to the one straight-line flow concept.
Study Details	• Study location: Japan • Study setting: Department of Radiology • Study dates: June 2010-December 2012 • Loss to follow-up: Oscillometric ABPI value could not be measured in 9 out of 216 limbs: 8 limbs due to diffuse calcification of the arterial wall and 3 limbs due to low blood pressure (two limbs had both of these conditions). These 9 limbs were excluded from the analysis. • Time between testing & Treatment: All patients underwent CTA within 1 month before or after the ABI measurement • Sources of funding: Not specified
Results	AUC for detecting ≥75% stenosis: 0.888 (95% CI: 0.825-0.952)
Quality Assessment (QUADA2)	**Patient selection:** Low risk of bias **Index test:** Low risk of bias **Reference standard:** Low risk of bias **Flow and timing:** High risk of bias. 9 out of 216 limbs were excluded, as ABPI could not be measured. 8 limbs due to diffuse calcification of the arterial wall and 2 limbs due to low blood pressure (2 limbs had both of these conditions). Furthermore, patients underwent CTA within 1 month before or after the ABPI measurement. **Overall risk of bias:** Moderate

Ichihashi S, Hashimoto T, Iwakoshi S, and Kichikawa K (2014) Validation study of automated oscillometric measurement of the ankle-brachial index for lower arterial occlusive disease by comparison with computed tomography angiography. Hypertension Research - Clinical & Experimental 37(6), 591-4	
	Directness: Partially directly applicable. Sub-group analysis carried out in patients with diabetes.

E.2 Jeevanatham (2014)

Jeevanantham V, Chehab B, Austria E, Shrivastava R, Wiley M, Tadros P, Dawn B, Vacek J L, and Gupta K (2014) Comparison of accuracy of two different methods to determine ankle-brachial index to predict peripheral arterial disease severity confirmed by angiography. American Journal of Cardiology 114(7), 1105-10	
Study type	Cross-sectional study
Aim(s)	(1) Study the diagnostic accuracy of LABI and HABI in the detection of PAD and total PAD burden (2) Study the diagnostic accuracy inpatients with diabetes in whom ABI determined by HABI method is often falsely elevated because of medial calcinosis (3) Assess the diagnostic utility for detection below the knee PAD that is unknown
Patient Characteristics	Inclusion criteria • Patients who had ABPI done within 6 months before the angiogram Exclusion criteria • Previous limb amputations proximal to the heads of metatarsals or proximal to the elbow in the upper limbs • previous bypass • stenting or prosthetic vascular reconstruction to the lower limbs or of the arteries of lower limb/ abdominal aorta or subclavian or axillary arteries • an ABPI>1.3 in both lower limbs • any abdominal or lower extremity vascular surgery or intervention between the time of having the ABI measurement and the first available angiography

Study Characteristics	
All Limbs (n= 260)	
Female (%)	41
Mean age (SD)	68±9
Body Mass Index (BMI)	29± 6
Diabetes (%)	31

Jeevanantham V, Chehab B, Austria E, Shrivastava R, Wiley M, Tadros P, Dawn B, Vacek J L, and Gupta K (2014) Comparison of accuracy of two different methods to determine ankle-brachial index to predict peripheral arterial disease severity confirmed by angiography. American Journal of Cardiology 114(7), 1105-10	
	<table><tr><td>Tobacco Use (%)</td><td>92</td></tr><tr><td>Cerebrovascular Accident (%)</td><td>12</td></tr><tr><td>Chronic Kidney Disease (%)</td><td>17</td></tr><tr><td>Coronary Artery Disease (%)</td><td>81</td></tr><tr><td>Hypertension (%)</td><td>85</td></tr><tr><td>Dyslipidemia (%)</td><td>75</td></tr><tr><td>Symptomatic (%)</td><td>94</td></tr><tr><td>Renal Artery Stenosis (%)</td><td>8</td></tr><tr><td>Carotid Artery Stenosis (%)</td><td>27</td></tr><tr><td>Left Ventricle Ejection Fraction</td><td>56±12</td></tr></table>
Sample Size	130 patients (260 limbs)
Index test(s)	ABPI ABPI was performed by an experienced examiner who was blinded to all clinical baseline parameters assessed. Measurements were performed, after a 5- to 10- minute rest, in the supine position with the upper body as flat as possible to minimise the effect of an increased tibial artery blood pressure. ABPI values were then calculated applying 2 different methods: The higher ankle pressure (either the posterior tibial or dorsalis pedis artery) was used as the numerator for the HABI. The lower ankle pressure (either posterior tibial or dorsalis pedis artery) was used as the numerator for the LABI method. An abnormal ABI was defined as <0.9 for both methods
Reference standard(s)	DSA Intra-arterial DSA was performed and assessed by consensus agreement by 2 experienced readers who were blinded to the clinical and ABPI data. Appropriate anteroposterior sequential views of the lower abdomen, pelvis, and the lower extremities were obtained. Oblique views were obtained for the iliac and the proximal femoral arteries. Percentage stenosis was defined as a >50% diameter reduction determined by visual estimation and by quantitative measurement assessment. Stenosis was calculated as the ratio of the residual target vessel lumen diameter to the diameter of the reference segment of artery. Angiographic disease was scored using the quantitative coronary assessment method (0=50%; 1=50%-75%; 2=>75% occlusion) of any lower extremity arterial segment.

Jeevanantham V, Chehab B, Austria E, Shrivastava R, Wiley M, Tadros P, Dawn B, Vacek J L, and Gupta K (2014) Comparison of accuracy of two different methods to determine ankle-brachial index to predict peripheral arterial disease severity confirmed by angiography. American Journal of Cardiology 114(7), 1105-10	
Study Details	• Study location: Kansas City, Kansas • Study setting: Tertiary Referral Academic Medical Centre • Study dates: July 2005 - June 2010 • Loss to follow-up: Not Specified • Time between testing & Treatment: Arteriographies were performed within a 6-month period from the ABI measurements • Sources of funding: Not specified
Results	AUC: Diagnosis of PAD defined by ≥ 50% stenosis in at least one segment by angiography: HABI: 0.609 (95% CI not reported) LABI: 0.675 (95% CI not reported) Diagnosis of PAD defined by ≥75% stenosis in at least one segment by angiography: HABI: 0.668(95% CI not reported) LABI: 0.748(95% CI not reported)
Quality Assessment (QUADA2)	**Patient selection:** Low risk of bias **Index test:** Low risk of bias **Reference standard:** Low risk of bias **Flow and timing:** High risk of bias. Arteriography performed within six month period from the ABPI measurement **Overall risk of bias:** Moderate **Directness:** Partially directly applicable. Sub-group analysis carried out in patients with diabetes. Furthermore, patients with ABPI over 1.3 excluded from study.

E.3 Kumar (2016)

Kumar M S, Lohiya A, Ramesh V, Behera P, Palepu S, and Rizwan S A (2016) Sensitivity and Specificity of Pulse Oximetry and Ankle-Brachial Index for Screening Asymptomatic Peripheral Vascular Diseases in Type 2 Diabetes Mellitus. Journal of the Association of Physicians of India 64(8), 38-43	
Study type	Cross-sectional study

<table>
<tr><th colspan="2">Kumar M S, Lohiya A, Ramesh V, Behera P, Palepu S, and Rizwan S A (2016) Sensitivity and Specificity of Pulse Oximetry and Ankle-Brachial Index for Screening Asymptomatic Peripheral Vascular Diseases in Type 2 Diabetes Mellitus. Journal of the Association of Physicians of India 64(8), 38-43</th></tr>
<tr><td>Aim</td><td>To compare pulse oximetry and ABPI with duplex ultrasonography as reference standard to determine the diagnostic accuracy for screening asymptomatic PVD in type 2 diabetes mellitus.</td></tr>
<tr><td>Patient Characteristics</td><td>Inclusion criteria
• Adults pre-diagnosed type 2 diabetes mellitus, either physician diagnosed or based on blood glucose records as per American Association (ADA) criteria, irrespective of control of blood glucose, duration of diagnosis, treatment and presence of other complications
• Not previously investigated for or diagnosed as PAD and asymptomatic with regards of PAD such as pain, swelling, ulcers, previous amputation.

Exclusion criteria
• Aged less than 40 years
• patients suffering from hypercoagulable states, congestive heart failure, valvular heart disease, suspected arteritis and collagen vascular disease,
• Patients who were unable to lie supine, for the period of testing
• extreme sick patients who required intensive care.

<table>
<tr><th colspan="3">Study Characteristics</th></tr>
<tr><td></td><td>PVD Present</td><td>PVD Absent</td></tr>
<tr><td>Female (%)</td><td>18.5</td><td>28</td></tr>
<tr><td>Age:</td><td></td><td></td></tr>
<tr><td>41-50 (%)</td><td>25.9</td><td>43</td></tr>
<tr><td>51-60 (%)</td><td>55.6</td><td>46.2</td></tr>
<tr><td>61-70 (%)</td><td>18.5</td><td>10.8</td></tr>
<tr><td>Diabetes Duration (years):</td><td></td><td></td></tr>
<tr><td><10 years (%)</td><td>18.5</td><td>59.1</td></tr>
<tr><td>≥10 years (%)</td><td>81.5</td><td>40.9</td></tr>
<tr><td>Currently Smoking (%)</td><td>74.1</td><td>31.2</td></tr>
<tr><td>Known CVD (%)</td><td>66.7</td><td>39.8</td></tr>
<tr><td>Cerebrovascular disease (%)</td><td>14.8</td><td>6.5</td></tr>
</table>
</td></tr>
</table>

Kumar M S, Lohiya A, Ramesh V, Behera P, Palepu S, and Rizwan S A (2016) Sensitivity and Specificity of Pulse Oximetry and Ankle-Brachial Index for Screening Asymptomatic Peripheral Vascular Diseases in Type 2 Diabetes Mellitus. Journal of the Association of Physicians of India 64(8), 38-43	
	Hypertension (%): 81.5 59.1
Sample Size	120 patients
Index test(s)	ABPI ABPI was performed followed by pulse oximetry on the same day. ABPI was calculated by measuring systolic BP of the brachial artery at the elbows and that of posterior tibial arteries at the ankles. ABPI values for each leg were calculated by dividing the ankle systolic BP by the elbow pressure and a value of <0.9 for any leg was considered positive for PVD. A patient was considered to be positive for PVD even if any one leg had abnormal results. Pulse Oximetry A handheld pulse oximeter was used to measure peripheral arterial oxygen saturation (SpO2) of both index fingers and both big toes. Toe saturation was measured in two positions, one in supine and other at 12-inch elevation from the horizontal plane. By pulse oximetry, PVD was considered present if toe saturation was less than finger saturation by >2% or if the foot saturation decreased by >2% in the elevated position.
Reference standard(s)	DUS Duplex ultrasonography of lower extremity arteries was performed using a Doppler ultrasonogram machine. An expert radiographer who was blind to results of index tests, conducted duplex ultrasonography within one-week of the initial assessment. Duplex ultrasonography of lower extremities was done at the level of femoral, popliteal, tibial, and posterior tibial and dorsalis pedis arteries bilaterally. The presence of monophasic waveforms in any one artery by duplex ultrasonography was taken as confirmatory evidence for PVD
Study Details	• Study location: Madurai, India • Study setting: Tertiary care hospital • Study dates: March - November 2012 • Loss to follow-up: Not Specified • Time between testing & Treatment: Within one-week of the initial assessment. • Sources of funding: Not Specified
Results	• Calculated Sensitivity Pulse Oximetry: 74.1 % (95% CI: 54.7-87.1%) ABPI: 70.4% (95% CI: 51.0-84.4%) • Calculated Specificity Pulse Oximetry: 95.7 % (95% CI: 89.1-98.4%)

Kumar M S, Lohiya A, Ramesh V, Behera P, Palepu S, and Rizwan S A (2016) Sensitivity and Specificity of Pulse Oximetry and Ankle-Brachial Index for Screening Asymptomatic Peripheral Vascular Diseases in Type 2 Diabetes Mellitus. Journal of the Association of Physicians of India 64(8), 38-43	
	ABPI: 87.1 %(95% CI: 78.6-92.5%) • Calculated Positive Likelihood Ratio Pulse Oximetry: 17.222 (95% CI: 6.436 - 46.086) ABPI: 5.454 (95% CI: 3.047-9.760) • Calculated Negative Likelihood Ratio Pulse Oximetry: 0.271 (95% CI: 0.143-0.513) ABPI: 0.340 (95% CI: 0.189-0.612)
Quality Assessment (QUADA2)	**Patient selection:** Low risk of bias **Index test:** Unclear risk of bias. Unclear blinding between index tests (ABPI and pulse oximetry) which were conducted on the same day, by the same investigator **Reference standard:** Low risk of bias **Flow and timing:** High risk of bias. One week interval between index test and reference test **Overall risk of bias:** Moderate **Directness:** Indirectly applicable. DUS used as reference standard, however PAD was identified by the presence of monophasic waveforms, which is an inappropriate threshold, as it does not show arterial disease. Threshold used to assess presence of PAD using pulse oximetry not appropriate.

E.4 Premalatha (2002)

Premalatha G, Ravikumar R, Sanjay R, Deepa R, and Mohan V (2002) Comparison of colour duplex ultrasound and ankle-brachial pressure index measurements in peripheral vascular disease in type 2 diabetic patients with foot infections. Journal of the Association of Physicians of India 50, 1240-4	
Study type	Cross-sectional study
Aim	Compare the specificity and sensitivity of ABPI measured by peripheral Doppler with the colour duplex ultrasound for diagnosis of PVD
Patient Characteristics	Inclusion criteria All patients admitted to the hospital with type 2 diabetes and severe foot infections

Premalatha G, Ravikumar R, Sanjay R, Deepa R, and Mohan V (2002) Comparison of colour duplex ultrasound and ankle-brachial pressure index measurements in peripheral vascular disease in type 2 diabetic patients with foot infections. Journal of the Association of Physicians of India 50, 1240-4

	Exclusion criteria None reported

Study Characteristics	
Female (%)	Not Specified
Mean Age (SD)	59.5±10.1
Body Mass Index (BMI)	24.2±3.5
Diabetes Duration (years)	11.7±8.1
Fasting plasma glucose (mg/dl)	9.5±2.0
Systolic Blood Pressure (mmHg)	136±19
Diastolic blood pressure (mmHg)	86±11
Treatment:	
OHA alone (%)	19
Insulin alone (%)	16
OHA and Insulin (%)	60
Diet (%)	5
Smoking (%)	24

Sample Size	100
Index test(s)	ABPI Continuous waveform Doppler (CWD) studies done on all patients. Blood pressure and velocity graph recordings were done on the brachial pulses in the upper arm. In the lower limb, recordings were done on the dorsalis pedis and posterior tibital pulses and the mean of these two readings were as the ankle pressure. ABI <0.9 in either foot defined as peripheral vascular disease: grade 1=ABI ≥0.9; grade 2=0.7 to 0.9; grade 3=0.5 to 0.7;grade 4 ≤0.5
Reference standard(s)	DUS High resolution colour duplex ultrasound conducted of the common iliac, external iliac and common femoral arteries. The superficial femoral artery was traced up to the popliteal fossa and the profunda was evaluated in its proximal segment. The frapopliteal vessels, anterior tibial, peroneal, posterior tibial and dorsalias pedis were also evaluated. PVD was diagnosed if

Premalatha G, Ravikumar R, Sanjay R, Deepa R, and Mohan V (2002) Comparison of colour duplex ultrasound and ankle-brachial pressure index measurements in peripheral vascular disease in type 2 diabetic patients with foot infections. Journal of the Association of Physicians of India 50, 1240-4	
	the stenosis in the artery was greater than 50% or had an occlusion. Stenosis was graded 1: 1-19%, grade 2: 20-49%, grade 3: 50-99% and grade 4: total occlusion.
Study Details	• Study location: India • Study setting: Tertiary care specialised diabetes centre • Study dates: Not Specified • Loss to follow-up: Not specified • Time between testing & Treatment: Not specified • Sources of funding: Not specified
Results	• Calculated Sensitivity: 70.6% (CI: 58.8%-80.2%) • Calculated Specificity: 88.5% (CI: 69.7%-96.2%) • Calculated Positive Likelihood Ratio: 6.118 (CI: 2.087-17.930) • Calculated Negative Likelihood Ratio: 0.332 (CI: 0.224-0.493)
Quality Assessment (QUADA2)	**Patient selection:** Low risk of bias **Index test**: Low risk of bias **Reference standard:** Unclear risk of bias**.** Unclear blinding between reference test and index test. **Flow and timing:** High risk of bias. Removal of patients with calcification from analysis and unclear time interval between reference and index test **Overall risk of bias**: Moderate **Directness:** Directly applicable

E.5 Romanos (2010)

Romanos MT, Raspovic A, and Perrin BM (2010) The reliability of toe systolic pressure and the toe brachial index in patients with diabetes.. Journal of foot and ankle research 3, 31	
Study type	Cross-sectional study
Aim	Determine the intra- and inter- rater reliability of the measurement of toe systolic pressure and the toe brachial index (TBI) in patients with diabetes using a manual measurement system

Romanos MT, Raspovic A, and Perrin BM (2010) The reliability of toe systolic pressure and the toe brachial index in patients with diabetes.. Journal of foot and ankle research 3, 31	
Patient Characteristics	Inclusion criteria • 21 years of age and older Exclusion criteria • Unable to lie supine for the duration of the tests • Presented with wounds or infection around the testing site • Individuals who has a vasometer condition such as Raynaud's disease
Sample Size	30
Index test(s)	TBI Participants were provided with pre-test guidelines to reduce the impact of external influences on measurements. This included refraining from tobacco smoking and caffeine intake for at least one hour prior to data collection. Prior to measurement, each participant lay supine with their legs at heart level for 20 minutes. This was to prevent hydrostatic effects on the pressure reading. Measurement sessions occurred one week apart. The raters were blinded to each other's results but not their own. The TBI was calculated as the ratio of the toe systolic pressure to the value of the arm brachial systolic pressures. Once the value of the brachial systolic pressure and the hallux systolic pressure were obtained, the calculation of the TBI was determined by dividing the toe brachial systolic pressure by the brachial systolic pressure.
Study Details	• Study location: Victoria, Australia • Study setting: University Podiatry Clinic • Study dates: Not specified • Loss to follow-up: Not specified • Sources of funding: Not specified
Results	Results • Mean Intra-rater reliability ICC: 0.75 (0.55-0.87) • Inter-rater reliability Session 1: 0.77 (0.62-0.87) Session 2: 0.81 (0.68-0.90)
Quality Assessment (QUADA2)	**Patient selection:** Low risk of bias **Index test:** High risk of bias. Raters not blinded for their own results. **Flow and timing:** Low risk of bias **Overall risk of bias:** Moderate

Romanos MT, Raspovic A, and Perrin BM (2010) The reliability of toe systolic pressure and the toe brachial index in patients with diabetes.. Journal of foot and ankle research 3, 31	
	Directness: Indirectly applicable. Patients not accurately measured for the presence of PAD

E.6 Tehan (2016)

Tehan P E, Bray A, and Chuter V H (2016) Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. Journal of Diabetes & its Complications 30(1), 155-60	
Study type	Cross-sectional study, Case-control study
Aim	Determine the sensitivity and specificity of ABPI, Continuous Wave Doppler (CWD) and Toe Brachial Index (TBI) in a population with and without diabetes.
Patient Characteristics	Inclusion criteria • Aged over 65 years • or aged over 50 years with history of diabetes • or aged over 50 years currently smoking • exertional leg pain or non-healing wounds Exclusion criteria • Known allergy to coupling gel • presence of a wound preventing Doppler probe or ankle cuff placement • Previous bilateral mastectomy preventing bilateral brachial blood pressure examination

Study Characteristics		
	DM Group	Non DM Group
Female (%)	34	41
Mean Age	72.47	74.21
Neuropathy (%)	12	13
History of Smoking (%)	58	46
Currently Smoking (%)	2	6
Known CVD (%)	31	32

Tehan P E, Bray A, and Chuter V H (2016) Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. Journal of Diabetes & its Complications 30(1), 155-60

	Mean ABPI	1.16	1.08
	Mean TBI	0.70	0.67
	Incompressible ankle pressure (%)	10	4
	Distal PAD (%)	36	36
	Proximal PAD (%)	13	8
	PAD, >50% Stenosis (%)	5	2
	PAD, >75% Stenosis (%)	5	2
	Occlusion (%)	33	37

Sample Size	117 patients (Diabetes= 72, No Diabetes=45)
Index test(s)	ABPI Bilateral brachial systolic pressures obtained in all participants using continuous wave Doppler and hand-held sphygmomanometer. Ankle systolic pressures of only right leg were taken. Both dorsalis pedis and posterior tibial artery pressures were recorded, with the higher of the two being used in calculation of the ABPI. Standard cut-off score for an abnormal ABPI of ≤ 0.90 or greater than 1.4. TBI A single toe systolic pressure was obtained by placing a photoplethysmograph (PPG) probe directly on the distal pulp of the right great toe affixed with adhesive tape. TBI was calculated by dividing the toe pressure by the highest brachial pressure. TBI normal values were considered ≥ 0.70. Doppler Waveform analysis Continuous Wave Doppler (CWD) waveforms were analysed by a single researcher who assessed each waveform, blinded to the results of CFDU and pressure measurement. CWD waveforms taken from the right side. Loss of multi-phasic pattern in either the dorsalis pedis or posterior tibial arteries demonstrated by low-resistance, slow systolic acceleration and no diastolic flow reversal were considered positive for PAD.
Reference standard(s)	DUS CFDU was performed following pressure measurements, from the abdominal aorta to the distal ankle on the right side.
Study Details	• Study location: New South Wales, Australia • Study setting: Private vascular clinic

Tehan P E, Bray A, and Chuter V H (2016) Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. Journal of Diabetes & its Complications 30(1), 155-60	
	• Study dates: August 2011- December 2013 • Loss to follow-up: Not specified • Time between testing & Treatment: All tests done in a single testing session • Sources of funding: Project funded through a University of Newcastle new stand grant and early career researcher grant
Results	• Sensitivity ABPI: 45.16 % (95% CI: 27.33-63.96) Continuous Wave Doppler: 74.19 %(95% CI: 55.38-88.11) TBI: 63.64 % (95% CI: 45.13-79.58) • Specificity ABPI: 92.68 % (95% CI: 80.05-98.38) Continuous Wave Doppler: 92.86 %(95% CI: 80.49-98.42) TBI: 82.05 % (95% CI: 66.46-92.43) • Positive Likelihood Ratio ABPI: 6.17 (95% CI: 1.94-19.62) Continuous Wave Doppler: 10.39 (95% CI:3.42-31.52) TBI: 3.55 (95% CI: 1.73-7.28) • Negative Likelihood Ratio ABPI:0.59 (95% CI:0.43-0.82) Continuous Wave Doppler: 0.28 (95% CI: 0.15-0.51) TBI: 0.44 (95% CI: 0.28-0.71) • AUC ≥ 50% Stenosis TBI: 0.75 (95% CI not reported) ABPI: 0.58 (95% CI not reported)
Quality Assessment (QUADA2)	**Patient selection:** Low risk of bias **Index test:** Low risk of bias

Tehan P E, Bray A, and Chuter V H (2016) Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. Journal of Diabetes & its Complications 30(1), 155-60	
	Reference standard: Low risk of bias **Flow and timing:** Low risk of bias **Overall risk of bias:** Low **Directness:** Directly applicable

E.7 Williams (2005)

Williams D T, Harding K G, and Price P (2005) An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care 28(9), 2206-2210	
Study type	Cross-sectional study, Case-control study
Aim	Evaluate the efficacy of foot pulses, the ABPI, the TBI and Doppler Waveform analysis in screening for lower-limb arterial disease in diabetes, by comparison with the gold standard non-invasive assessment, colour duplex imaging.
Patient Characteristics	Inclusion criteria • None reported Exclusion criteria • Smoking and other causes of peripheral arterial disease • History of reconstructive vascular surgery • other causes of peripheral vascular disease • skin changes associated with venous disease • Pyrexia • Significant cardiorespiratory and/ or renal disease **Study Characteristics** Female (%): 25 Age: 63-69 Mean Diabetes Duration: 11-24 years
Sample Size	130 limbs from 68 individuals

Williams D T, Harding K G, and Price P (2005) An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care 28(9), 2206-2210	
Index test(s)	ABPI Brachial pressures were measured using index finger PPG and a hand held Doppler unit. The higher value was used in calculating the ABPI. ABPI value <0.9 was used as indicator of significant PAD. TBI Toe pressures were measured by photoplethysmography (PPG) method. Toe pressures were taken at 3- and 5- min intervals, and a mean was calculated. The higher value was used in calculating the TBI. TBI value <0.75 was used as a indicator of significant POAD. Doppler Waveform analysis Both qualitative and quantitative Doppler waveform analysis was performed on the dorsalis pedis and posterior tibial arteries. Qualitative waveform analysis was performed by visual interpretations of continuously displayed waveforms. The one screen loss of reverse flow (loss of triphasic signal) was used as an indicator of significant arterial disease. Quantitative waveform analysis analyses were performed and pulsatility index, resistance index and spectral broadening index were recorded for each artery.
Reference standard(s)	DUS CDI performed at the end of each visit. All individuals were scanned from the common femoral artery to the distal third of the tibial and peroneal arteries. Arterial disease on CDI was deemed significant when occlusions, single or multiple stenoses, or diffuse stenotic disease in the femoropopliteal segments, individually or collectively caused significant velocity change and flow disturbance locally and resulted in loss of reverse flow distally.
Study Details	• Study location: Wales, UK • Study setting: Diabetic foot clinics • Study dates: Study performed over 8 months (dates not specified) • Loss to follow-up: Not specified • Time between testing & Treatment: All tests performed at one visit. • Sources of funding: Financial aid provided by departmental funds (Wound Healing Research Unit, Department of Surgery, University of Wales College of Medicine
Results	• Calculated Sensitivity Diabetes without Neuropathy ABPI: 93.8 % (95% CI: 46.1-99.6) TBI: 85.7 % (95% CI: 41.9-98.0) WFA: 93.8% (95% CI: 46.1-99.6) Diabetes with Neuropathy

Williams D T, Harding K G, and Price P (2005) An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care 28(9), 2206-2210	
	ABPI: 53.3% (95% CI: 29.3-75.9) TBI: 96.9 % (95% CI: 65.0-99.8) WFA: 93.8% (95% CI: 66.5-99.1) • Calculated Specificity Diabetes without Neuropathy ABPI: 86.5 % (95% CI: 67.6-95.2) TBI: 64% (95% CI: 44.0-80.1) WFA: 90.4% (95% CI: 71.8-97.2) Diabetes with Neuropathy ABPI: 95.1% (95% CI: 82.5-98.8) TBI: 60.7% (95% CI: 45.4-74.2) WFA: 65.9% (95% CI: 50.3-78.6) • Calculated Positive Likelihood Ratio Diabetes without Neuropathy ABPI: 6.964 (95% CI: 2.586-18.759) TBI: 2.381 (95% CI: 1.302-4.355) WFA: 9.750 (95% CI: 2.960-32.113) Diabetes with Neuropathy ABPI: 10.933 (95% CI: 2.611-45.787) TBI: 2.466 (95% CI: 1.676-3.628) WFA: 2.746 (95% CI: 1.762-4.278) • Calculated Negative Likelihood Ratio Diabetes without Neuropathy ABPI: 0.072 (95% CI: 0.005-1.062) TBI: 0.223 (95% CI: 0.036-1.403)

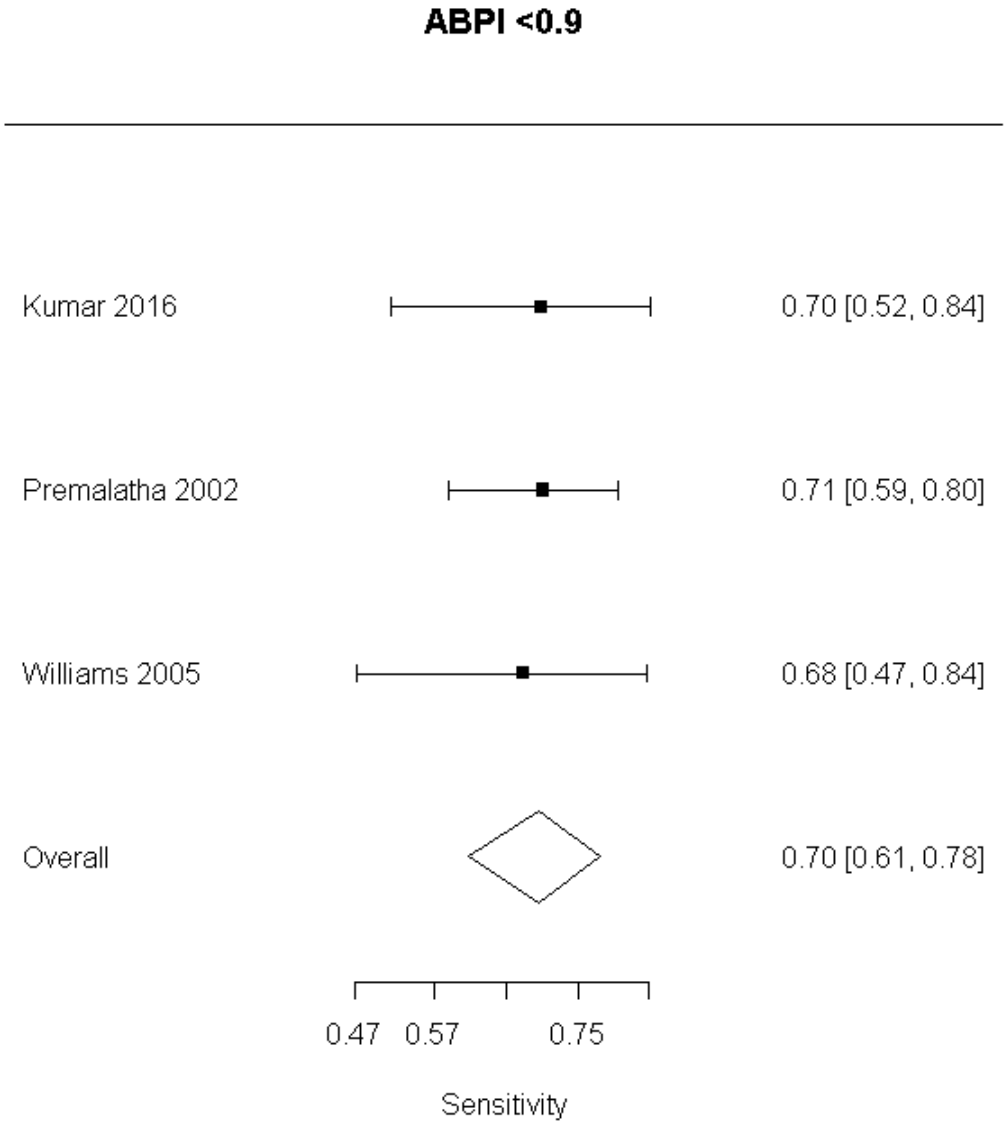
Williams D T, Harding K G, and Price P (2005) An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care 28(9), 2206-2210	
	WFA: 0.069 (95% CI:0. 005-1.015) Diabetes with Neuropathy ABPI: 0. 491 (95% CI:0. 284-0.846) TBI: 0. 051 (95% CI:0. 003-0.796) WFA: 0.095 (95% CI:0. 014-0.641)
Quality Assessment (QUADA2)	**Patient selection:** Unclear risk of bias. Inclusion criteria not described. **Index test:** Low risk of bias **Reference standard:** High risk of bias. Unclear blinding between reference standard and index test **Flow and timing:** Unclear risk of bias. Unclear if all patients received index tests and reference standard. **Overall risk of bias:** Moderate **Directness:** Indirectly applicable. Patients did not present characteristics outlined in study protocol (Appendix A). While DUS was used as reference standard was only considered to be present if detected from the common femoral artery to the popliteal artery. Patients with diabetes experience PAD below the knee.

1

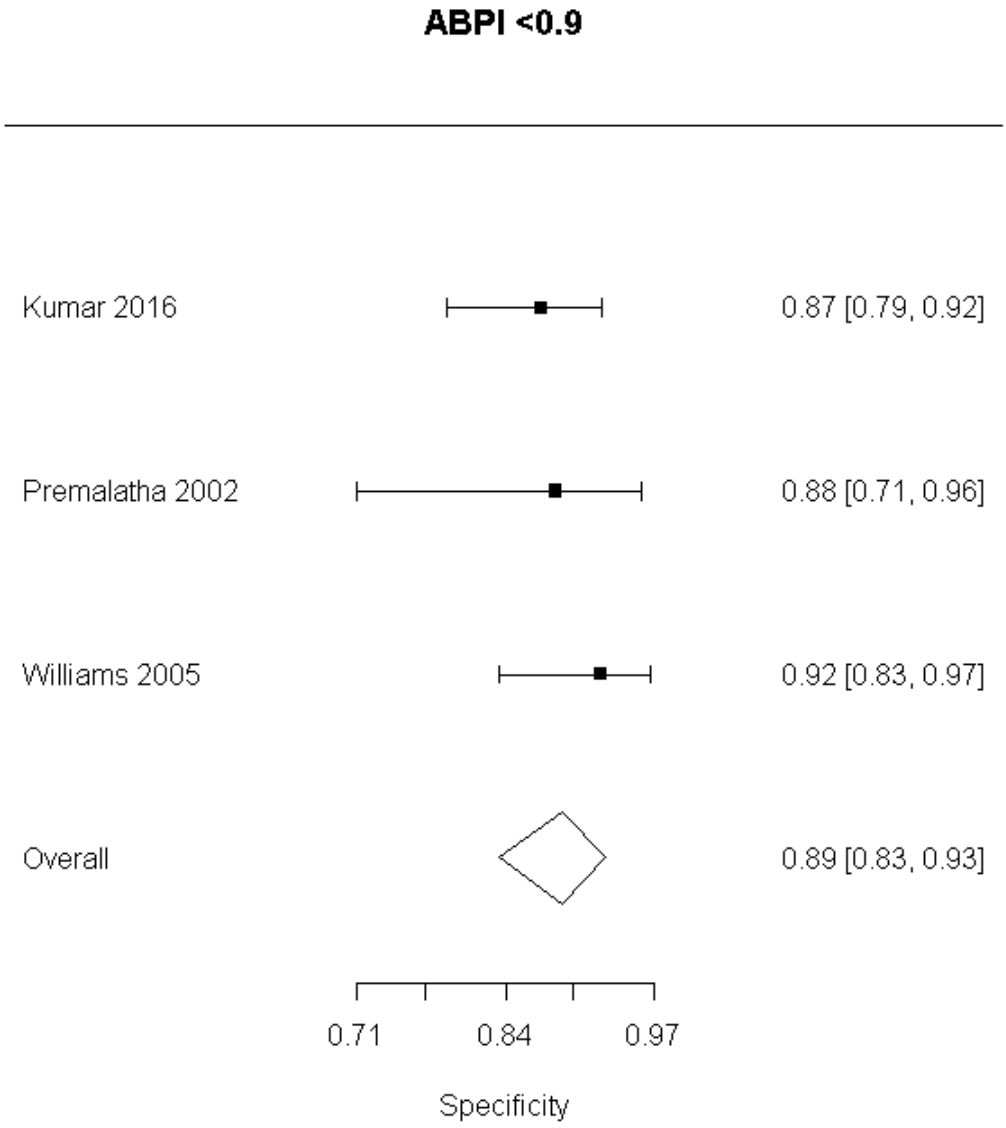
Appendix F – Forest plots

Ankle Brachial Pressure Index using Doppler compared to imaging

Sensitivity

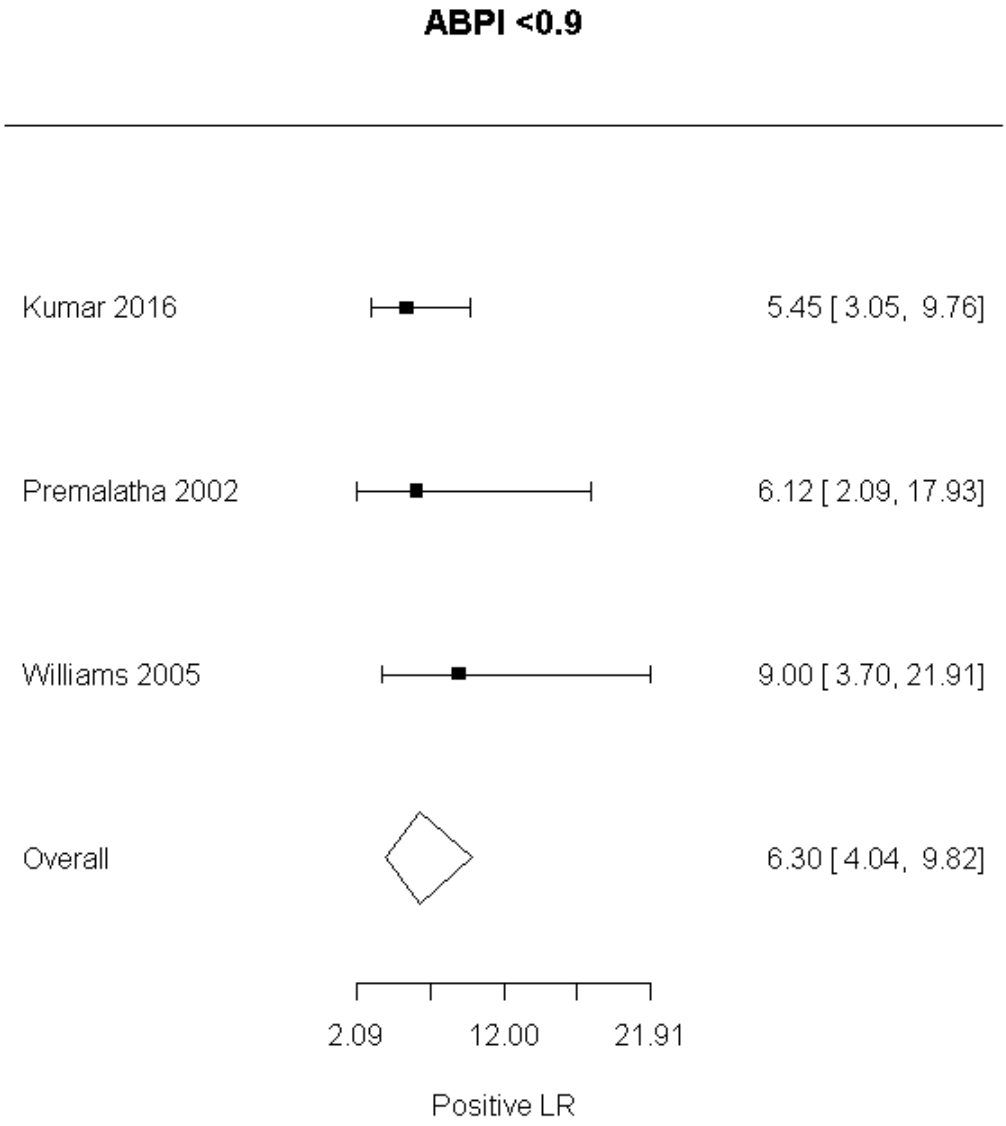


1 **Specificity**

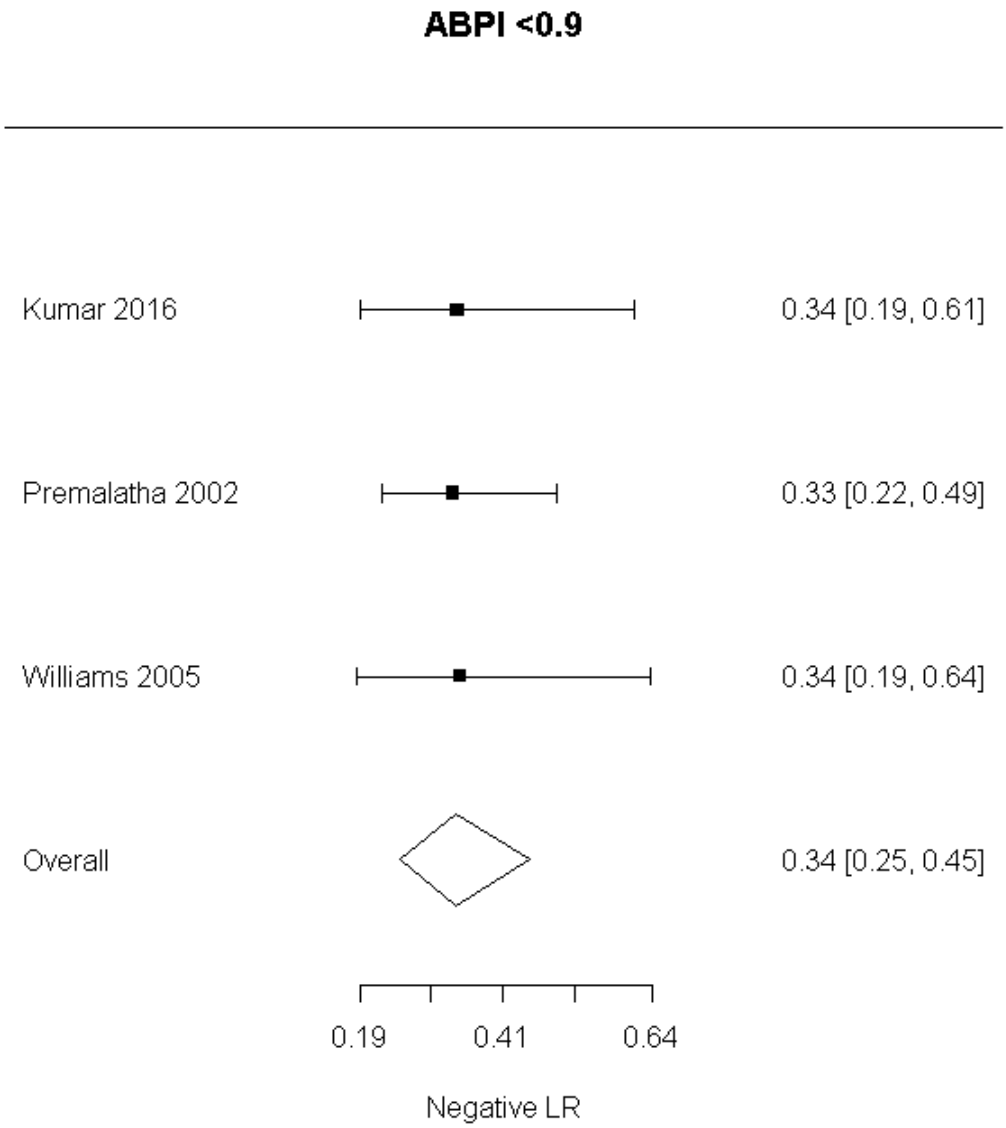


2
3

Positive likelihood ratios



Negative likelihood ratios



1 Appendix G – GRADE tables

2 Diagnostic Test Accuracy

3 Ankle Brachial Pressure Index using Doppler compared to imaging

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
Reference Standard- DUS; ABPI cut-off <0.90											
3 Premalatha (2002), Williams (2005), Kumar (2016)	Prospective Cross sectional	302 measurements (Combination of patients and limbs)	70.1% (61.2%, 77.7%)	88.9% (83.4%, 92.7%)	LR+	6.299 (4.042, 9.817)	Serious[1]	Not serious	Very Serious[2]	Not serious	Very low
					LR-	0.337 (0.252, 0.450)	Serious[1]	Not serious	Very Serious[2]	Not serious	Very low
Reference Standard- DUS; ABPI cut- off ≤ 0.90 or greater than 1.4											
1 Tehan (2016)	Prospective Cross sectional	72 patients	45.16% (27.33%, 63.96%)	92.68% (80.05%, 98.38%)	LR+	6.17 (1.94, 19.62)	No serious	N/A[3]	Not serious	Serious[4]	Moderate
					LR-	0.59 (0.43, 0.82)	Not serious	N/A[3]	Not serious	Serious[4]	Moderate
Reference Standard- DUS; ABPI cut- off <0.90, in patients without neuropathy											
1 Williams (2005)	Prospective Cross sectional	32 limbs	93.8% (46.1%, 99.6%)	86.5% (67.6%, 95.2%)	LR+	6.964 (2.586, 18.759)	Serious[5]	N/A[3]	Very serious[6]	Not serious	Very low
					LR-	0.072 (0.005, 1.062)	Serious[5]	N/A[3]	Very serious[6]	Serious[4]	Very Low
Reference Standard- DUS; ABPI cut- off <0.90, in patients with neuropathy											
1		56 limbs			LR+	10.933	Serious[5]	N/A[3]	Very serious[6]	Not serious	Very Low

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
Williams (2005)	Prospective Cross sectional		53.3% (29.3%, 75.9%)	95.1% (82.5%, 98.8%)		(2.611, 45.787)					
					LR-	0.491 (0.284, 0.846)	Serious[5]	N/A[3]	Very serious[6]	Serious[4]	Very low

1. Downgrade 1 level for serious risk of bias due to unclear blinding between reference test and index test and removal of patients with calcification from analysis.
2. Downgrade 2 levels for very serious indirectness. Inadequate assessment of PAD using reference standard and inappropriate threshold used for reference test.
3. Inconsistency not applicable as evidence from a single study.
4. Downgrade 1 level as 95% confidence interval of likelihood ratio crosses one end of a defined MID interval (0.5, 2)
5. Downgrade 1 level for serious risk of bias unclear blinding between index test and reference test
6. Downgrade 2 levels for very serious indirectness. Inadequate assessment of PAD using reference standard and patients did not present with active foot disease, rest pain or signs suggestive of lower-limb critical ischemia.

1 **Toe Brachial Index compared to imaging**

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
Reference Standard- DUS; TBI cut-off <0.70											
1 Tehan (2016)	Prospective Cross sectional	72 patients	63.64% (45.13%, 79.58%)	82.05% (66.46%, 92.43%)	LR+	3.55 (1.73, 7.28)	Not serious	N/A[1]	Not serious	Serious[2]	Moderate
					LR-	0.44 (0.28, 0.71)	Not serious	N/A[1]	Not serious	Serious[2]	Moderate
Reference Standard- DUS; TBI cut-off <0.75, in patients without neuropathy											
1 Williams (2005)	Prospective Cross sectional	32 limbs	85.7% (41.9%, 98.0%)	64% (44.0 %, 80.1%)	LR+	2.381 (1.302, 4.355)	Serious [3]	N/A[1]	Very Serious[4]	Serious[2]	Very low

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
					LR-	0.223 (0.036, 1.403)	Serious [3]	N/A[1]	Very Serious[4]	Serious[2]	Very low
Reference Standard- DUS; TBI cut-off <0.75, in patients with neuropathy											
1 Williams (2005)	Prospective Cross sectional	56 limbs	96.9% (65.0%, 99.8%)	60.7% (45.4, 74.2%)	LR+	2.466 (1.676, 3.628)	Serious [3]	N/A[1]	Very Serious[4]	Serious[2]	Very low
					LR-	0.051 (0.003, 0.796)	Serious [3]	N/A[1]	Very Serious[4]	Serious[2]	Very low

1. Inconsistency not applicable as evidence from a single study
2. Downgrade 1 level as 95% confidence interval of likelihood ratio crosses one end of a defined MID interval (0.5, 2)
3. Downgrade 1 level for serious risk of bias unclear blinding between index test and reference test
4. Downgrade 2 levels for very serious indirectness. Inadequate assessment of PAD using reference standard and patients did not present with active foot disease, rest pain or signs suggestive of lower-limb critical ischemia.

1 **Doppler Waveform Analysis compared to imaging**

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
Reference Standard- DUS, Waveform Analysis cut- off: loss of multiphasic waveform											
1 Tehan (2016)	Prospective Cross sectional	72 patients	74.19 (55.38, 88.11%)	92.86% (80.49, 98.42)	LR+	10.39 (3.42, 31.52)	Not serious	N/A[1]	Not serious	Not serious	High
					LR-	0.28 (0.15, 0.51)	Not serious	N/A[1]	Not serious	Serious[2]	Moderate
Reference Standard- DUS, Waveform Analysis cut- off: loss of triphasic waveforms, in patients without neuropathy											
1 Williams (2005)	Prospective Cross sectional	32 limbs	93.8% (46.1, 99.6%)	90.4% (71.8, 97.2)	LR+	9.750 (2.960, 32.113)	Serious[3]	N/A[1]	Very Serious[4]	Not serious	Very Low

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
					LR-	0.069 (0.005, 1.015)	Serious[3]	N/A[1]	Very Serious[4]	Serious[2]	Very low
Reference Standard- DUS, Waveform Analysis cut- off: loss of triphasic waveforms, in patients with neuropathy											
1 Williams (2005)	Prospective Cross sectional	57 limbs	93.8% (66.5, 99.1%)	65.9% (50.3, 78.6%)	LR+	2.746 (1.762, 4.278)	Serious[3]	N/A[1]	Very Serious[4]	Serious[2]	Very low
					LR-	0.095 (0.014, 0.641)	Serious[3]	N/A[1]	Very Serious[4]	Serious[2]	Very low

1. Inconsistency not applicable as evidence from a single study
2. Downgrade 1 level as 95% confidence interval of likelihood ratio crosses one end of a defined MID interval (0.5, 2)
3. Downgrade 1 level for serious risk of bias unclear blinding between index test and reference test
4. Downgrade 2 levels for very serious indirectness. Inadequate assessment of PAD using reference standard and patients did not present with active foot disease, rest pain or signs suggestive of lower-limb critical ischemia.

1 Pulse Oximetry compared to imaging

No. of Studies	Study Design	Sample Size	Sensitivity (95% CI)	Specificity (95% CI)	LRs	Effect Size (95% CI)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Quality
Reference Standard- DUS, Pulse Oximetry cut-off: Toe saturation less than finger saturation >2% or if foot saturation decreased by >2% in elevated position											
1 Kumar (2016)	Prospective Cross sectional	120 patients	74.1% (54.7, 87.1%)	95.7% (89.1, 98.4%)	LR+	17.222 (6.436, 46.086)	Serious[1]	N/A[2]	Very serious[3]	Not serious	Very low
					LR-	0.271 (0.143, 0.513)	Serious[1]	N/A[2]	Very serious[3]	Serious[4]	Very low

1. Downgrade 1 level for serious risk of bias due to time interval between index test and reference standard. Reference test conducted within a week of initial assessment.
2. Inconsistency not applicable as evidence from a single study
3. Downgrade 2 levels for serious indirectness. Inappropriate threshold used for index test and reference test
4. Downgrade 1 level as 95% confidence interval of likelihood ratio crosses one end of a defined MID interval (0.5, 2)

1 Severity of PAD

2 Reference Standard: DUS- ≥ 50% stenosis

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	AUC	Quality
Doppler ABPI, cut- off <0.90								
1 Tehan (2016)	Prospective Cross sectional	72 patients	Not serious	Not serious	N/A[1]	Very serious[2]	0.58 (95% CI not reported)	Low
TBI, cut- off <0.90								
1 Tehan (2016)	Prospective Cross sectional	72 patients	Not serious	Not serious	N/A[1]	Very serious[2]	0.75 (95% CI not reported)	Low

1. Inconsistency not applicable as evidence from a single study
2. 95% CI not reported, downgrade 2 levels

3 Reference Standard: CTA- ≥75% stenosis

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	AUC	Quality
Oscillometric ABPI, cut-off value:0.86								
Ichihashi (2014)	Retrospective Cross sectional	58 patients	Serious[1]	Serious[2]	N/A[3]	Not serious	0.888 (0.825, 0.952)	Very Low

1. Downgrade 1 level for serious risk of bias due to time interval between index test and reference standard. Reference standard carried out one month before or after ABPI measurement.
2. Downgrade 1 level for serious indirectness. Study conducted sub-group analysis on patients with diabetes
3. Inconsistency not applicable as evidence from a single study

4 Reference Standard: DSA- ≥ 50% stenosis

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	AUC	Quality
Low Ankle Brachial Index Method using Doppler ABPI, cut-off value: <0.9								

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	AUC	Quality
Jeevanantham (2014)	Retrospective Cross sectional	67 limbs	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	0.675 (95% CI not reported)	Very Low
High Ankle Brachia Index Method using Doppler ABPI, cut-off value: <0.9								
Jeevanantham (2014)	Retrospective Cross sectional	61 limbs	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	0.609 (95% CI not reported)	Very Low

1. Downgrade 1 level for serious risk of bias due to interval between index and reference test. Arteriographies were performed within 6 month period from the ABPI measurement.
2. Downgrade 1 level for serious indirectness. Study conducted sub-group analysis on patients with diabetes.
3. Inconsistency not applicable as evidence from a single study.
4. 95% CI not reported, downgrade 2 levels.

1 **Reference Standard: DSA- ≥75%stenosis**

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	AUC	Quality
Low Ankle Brachial Index Method using Doppler ABPI, cut-off value: <0.9								
Jeevanantham (2014)	Retrospective Cross sectional	67 limbs	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	0.784 (95% CI not reported)	Very Low
High Ankle Brachia Index Method using Doppler ABPI, cut-off value: <0.9								
Jeevanantham (2014)	Retrospective Cross sectional	61 limbs	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	0.668 (95% CI not reported)	Very Low

1. Downgrade 1 level for serious risk of bias due to interval between index and reference test. Arteriographies were performed within 6 month period from the ABPI measurement, which can lead to misclassification.
2. Downgrade 1 level for serious indirectness. Study conducted sub-group analysis on patients with diabetes.
3. Inconsistency not applicable as evidence from a single study.
4. 95% CI not reported, downgrade 2 levels.

1 Inter- and intra-operator reliability

2 Inter-rater agreement for TBI

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	Inter-rater Reliability (ICC) (95% CI)	Quality
Inter-rater agreement between 3 raters during 2 sessions								
Romanos (2010)	Prospective	30	Not Serious	Very Serious[1]	N/A[2]	Not serious	Session 1: 0.77 (0.62, 0.87) Session 2:0.81 (0.68, 0.90)	Low

1. Downgrade 2 levels for very serious indirectness. Patients were not accurately measured for the presence of PAD
2. Inconsistency not applicable as evidence from a single study

3 Intra-rater agreement for TBI

No. Of Studies	Study Design	Sample Size	Risk of Bias	Indirectness	Inconsistency	Imprecision	Mean Intra-rater Reliability (ICC) (95% CI)	Quality
Mean Intra-reliability among 3 raters								
Romanos (2010)	Prospective	30	Serious[1]	Very Serious[2]	N/A[3]	Not serious	0.75 (0.55, 0.87)	Very Low

1. Downgrade 1 level for serious risk of bias. Raters were not blinded to their own result.
2. Downgrade 2 levels for very serious indirectness. Patients were not accurately measured for the presence of PAD
3. Inconsistency not applicable as evidence from a single study

4

1 Appendix H – Excluded studies

2 Clinical studies

Author	Reason for Exclusion
Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, And Criqui MH (2008) The Association Between Elevated Ankle Systolic Pressures And Peripheral Occlusive Arterial Disease In Diabetic And Nondiabetic Subjects. Journal Of Vascular Surgery 48(5), 1197-203	Not possible to calculate a 2x2 table from data presented in the study
Alnaeb M E, Crabtree V P, Boutin A, Mikhailidis D P, Seifalian A M, And Hamilton G (2007) Prospective Assessment Of Lower-Extremity Peripheral Arterial Disease In Diabetic Patients Using A Novel Automated Optical Device. Angiology 58(5), 579-85	Not possible to calculate a 2x2 table from data presented in the study
An W, Xian L, Zhao L, Detrano R, Criqui M, And Wu Y (2010) Distribution Of The Ankle-Brachial Index And Peripheral Arterial Disease In Middle-Aged And Elderly Chinese: A Population-Based Study Of 18,000 Men And Women. Circulation 122 (2), E43	Conference abstract
Aubert C E, Cluzel P, Kemel S, Michel P L, Lajat-Kiss F, Dadon M, Hartemann A, And Bourron O (2014) Influence Of Peripheral Vascular Calcification On Efficiency Of Screening Tests For Peripheral Arterial Occlusive Disease In Diabetes--A Cross-Sectional Study. Diabetic Medicine 31(2), 192-9	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD
Barshes N R, Flores E, Belkin M, Kougias P, Armstrong D G, Mills J L, And Sr (2016) The Accuracy And Cost-Effectiveness Of Strategies Used To Identify Peripheral Artery Disease Among Patients With Diabetic Foot Ulcers. Journal Of Vascular Surgery 64(6), 1682-1690.E3	Review article but not a systematic review. Cost effective analysis.
Bell A D, Roussin A, Popovici-Toma D, Girard M, Chiu J F, And Huckell V (2013) The Value Of Routine Screening For Peripheral Arterial Disease In Stable Outpatients With A History Of Coronary Artery Or Cerebrovascular Disease. International Journal Of Clinical Practice 67(10), 996-1004	Reference standard in study does not match to that specified in protocol The sensitivity and specificity of the Edinburgh Claudication Questionnaire were assessed against the ABPI measurements.
Bell A, Chiu J F, Girard M, And Buithieu J (2011) The Value Of Routine Screening For Diffuse Vascular Disease In The Canadian Post-ACS/Ischemic Stroke/TIA General Practice Population With No Previously Documented Peripheral Arterial Disease. European Heart Journal 32, 88	Conference abstract
Bendermacher B L. W, Teijink J A. W, Willigendael E M, Bartelink M L, Buller H R, Peters R J. G, Boiten J, Langenberg M, And Prins M H (2006) Symptomatic Peripheral Arterial Disease: The Value Of A Validated Questionnaire And A Clinical Decision Rule. British Journal Of General Practice 56(533), 932-944	Study does not contain any relevant index tests Study only focused on Edinburgh Claudication questionnaire.
Bhise S R, Darshan A, And Kothiwale V A (2014) Correlation Of Inter Arm Systolic Blood Pressure Difference (IASBPD) To Ankle Brachial Index (ABI) In Detecting Peripheral Vascular Disease In Type Two Diabetes Mellitus Patients. Diabetes Research And Clinical Practice 106, S49-S50	Conference abstract
Bonham P A (2006) Get The LEAD Out: Noninvasive Assessment For Lower Extremity Arterial Disease Using Ankle Brachial Index And Toe Brachial Index Measurements. Journal Of Wound, And Ostomy And Continence Nursing 33(1), 30-41	Review article but not a systematic review
Boyko E J, Ahroni J H, Davignon D, Stensel V, Prigeon R L, And Smith D G (1997) Diagnostic Utility Of The History And Physical Examination	Does not contain a population of adults (≥ 18 years old) with

Author	Reason for Exclusion
For Peripheral Vascular Disease Among Patients With Diabetes Mellitus. Journal Of Clinical Epidemiology 50(6), 659-68	diabetes with suspected PAD Population contained individuals presenting with PAD
Brown J, Rosati S, Newton D, Peysha J, Amendola M, Wolfe L, And Levy M (2015) (RF). Peak Ankle Velocities And Average Ankle Velocities Utilized For Identifying Critical Limb Ischemia. Annals Of Vascular Surgery 29 (4), 636	Conference abstract
Brownrigg J R, Hinchliffe R J, Apelqvist J, Boyko E J, Fitridge R, Mills J L, Reekers J, Shearman C P, Zierler R E, Schaper N C, International Working Group On The Diabetic, And Foot (2016) Effectiveness Of Bedside Investigations To Diagnose Peripheral Artery Disease Among People With Diabetes Mellitus: A Systematic Review. Diabetes/Metabolism Research Reviews 32 Suppl 1, 119-27	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed.
Bundo M, Urrea M, Munoz-Ortiz L, Perez C, Llussa J, Fores R, Alzamora M T, And Toran P (2013) Measurement Of The Ankle Brachial Index With A Non-Mercury Sphygmomanometer In Diabetic Patients: A Concordance Study. BMC Cardiovascular Disorders 13, 15	Reference standard in study does not match to that specified in protocol Mercury sphygmomanometer was considered gold standard
Castronuovo J J, Jr , Adera H M, Smiell J M, And Price R M (1997) Skin Perfusion Pressure Measurement Is Valuable In The Diagnosis Of Critical Limb Ischemia. Journal Of Vascular Surgery 26(4), 629-37	Study does not contain any relevant index tests Study examined the accuracy of skin perfusion pressure in predicting critical limb ischemia
Chang L H, Chu C H, Lin H D, Kwok C F, Won J G, Chen H S, And Lin L Y (2015) The Ankle Brachial Index Is Associated With Prognosis In Patients With Diabetic Kidney Disease. Diabetes Research & Clinical Practice 108(2), 316-22	Study does not match objectives of review. Study evaluated the influence of PAD on patients with diabetic kidney disease
Chevtchouk L, Da Silva , M H S, Do Nascimento, And O J M (2017) Ankle-Brachial Index And Diabetic Neuropathy: Study Of 225 Patients. Arquivos De Neuro-Psiquiatria 75(8), 533-538	Outcomes of interest were not reported Study evaluated neuropathic pain and peripheral vascular disease in diabetics
Chin J A, Wang E C, And Kibbe M R (2011) Evaluation Of Hyperspectral Technology For Assessing The Presence And Severity Of Peripheral Artery Disease. Journal Of Vascular Surgery 54(6), 1679-88	Study does not contain any relevant index tests Study examined hyperspectral imaging
Clairotte C, Retout S, Potier L, Roussel R, And Escoubet B (2009) Automated Ankle-Brachial Pressure Index Measurement By Clinical Staff For Peripheral Arterial Disease Diagnosis In Nondiabetic And Diabetic Patients. Diabetes Care 32(7), 1231-6	Reference standard in study does not match to that specified in protocol Study compared Osc-ABPI with Doppler- ABPI
Cloete N, Kiely C, Colgan P, Haider N, O'Neill S, Madhavan P, And Moore D (2009) Reproducibility Of Toe Pressure Measurements. Journal For Vascular Ultrasound 33(3), 129-132	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Study included patients with symptomatic peripheral vascular disease
Crawford F, Welch K, Andras A, And Chappell F M (2016) Ankle Brachial Index For The Diagnosis Of Lower Limb Peripheral Arterial Disease. Cochrane Database Of Systematic Reviews 2016 (9) (No Pagination)(CD010680),	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed. Systematic review did not focus on patients with diabetes with suspected PAD

Author	Reason for Exclusion
Dachun Xu, Jue Li, Liling Zou, Yawei Xu, Dayi Hu, Pagoto S L, And Yunsheng Ma (2010) Sensitivity And Specificity Of The Ankle--Brachial Index To Diagnose Peripheral Artery Disease: A Structured Review. Vascular Medicine 15(5), 361-9	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed. Systematic review did not focus on patients with diabetes with suspected PAD
Desai M Y, Crabtree V, Davis M, Tsui J, Myint F, Baker D, Seifalian A M, And Hamilton G (2010) Efficacy Of Ankle-Brachial Pressure Index In Patients With Diabetes Mellitus: Can It Be Adopted As A Screening Tool?. Interactive Cardiovascular And Thoracic Surgery 10, S92	Conference abstract
Diehm C, Schuster A, Allenberg J R, Darius H, Haberl R, Lange S, Pittrow D, Von Stritzky , B , Tepohl G, And Trampisch H J (2004) High Prevalence Of Peripheral Arterial Disease And Co-Morbidity In 6880 Primary Care Patients: Cross-Sectional Study. Atherosclerosis 172(1), 95-105	Reference standard in study does not match to that specified in protocol Doppler ABPI used as reference standard
El-Menyar A, Amin H, Rashdan I, Souliman K, Deleu D, Saadat K, Al Mahmeed, W , Bakir S, Wasif A, Ben Brek, A , Bazargani N, Ahmed Abdel, Aziz , Singh R, Hatou I, Mahmoud H, Al Suwaidi, And J (2009) Ankle-Brachial Index And Extent Of Atherosclerosis In Patients From The Middle East (The AGATHA-ME Study): A Cross-Sectional Multicenter Study. Angiology 60(3), 329-34	Study does not match objectives of review. Study assessed the extent of atherothrombosis and the use of ABPI
Espeland M A, Regensteiner J G, Jaramillo S A, Gregg E, Knowler W C, Wagenknecht L E, Bahnson J, Haffner S, Hill J, Hiatt W R, And Look Ahead Study Group (2008) Measurement Characteristics Of The Ankle-Brachial Index: Results From The Action For Health In Diabetes Study. Vascular Medicine 13(3), 225-33	Study does not match objectives of review Study compared different systolic blood pressure protocols for measuring ABPI.
Faglia E, Clerici G, Caminiti M, Quarantiello A, Curci V, And Somalvico F (2010) Evaluation Of Feasibility Of Ankle Pressure And Foot Oximetry Values For The Detection Of Critical Limb Ischemia In Diabetic Patients.. Vascular And Endovascular Surgery 44(3), 184-9	Study does not contain any relevant index tests Study examined ankle pressure and transcutaneous oxygen tension (TCPO2)
Formosa C, Gatt A, Mizzi A, Mizzi S, Cassar K, Camilleri K P, Azzopardi C, Deraffaele C, Falzon O, Cristina S, And Chockalingam N (2014) Hidden Dangers Revealed By Misdiagnosed Peripheral Arterial Disease Using ABPI Measurement. Diabetic Medicine 31, 44	Conference abstract
Formosa Cynthia, Gatt Alfred, And Chockalingam Nachiappan (2012) Screening For Peripheral Vascular Disease In Patients With Type 2 Diabetes In Malta In A Primary Care Setting. Quality In Primary Care 20(6), 409-414	Study does not match objectives of review Study examined the occurrence of PVD in a primary care setting using ABPI
Forsythe R O, And Hinchliffe R J (2016) Assessment Of Foot Perfusion In Patients With A Diabetic Foot Ulcer. Diabetes/Metabolism Research Reviews 32 Suppl 1, 232-8	Review article but not a systematic review
Goyal P, Joshi S, Salazar J, Pachinathan X, And Gold R (2013) Role Of Pulse Volume Recording Waveforms In Detection Of Infracenicular Arterial Disease In Symptomatic Diabetic Patients. Journal Of Vascular And Interventional Radiology 24 (1), 145.E28	Conference abstract
Hartemann A, Aubert C E, Cluzel P, Kemel S, Michel P L, Lajat-Kiss F, Dadon M, And Bourron O (2013) Relationship Between Peripheral Vascular Calcification And Accuracy Of Ankle Brachial Index And Pulse Palpation To Screen Peripheral Arterial Occlusive Disease. Diabetologia 56, S530-S531	Conference abstract
Hembling B P, Hubler K C, Richard P M, O'Keefe W A, Husfloen C, Wicks R, And Dressor H (2007) The Limitations Of Ankle Brachial Index	Reference standard in study does not match to that specified

Author	Reason for Exclusion
When Used Alone For The Detection/Screening Of Peripheral Arterial Disease In A Population With An Increased Prevalence Of Diabetes. Journal For Vascular Ultrasound 31(3), 149-151	in protocol Wave form analysis used as reference standard
Hiremath R, Gowda G, Ibrahim J, Reddy H T, Chodiboina H, And Shah R (2017) Comparison Of The Severity Of Lower Extremity Arterial Disease In Smokers And Patients With Diabetes Using A Novel Duplex Doppler Scoring System. Ultrasonography 36(3), 270-277	Study does not contain any relevant index tests Study examined the diagnostic feasibility of a novel screening system of PAD.
Hoyer C, Paludan J P, Pavar S, Biurrun Manresa, J A, And Petersen L J (2014) Reliability Of Laser Doppler Flowmetry Curve Reading For Measurement Of Toe And Ankle Pressures: Intra- And Inter-Observer Variation. European Journal Of Vascular & Endovascular Surgery 47(3), 311-8	Study does not contain any relevant index tests Study examined laser Doppler flowmetry
Hoyer C, Sandermann J, And Petersen L J (2013) The Toe-Brachial Index In The Diagnosis Of Peripheral Arterial Disease. Journal Of Vascular Surgery 58(1), 231-8	Review article but not a systematic review
Ikem R, Ikem I, Adebayo O, And Soyoye D (2010) An Assessment Of Peripheral Vascular Disease In Patients With Diabetic Foot Ulcer. Foot 20(4), 114-7	Outcomes of interest were not reported Study evaluated the occurrence of peripheral vascular disease using ABPI
Ix J H, Miller R G, Criqui M H, And Orchard T J (2012) Test Characteristics Of The Ankle-Brachial Index And Ankle-Brachial Difference For Medial Arterial Calcification On X-Ray In Type 1 Diabetes. Journal Of Vascular Surgery 56(3), 721-7	Outcomes of interest were not reported Study examined the test characteristics of ABPI and ankle brachial difference (ABD) measurements for medial arterial calcification.
Jaffer U, Aslam M, And Standfield N (2009) Comparison Of Doppler Ultrasound, Photoplethysmographic, And Pulse-Oximetric Calculated Pressure Indices To Detect Peripheral Arterial Occlusive Disease. Vascular Disease Management 6(4), 100-105	Reference standard in study does not match to that specified in protocol Doppler ABPI used as reference standard
Janssen A (2005) Pulsatility Index Is Better Than Ankle-Brachial Doppler Index For Non-Invasive Detection Of Critical Limb Ischaemia In Diabetes. VASA. Zeitschrift Fur Gefasskrankheiten 34(4), 235-241	Full text paper not available
Jayaraj Arjun, And Blomberg Jane (2013) Comparison Of Automated Oscillometric Measurement Of Ankle Brachial Index With Standard Doppler Measurement As A Screening Tool For Peripheral Artery Disease. Journal For Vascular Ultrasound 37(2), 71-75	Outcomes of interest were not reported Study examined the correlation between oscillometric measurement of ABI with Doppler ultrasound measurement of ABI
Jirkovska A, Boucek P, Woskova V, Bartos V, And Skibova J (2001) Identification Of Patients At Risk For Diabetic Foot: A Comparison Of Standardized Noninvasive Testing With Routine Practice At Community Diabetes Clinics. Journal Of Diabetes & Its Complications 15(2), 63-8	Outcomes of interest were not reported Study compared different non-invasive tests in predicting the development of diabetic foot.
Koelemay M J. W, Legemate D A, Van Gurp , J A, De Vos , H , Balm R, And Jacobs M J. H. M (2001) Interobserver Variation Of Colour Duplex Scanning Of The Popliteal Tibial And Pedal Arteries. European Journal Of Vascular And Endovascular Surgery 21(2), 160-164	Study does not contain any relevant index tests Study examined peak systolic velocity recording
Kollias A, Xilomenos A, Protogerou A, Dimakakos E, And Stergiou G S (2011) Automated Determination Of The Ankle-Brachial Index Using An Oscillometric Blood Pressure Monitor: Validation Vs. Doppler	Reference standard in study does not match to that specified in protocol

Author	Reason for Exclusion
Measurement And Cardiovascular Risk Factor Profile. Hypertension Research - Clinical & Experimental 34(7), 825-30	Study compared automated ABPI to Doppler ABPI
Laroche P, And Diegel U (2012) Automated Combination Of The Oscillometric Ankle-Brachial Index And Of The Edinburgh Questionnaire For The Screening And Follow-Up Of Peripheral Arterial Disease. Archives Of Cardiovascular Diseases Supplements 4 (1), 85	Conference abstract
Lewis JE, And Owens DR (2010) The Pulse Volume Recorder As A Measure Of Peripheral Vascular Status In People With Diabetes Mellitus.. Diabetes Technology & Therapeutics 12(1), 75-80	Reference standard in study does not match to that specified in protocol Colour wave form analysis listed as reference standard
Li Q, Zeng H, Liu F, Shen J, Li L, Zhao J, Zhao J, And Jia W (2015) High Ankle-Brachial Index Indicates Cardiovascular And Peripheral Arterial Disease In Patients With Type 2 Diabetes. Angiology 66(10), 918-24	Study does not match objectives of review Study examined ABPI and CVD risk.
Likaj E, Caco G, Seferi S, Rroji M, Barbullushi M, And Thereska N (2012) ABI To Evaluate Peripheral Arterial Damage In Hemodialysis Patients. Nephrology Dialysis Transplantation 27, Ii250	Conference abstract
Lindner J R, Womack L, Barrett E J, Weltman J, Price W, Harthun N L, Kaul S, And Patrie J T (2008) Limb Stress-Rest Perfusion Imaging With Contrast Ultrasound For The Assessment Of Peripheral Arterial Disease Severity. Jacc: Cardiovascular Imaging 1(3), 343-50	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Population contained individuals presenting with PAD
Liu F, Shen J, Zhao J, Zeng H, Li L, Zhao J, Lu F, Bao Y, And Jia W (2013) Cystatin C: A Strong Marker For Lower Limb Ischemia In Chinese Type 2 Diabetic Patients?. Plos One 8(7), E66907	Study does not contain any relevant index tests Study looked at Cystatin C levels
Mackaay A J. C, Beks P J, Dur A H. M, Bischoff M, Scholma J, Heine R J, And Rauwerda J A (1995) Is Toe Pressure A Better Parameter Of Peripheral Vascular Integrity Than Ankle Pressure? Comparison Of Diabetic With Nondiabetic Subjects In Dutch Epidemiological Study. Journal Of Vascular Technology 19(1), 5-9	Outcomes of interest were not reported Diagnostic test accuracy not measured
Mancera-Romero J, Rodriguez-Morata A, Sanchez-Chaparro M A, Sanchez-Perez M, Paniagua-Gomez F, Hidalgo-Conde A, And Valdivielso P (2013) Role Of An Intermittent Claudication Questionnaire For The Diagnosis Of PAD In Ambulatory Patients With Type 2 Diabetes. International Angiology 32(5), 512-517	Reference standard in study does not match to that specified in protocol ABPI used as reference standard
Mehlsen J, Wiinberg N, And Bruce C (2008) Oscillometric Blood Pressure Measurement: A Simple Method In Screening For Peripheral Arterial Disease. Clinical Physiology & Functional Imaging 28(6), 426-9	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD
Mourad J J, Cacoub P, Collet J P, Becker F, Pinel J F, Huet D, Sevestre-Pietri M A, Priollet P, Committee Ellipse Scientific, And Study Investigators (2009) Screening Of Unrecognized Peripheral Arterial Disease (PAD) Using Ankle-Brachial Index In High Cardiovascular Risk Patients Free From Symptomatic PAD. Journal Of Vascular Surgery 50(3), 572-80	Reference standard in study does not match to that specified in protocol Reference standard not stated.
Nam S C, Han S H, Lim S H, Hong Y S, Won J H, Bae J I, And Jo J (2010) Factors Affecting The Validity Of Ankle-Brachial Index In The Diagnosis Of Peripheral Arterial Obstructive Disease. Angiology 61(4), 392-6	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD
Narula A, Benenstein R J, Duan D, Zagha D, Li L, Choy-Shan A, Konigsberg M W, Lau G, Phillips L M, Saric M, Vreeland L, And Reynolds H R (2016) Ankle-Brachial Index Testing At The Time Of Stress Testing In Patients Without Known Atherosclerosis. Clinical Cardiology 39(1), 24-9	Outcomes of interest were not reported Diagnostic test accuracy not measured

Author	Reason for Exclusion
Ng S Y, Cheng S W, Chu W L, Lui S L, And Lo W K (2003) Screening By Trained Nurses For Peripheral Vascular Disease In Continuous Ambulatory Peritoneal Dialysis Patients With And Without Diabetes. Peritoneal Dialysis International 23 Suppl 2, S134-8	Outcomes of interest were not reported Logistic regression models not shown
Novak Z, Alcocer F, Ovalle F, Rooney D, Lowman B G, Combs B R, And Jordan W D (2013) Lower Extremity Peripheral Artery Disease Screening In Adults With Diabetes Mellitus. Journal Of Vascular Surgery 1), 70S-71S	Conference abstract
Ogata H, Kumata-Maeta C, Shishido K, Mizobuchi M, Yamamoto M, Koiwa F, Kinugasa E, And Akizawa T (2010) Detection Of Peripheral Artery Disease By Duplex Ultrasonography Among Hemodialysis Patients. Clinical Journal Of The American Society Of Nephrology: CJASN 5(12), 2199-206	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Study did not contain patients with diabetes, suspected of PAD.
Ozdemir B A, Brownrigg J R, Jones K G, Thompson M M, And Hinchliffe R J (2013) Systematic Review Of Screening Investigations For Peripheral Arterial Disease In Patients With Diabetes Mellitus. Surgical Technology International 23, 51-8	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed. Study design and reference standards included do not match review.
Pahlsson H I, Lund K, Jorneskog G, Gush R, And Wahlberg E (2008) The Validity And Reliability Of Automated And Manually Measured Toe Blood Pressure In Ischemic Legs Of Diabetic Patients. European Journal Of Vascular & Endovascular Surgery 36(5), 576-81	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Population contained individuals presenting with PAD
Papanas N, Kakagia D, Papatheodorou K, Papazoglou D, Alexandridou M, Pagkalos A, Karadimas Ej, And Maltezos E (2010) Lanarkshire Oximetry Index As A Diagnostic Tool For Peripheral Arterial Disease In Type 2 Diabetes: A Pilot Study. Angiology 61(4), 388-391	Reference standard in study does not match to that specified in protocol ABPI used as reference standard
Parameswaran G I, Brand K, And Dolan J (2005) Pulse Oximetry As A Potential Screening Tool For Lower Extremity Arterial Disease In Asymptomatic Patients With Diabetes Mellitus. Archives Of Internal Medicine 165(4), 442-6	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Exclusion criteria included known lower extremity arterial disease (LEAD) or symptoms of LEAD (e.g. intermittent claudication)
Park S C, Choi C Y, Ha Y I, And Yang H E (2012) Utility Of Toe-Brachial Index For Diagnosis Of Peripheral Artery Disease. Archives Of Plastic Surgery 39(3), 227-231	Not a relevant study design (cross sectional or cohort study) Case- series
Pita-Fernandez S, Lopez-Calvino B, Seoane-Pillado T, Arceo-Vila A, Perez-Garcia S, Garcia-Alonso P, Neira-Vazquez M J, And Pertega-Diaz S (2012) Prevalence Of Cardiovascular Risk Factors, Chronic Kidney Disease And Peripheral Arteriopathy In A General Population Sample Aged 65 Years Or Older. European Journal Of Epidemiology 1), S187-S188	Conference abstract
Poots J, Kennedy R, Dennison T, Gatt M, Blair P H, Mckinley A, And Harkin D W (2011) Nurse-Led Rapid Access Vascular Examination Clinic Triage Reduces Inappropriate Referrals For Peripheral Arterial Disease. Irish Journal Of Medical Science 180(2), 363-7	Reference standard in study does not match to that specified in protocol ABPI used as reference standard

Author	Reason for Exclusion
Potier L, Abi Khalil, C, Mohammedi K, And Roussel R (2011) Use And Utility Of Ankle Brachial Index In Patients With Diabetes. European Journal Of Vascular & Endovascular Surgery 41(1), 110-6	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed.
Prasad A, Gonzalez N, Mohamad M, Garcia M, Watt G, Vatcheva K, Laing S, Mccormick J, And Fisher-Hoch S (2017) The Prevalence Of Subclinical Lower Extremity Peripheral Arterial Disease In Mexican Americans: Results From The Cameron County Hispanic Cohort Study. Journal Of The American College Of Cardiology 69 (11 Supplement 1), 2045	Conference abstract
Rheeder P, Van Wyk , J T, Stolk R P, And Grobbee D E (2004) Assessing Peripheral Arteries In South African Black Women With Type 2 Diabetes Mellitus. South African Medical Journal. Suid-Afrikaanse Tydskrif Vir Geneeskunde 94(5), 379-83	Study does not match objectives of review Study examined concordance between ankle Doppler indices and toe systolic blood pressures indices
Salles-Cunha Sergio X, Braga Filipe A, Caiafa Jackson S, Melo Larissa H. A, Castro Aldemar A, And Pitta Guilherme B. B (2012) Diastolic Ankle-Brachial Indices As A Complementary Measure To Screen For Peripheral Arterial Disease In Diabetic Patients. Journal For Vascular Ultrasound 36(3), 205-209	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD
Sarkar A, Das S, Maiti S, Mukherjee S, Ray B, Ray A, And Mandal D (2014) Role Of Ankle Brachial Pressure Index (ABPI) In Early Diagnosis Of The Vascular Complications Of Diabetes Mellitus Patients From Eastern India. Biomedicine (India) 34(1), 120-126	Full text paper not available
Shirasu T, Hoshina K, Akagi D, Miyahara T, Yamamoto K, And Watanabe T (2016) Pulse Volume Recordings To Identify Falsely Elevated Ankle Brachial Index. Asian Cardiovascular & Thoracic Annals 24(6), 517-22	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Population contained individuals presenting with PAD
Silvestro A, Diehm N, Savolainen H, Do D D, Vogelea J, Mahler F, Zwicky S, And Baumgartner I (2006) Falsely High Ankle-Brachial Index Predicts Major Amputation In Critical Limb Ischemia. Vascular Medicine 11(2), 69-74	Outcomes of interest were not reported Diagnostic test accuracy not measured
Stoekenbroek (2015) Stoekenbroek R M, Ubbink D T, Reekers J A, And Koelemay M J (2015) Hide And Seek: Does The Toe-Brachial Index Allow For Earlier Recognition Of Peripheral Arterial Disease In Diabetic Patients?. European Journal Of Vascular & Endovascular Surgery 49(2), 192-8	Outcomes of interest were not reported Study compared the difference between ABPI and toe brachial index (TBI)
Stoffers H E, Kester A D, Kaiser V, Rinkens P E, And Knottnerus J A (1997) Diagnostic Value Of Signs And Symptoms Associated With Peripheral Arterial Occlusive Disease Seen In General Practice: A Multivariable Approach. Medical Decision Making 17(1), 61-70	Reference standard in study does not match to that specified in protocol Referenced standard not clearly stated
Su I H, Shie R F, Chu S Y, Hsieh H C, Ko P J, And Yu S Y (2014) Duplex Waveform Grade Disparity Score Predicts Long CTO Of PAD. Experimental And Clinical Cardiology 20(8), 2165-2180	Reference standard in study does not match to that specified in protocol Pulse wave Doppler analysis carried out but graded to form Waveform Grade Disparity Score
Tehan P E, Santos D, And Chuter V H (2016) A Systematic Review Of The Sensitivity And Specificity Of The Toe-Brachial Index For Detecting Peripheral Artery Disease. Vascular Medicine 21(4), 382-9	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed.

Author	Reason for Exclusion
	Systematic review did not focus on patients with diabetes with suspected PAD
Thejaswini K O, Roopakala M S, Dayananda G, Chandrakala S P, Prasanna Kumar, And K M (2013) A Study Of Association Of Ankle Brachial Index (ABI) And The Highly Sensitive C - Reactive Protein (Hscrp) In Type 2 Diabetic Patients And In Normal Subjects. Journal Of Clinical And Diagnostic Research 7(1), 46-50	Study does not match objectives of review Study compared ABPI to highly sensitive C- reactive protein in type 2 DM patients
Tsai C Y, Chu S Y, Wen Y W, Hsu L A, Chen C C, Peng S H, Huang C H, Sun J H, And Huang Y Y. (2013). The Value Of Doppler Waveform Analysis In Predicting Major Lower Extremity Amputation Among Dialysis Patients Treated For Diabetic Foot Ulcers. Diabetes Research & Clinical Practice, 100(2), Pp.181-8.	Study does not match objectives of review Study examined the predictors for lower extremity amputation in patients
Van Tongeren , R B, Bastiaansen A J. N. M, Van Wissen , R C, Le Cessie , S , Hamming J F, Van Bockel , And J H (2010) A Comparison Of The Doppler-Derived Maximal Systolic Acceleration Versus The Ankle-Brachial Pressure Index Or Detecting And Quantifying Peripheral Arterial Occlusive Disease In Diabetic Patients. Journal Of Cardiovascular Surgery 51(3), 391-398	Study does not contain any relevant index tests Study focused on Doppler derived maximal systolic acceleration(ACCmax)
Verberk W J, Kollias A, And Stergiou G S (2012) Automated Oscillometric Determination Of The Ankle-Brachial Index: A Systematic Review And Meta-Analysis. Hypertension Research 35(9), 883-891	Systematic review did not meet inclusion and exclusion criteria for the review. Included studies were reviewed. Systematic review did not focus on patients with diabetes with suspected PAD
Vogelberg KH, And Stork W (1988) Measurement Of Pulse Reappearance Time In Diagnosis Of Peripheral Vascular Disease In Diabetes.. Diabetes Care 11(4), 345-50	Does not contain a population of adults (≥ 18 years old) with diabetes with suspected PAD Population contained individuals presenting with PAD
Wukich D K, Shen W, Raspovic K M, Suder N C, Baril D T, And Avgerinos E (2015) Noninvasive Arterial Testing In Patients With Diabetes: A Guide For Foot And Ankle Surgeons. Foot & Ankle International 36(12), 1391-9	Study does not match objectives of review Diagnostic test accuracy not measured
Zhang H, Li X Y, Si Y J, Lu X L, Luo X S, And Liu Z Y (2010) Manifestation Of Lower Extremity Atherosclerosis In Diabetic Patients With High Ankle-Brachial Index. Chinese Medical Journal 123(7), 890-4	Outcomes of interest were not reported Study examined the manifestation of lower extremity atherosclerosis lesions in patients with high ABPI

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Appendix I - Research Recommendations

1. What is the most clinically and cost- effective diagnostic tool to establish the presence of PAD in people with diabetes?

People with diabetes are at a higher risk of cardiovascular events and foot problems such as diabetic neuropathy (nerve damage and degeneration), foot ulcer and limb loss. So it is important to have an effective test for diagnosing peripheral arterial disease in this group. At present there are only studies of very low quality (retrospective and prospective cross-sectional studies) containing small sample sizes. Diagnostic accuracy studies are needed to address this issue, ideally containing cost-utility analysis, comparing diagnostic tools with imaging. In order to explore the importance of early diagnosis, different clinical setting where diagnostic tests are performed should be explored.

Table I.1: What is the most clinically and cost- effective diagnostic tool to establish the presence of PAD in people with diabetes?

PICO	**Population:** People (adults aged ≥ 18 years) with diabetes who have suspected PAD. **Index tests:** Any relevant index non-invasive diagnostic test including: • Ankle brachial pressure index (ABPI) • Post exercise ankle brachial index • Toe brachial index • Doppler Wave form analysis **Reference standard:** • Imaging · Magnetic resonance imaging (MRI) · Computed tomography angiography (CTA) **Outcomes:** • Specificity • Sensitivity • Positive likelihood ratio • Negative likelihood ratio
Current evidence base	Retrospective and prospective cross sectional studies containing small sample sizes.
Study design	Diagnostic accuracy study containing cost-utility analysis
Other comments	This study should take into account the different clinical and community settings where diagnostic tests are performed.

2. What is the most clinically and cost effective diagnostic tool to establish severity of PAD and the impact of mortality, morbidity and limb amputation in people with diabetes?

Limited evidence suggests that Doppler ankle brachial pressure index, toe brachial index and oscillometric ankle brachial index, accurately diagnose severity of peripheral arterial disease. However, further research is needed using a robust diagnostic study design (such as a randomised controlled trial) to explore the clinical and cost effectiveness of tools in establishing the severity of disease and outcomes in people with diabetes. Studies should also explore the use of tools in different populations, such as those with neuropathy, and in different settings, for example, nursing homes, where access to services and diagnostic equipment may differ.

Table I.2: What is the most clinically and cost effective diagnostic tool to establish severity of PAD and the impact of mortality, morbidity and limb amputation in people with diabetes?

PICO	**Population:** People (adults aged ≥ 18 years) with diabetes who have suspected PAD. **Index tests:** Any relevant index non-invasive diagnostic test including: • Ankle brachial pressure index (ABPI) • Post exercise ankle brachial index • Toe brachial index • Doppler Wave form analysis **Reference standard:** • Imaging · Magnetic resonance imaging (MRI) · Computed tomography angiography (CTA) **Outcomes:** • Logistic regression model fit • Area under the curve • Critical limb ischemia
Current evidence base	Retrospective and prospective cross sectional studies containing small sample sizes.
Study design	Diagnostic accuracy study containing cost-utility analysis
Other comments	This study should take into account the different clinical and community settings where diagnostic tests are performed.

3. What is the inter- and intra-rater reliability of assessment tools for the diagnosis of PAD in people with diabetes?

Identifying peripheral arterial disease can be a challenge because diagnostic tests are conducted in a number of different settings by healthcare professionals with varying experience of using assessment tools. Data on inter- and intra-rater reliability of point-of-care assessment tools are needed to inform future recommendations for practice. The study should compare diagnostic tests with gold standard imaging. Different clinical and community settings, such as UK primary care setting, should also be taken into account.

Table I.3: What are the inter- and intra-rater reliability of assessment tools for the diagnosis of PAD in people with diabetes?

PICO	**Population:** People (adults aged ≥ 18 years) with diabetes who have suspected PAD. **Intervention:** Any relevant index non-invasive diagnostic test including: • Ankle brachial pressure index (ABPI) • Post exercise ankle brachial index • Toe brachial index • Doppler Wave form analysis • Pulse oximetry **Outcomes:** • Inter- and intra-operative reliability
Current evidence base	One cross sectional study with a sample of 30
Study design	Cross-sectional study
Other comments	This study should take into account the different clinical and community settings where diagnostic tests are performed.

Appendix J - References

Included Studies

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