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PROTOCOL

Assessment of the diagnostic accuracy of automated ankle brachial pressure index devices in patients with diagnosed or suspected peripheral arterial disease: protocol for a systematic review and meta-analysis

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Plain English Summary

Why we are undertaking this work: Peripheral arterial disease is a common condition where narrowing of the blood vessels in the legs can reduce blood flow. This may cause symptoms that include calf, thigh and/or buttock pain when walking and this can progress to cause pain at rest and leg ulcers. The ankle brachial pressure index is a measurement that can be used to assess peripheral arterial disease. Currently, this is measured manually using a blood pressure cuff and ultrasound probe, though time constraints and staff training limit its widespread use. This causes difficulty in the assessment and diagnosis of peripheral arterial disease, particularly in primary care. There are automated ankle brachial pressure index devices available, which may alleviate some of this difficulty. However, there is limited evidence regarding their accuracy in diagnosing peripheral arterial disease.

What we aim to do: We plan to review the current evidence available for the accuracy of automated ankle brachial pressure index devices in people with known or suspected peripheral arterial disease. We will look at studies that have compared automated devices with the current methods used for diagnosing peripheral arterial disease including manual doppler ankle brachial pressure index measurements and vascular imaging.

What this means: We hope the results from this review will be used to inform clinical practice and guide future clinical trials.

Key words: ankle brachial pressure index (ABPI), oscillometry, doppler, peripheral arterial disease (PAD)

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Abstract

Background: The ankle brachial pressure index (ABPI) is a common diagnostic tool used in the assessment of peripheral arterial disease (PAD). The Doppler ultrasound technique is regarded as the gold-standard method for ABPI measurement; however, time constraints and operator experience limit widespread application in clinical practice, particularly in a primary care setting. Automated ABPI devices are not currently widely used due to a lack of evidence regarding their diagnostic accuracy. The aim of this proposed systematic review and meta-analysis is to explore the current evidence for the accuracy of automated ABPI devices in people with known or suspected PAD.

Methods: Systematic searches of electronic databases and grey literature will be performed. We plan to include studies of adult patients with diagnosed or suspected PAD that have compared automated ABPI device readings with manual Doppler ABPI measurements or confirmed the diagnosis of PAD using vascular imaging. Two independent reviewers will screen identified literature for inclusion and perform data extraction. Extracted data will include study and participant characteristics, a description of the index and reference tests, outcome measures and main findings. The methodological quality of selected studies will be assessed using QUADAS-2 and QUADAS-C. Meta-analysis will be performed for studies with paired designs using a bivariate random-effect model to provide pooled estimates of summary accuracy statistics. We intend to conduct subgroup analyses and meta-regression for suspected sources of heterogeneity.

Discussion: This review aims to assess the diagnostic accuracy of automated ABPI devices for detecting PAD in patients with known or suspected PAD compared with manual Doppler ABPI measurements or vascular imaging. These results will be used to inform clinical practice and guide future trials.

Background

Target condition being diagnosed

Peripheral arterial disease (PAD) is a prevalent cardiovascular disease, estimated to affect approximately 236 million people worldwide.[1] PAD is characterised by progressive narrowing of the arterial lumen, reducing blood flow to the distal extremities.[2] Classic symptoms include exertional calf, thigh and/or buttock pain known as intermittent claudication, and with disease progression patients may develop ischaemic rest pain, arterial ulceration and limb loss.[3] The presence of PAD is also associated with an increased risk of myocardial infarction, ischaemic stroke, and death.[4,5] However, more than 50% of patients with PAD are asymptomatic and are therefore commonly underdiagnosed and undertreated.[6] Detection of symptomatic or asymptomatic PAD is crucial to allow for the appropriate management to reduce disease progression and associated cardiovascular morbidities.

Index test and alternative tests

The ankle brachial pressure index (ABPI) is a non-invasive diagnostic tool widely used in the assessment of PAD and is a vital part of the clinical pathway. ABPI values of <0.9 are regarded as diagnostic for PAD, with lower values indicating increasing severity.[7,8] The manual Doppler ultrasound technique is considered the gold-standard method for ABPI measurements.[9] This technique uses a sphygmomanometer and Doppler ultrasound probe for accurate arterial flow readings in the brachial arteries of both arms, and usually the posterior tibial and dorsalis pedis arteries of both legs. The index is calculated for each leg by dividing the highest of the ankle pressures by the highest arm pressure.[10]

Imaging modalities can be used in the assessment of PAD, particularly when revascularisation procedures are being considered. These include duplex ultrasonography, contrast-enhanced magnetic resonance angiography (MRA) and computed tomography angiography (CTA). Duplex ultrasonography is the first-line imaging technique for patients being considered for revascularisation. It is easily accessible and inexpensive but is limited in the assessment of multi-level stenoses and heavily calcified vessels.[11] MRA has a high diagnostic accuracy for PAD and is used in patients who require further imaging following duplex ultrasonography prior to revascularisation. CTA can also be used as an alternative imaging method when MRA is contraindicated or not tolerated.[10]

Clinical pathway

In the UK, an initial PAD assessment should be performed in the primary care setting. A patient who presents with features of intermittent claudication, defined as reproducible calf, thigh and/or buttock pain on exertion, or with features of critical limb-threatening ischaemia, defined as the presence of chronic rest pain, skin changes such as ulceration, non-healing wounds and/or gangrene, should be assessed for possible PAD. Such an assessment is also indicated in patients with diabetes, unexplained leg pain, those who require compression hosiery and those being considered for interventions to the leg or foot. The assessment for PAD involves a clinical history, lower limb examination and ABPI measurement.[10]

An ABPI value of <0.9 is regarded as confirming the presence of PAD, though a resting ABPI value of ≥0.9 does not necessarily exclude the diagnosis of PAD, particularly in the presence of a positive history, risk factors, or if the value is >1.4.[12,13] Regardless, ABPI assessments performed in primary care facilitate earlier PAD diagnosis, therefore improving patient outcomes.[14,15] In addition, most PAD management can also be executed in the primary care setting with referral to secondary care only indicated in the case of non-responding or worsening symptoms of intermittent claudication or in the case of critical limb-threatening ischaemia.

An outline of the initial assessment and management pathway for patients presenting to primary care with varying degrees of suspected PAD is summarised in Figure 1, based on current guidelines from the National Institute for Health and Care Excellence (NICE).[10] To follow these guidelines on assessment and management, it is important that ABPI measurements are widely available in the primary care setting.

However, manual ABPI measurements can be time-consuming, as a period of supine rest is recommended prior to the measurement being taken and the blood pressure in each of the six arteries is measured separately.[16] This, in combination with the limited expertise available in the primary care setting, means that ABPI measurements are often not performed when indicated, resulting in secondary care referrals being made earlier than necessary to diagnose or exclude PAD.[17,18] These factors may also preclude the measurement of ABPI, when indicated, in other healthcare settings outside of a vascular centre.

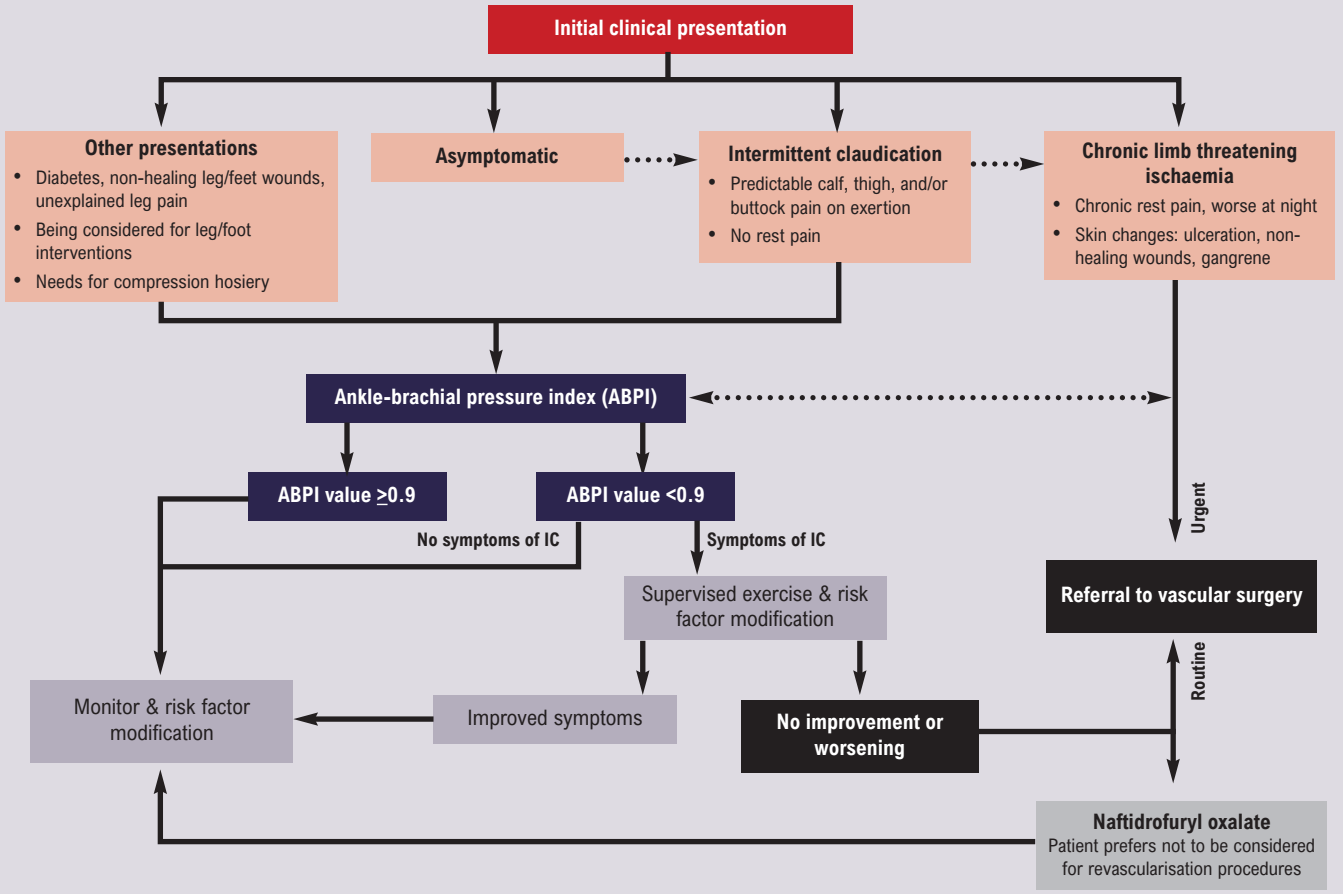
Rationale

Automated devices are becoming increasingly common for brachial blood pressure measurements in clinical practice, largely due to their simplicity and accuracy when compared to the traditional auscultation of Korotkoff sounds.[19] Such devices are also available for automated ABPI measurements. However, they are not currently widely accepted by the vascular, and wider, community due to limited evidence surrounding their accuracy and diagnostic performance in PAD. It is also not clear whether the diagnostic accuracy differs between device manufacturers.

Automated ABPI devices have the potential to replace manual ABPI measurements, which may negate the need for many secondary care referrals, particularly if PAD is not present, patients are asymptomatic or symptoms are mild.[10] Additionally, automated devices may improve accessibility to ABPI measurements in a variety of community and non-vascular settings. As such, these devices have the potential to improve patient care and alter the clinical pathway, better aligning it to what is recommended in the NICE guidelines (ie, diagnosis and management in primary care).

A previous systematic review was conducted in 2012, considering the reliability of automated ABPI devices. This review

Figure 1 Pathway for the initial assessment and management of patients with PAD.



concluded that automated ABPI devices are valid and provide a practical alternative for the detection of PAD. However, sensitivity was low at 69%, prohibiting automated devices from replacing manual ABPI measurements due to their inferior test accuracy.[20] In the 10 years following this study, new automated devices have been developed which may have improved sensitivity and specificity for PAD diagnosis. Therefore, the aim of this study is to provide an updated review of the evidence considering the role of automated ABPI devices in the detection of PAD in patients with known or suspected PAD.

Objectives

Our primary objective is to determine the diagnostic accuracy of automated ABPI devices for detecting or excluding PAD in people with known or suspected PAD.

Our secondary objectives are to identify whether the accuracy of these measures is altered by differences between device manufacturers, study setting (ie, primary and secondary care) and participant characteristics.

Methods

Protocol development

This protocol has been developed using the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA).[21,22]

Eligibility criteria

Types of studies

We plan to include all cross-sectional comparative studies written in the English language which evaluate the accuracy of automated ABPI devices for diagnosing or excluding PAD. Only fully paired direct comparisons will be included whereby each patient was tested using an automated ABPI device and via the manual method or another reference standard. Patients may also be randomised to receive one (of multiple) automated device or randomised to be assessed via an automated ABPI device or via the manual method. Such studies will be included if an appropriate reference standard is

also used for each randomised patient. No exclusions will be made based on methodological quality or sample size.

Participants

Studies with adult participants (18 years of age and older), of any sex, in any clinical setting, who have suspected or previously diagnosed PAD will be eligible for inclusion. For those with suspected PAD, we will include all groups for whom an ABPI is indicated according to the NICE guidelines.[10] This includes patients who (i) have symptoms suggestive of peripheral arterial disease; or (ii) have diabetes, non-healing wounds on the lower limbs or unexplained leg pain; or (iii) are being considered for lower limb interventions; or (iv) need to use compression hosiery.

Index test

The index test to be reviewed is automated ABPI, captured by oscillometric or plethysmographic devices. Any automated ABPI device and method will be included, regardless of whether the device has been validated for use in PAD. An ABPI value of <0.9 is widely regarded as the cut-off value for diagnosing PAD; however, studies will not be excluded if they have used different threshold values and this will be accounted for during statistical analysis.

Target condition

PAD is the target condition for this systematic review, which the index and reference tests are intended to identify or exclude. Studies may categorise PAD into asymptomatic, intermittent claudication and critical limb-threatening ischaemia. No exclusions will be made based on categorisation.

Comparative test and reference standards

The comparative test considered to be the reference standard in this review will be the manual Doppler ABPI measurements. Manual Doppler ABPI measurements should be taken using a sphygmomanometer and Doppler ultrasound probe and any recognised method for calculating ABPI will be included. Additional reference standards used to confirm the presence or absence of PAD can include Doppler ultrasonography, MRA or CTA. Studies that include additional measures to assess vascular status, such as toe brachial pressure index, will be included; however, these data will not be included in the analysis.

Search strategy

Electronic searches

Systematic searches will be performed using the MEDLINE, EMBASE, CENTRAL, and CINAHL databases. MeSH terms with full text synonyms will be searched and include ("peripheral arterial disease" or "peripheral arter* disease") and ("ankle brachial index" or "ankle brachial pressure ind*") and ("oscillometr*" or "plethysmograph*"). A draft search is shown in Appendix 1 (online at www.jvsgbi.com). Searches will be restricted to articles written in the English language; no date restrictions will be applied.

Searching other sources

The reference lists of all included studies and screened full texts will be manually reviewed for additional relevant papers. Clinical trial registries including ClinicalTrials.gov and the Clarivate Web of Science: Conference Proceedings Citation Index will be searched for ongoing studies and authors will be contacted for results where possible.

Data collection and analysis

Selection of studies

Search results will be uploaded onto the Covidence systematic review software, which automatically removes duplicated articles.[23] The titles and abstracts will be screened for eligibility by two independent reviewers, and full texts of potentially relevant articles will then be independently reviewed for inclusion. Any disagreement between reviewers at either stage will be resolved by consensus or with a third reviewer. When full texts are not obtainable via conventional access methods, the authors and publishing journal will be approached to request the full article text. The number of search hits, number of duplicates removed, number of full texts reviewed, number of full texts excluded with reasons and the number of studies included will be reported using the PRISMA flow diagram.

Data extraction and management

Extraction of relevant data will be performed by two independent reviewers and recorded on two separate Microsoft Excel spreadsheets, using a bespoke data extraction form. Data extraction will be based on the Cochrane handbook.[24] The extracted data will include: (i) study characteristics including year of publication, country, study design, sample size, duration, setting, and inclusion and exclusion criteria; (ii) participant characteristics including age, sex and comorbidities; (iii) description of the index test including automated device name, operator and device validation; (iv) description of the reference test(s) including equipment, operator and method for calculating ABPI if appropriate; and (v) findings related to primary and secondary outcomes, including results to recreate 2x2 diagnostic tables for estimating test accuracy. Any discrepancies in the extracted data will be resolved by reviewing the original article.

Assessment of methodological quality

Studies that meet the eligibility criteria will be appraised for risk of bias and applicability by two independent assessors using the quality assessment of diagnostic accuracy studies (QUADAS-2) tool and the QUADAS-C extension for comparative diagnostic accuracy studies.[25,26] The QUADAS-C tool is shown in Appendix 2 (online at www.jvsgbi.com). Any disagreement between reviewers will be resolved by consensus or with a third reviewer. Each study will be assessed on patient selection, index test, reference standard, and flow and timing, with each domain being classified into one of three categories: (i) high risk of bias; (ii) unclear risk of

bias; and (iii) low risk of bias. The effect of methodological quality will be accounted for in subgroup analyses.

Statistical analysis and data synthesis

Statistical analysis will be performed using R package mada in R language version 4.1.[27] Initial data synthesis will include cross tabulation of the binary outcomes 'PAD' or 'no PAD' for automated ABPI against the reference standard, manual ABPI in diagnostic 2x2 tables (ie, true positives, true negatives, false positives and false negatives). If 2x2 tables are not provided directly, they will be back calculated from raw data where possible.[24] Where data are missing to allow construction of 2x2 tables, the study authors will be contacted.

Studies with fully paired designs will be entered into a meta-analysis. The patient will be the unit of analysis. Due to expected variations in the unit of analysis used by included studies, an analysis will be performed to evaluate the impact of the unit of analysis (ie, patient vs limb). Forest plots with 95% confidence intervals (CI) and summary receiver operator characteristic (SROC) curves with 95% prediction and 95% confidence regions will be produced as part of initial exploratory analyses. Given the anticipation of a common threshold (ABPI <0.9) and for substantial study heterogeneity, as is expected in a meta-analysis of diagnostic test accuracy, we will use a bivariate random-effect model to provide pooled estimates of summary accuracy statistics.[21] If there is evidence of a threshold effect, the hierarchical SROC model will be used.[28] All SROC curves will be plotted with studies as weighted data points.

We plan to perform subgroup analyses and meta-regression for: (i) study characteristics (eg, study design, study setting and study quality); (ii) participant characteristics (eg, age, sex, diabetes, hypertension, smoking status and PAD severity); and (iii) comparative index test characteristics (eg, unit of analysis, ABPI calculation method, automated device type, device validation status, reference standard and threshold effect, if appropriate). This will allow us to investigate the impact of these subgroups on automated ABPI diagnostic test accuracy.

Investigations of heterogeneity

Study heterogeneity will be assessed by visual inspection of coupled forest plots and SROC plots. We expect that included studies will use a common ABPI threshold of 0.9; however, there may be slight variation in the threshold used due to equipment calibration and differences between operators.

We intend to use Spearman's correlation coefficient to test for the presence of a threshold effect as a source of heterogeneity. For this, we will use the sensitivity and specificity of all studies and r $\geq$0.6 will indicate the presence a threshold effect.[29] The aforementioned subgroup analysis will also allow us to investigate the effect of these sources of heterogeneity on automated ABPI diagnostic test accuracy.

KEY MESSAGES

- ABPI is a common diagnostic tool used in the assessment of PAD.
- Automated ABPI devices are not currently widely used due to a lack of evidence regarding their diagnostic accuracy.
- We aim to summarise the current evidence for the accuracy of automated ABPI devices in people with known or suspected PAD.

Assessment of reporting bias

The presence of publication bias will be assessed visually using a funnel plot. If more than 10 studies are included in the analysis, funnel plot asymmetry will be examined using Deeks' test.[30]

Discussion

This protocol outlines a systematic review to assess the diagnostic accuracy of automated ABPI devices for detecting or excluding PAD in people with known or suspected PAD. The manual Doppler ABPI method is currently the recommended first-line investigation for PAD, though there are certain drawbacks such as the time and expertise required for measurement. These limitations also mean that ABPI measurements are rarely obtained in primary care, as is recommended in NICE guidelines. This leads to referrals to secondary care to diagnose or exclude PAD. In addition, it also means that ABPI measurements are rarely obtained in other settings including community healthcare services, prison healthcare services and non-vascular district general hospitals. Automated devices have the potential to overcome some of these drawbacks, making ABPI measurements more accessible in a variety of settings and reducing the need for some secondary care referrals. These devices are not currently widely accepted due to concerns surrounding their accuracy, particularly their sensitivity.[20] However, the contemporaneous evidence for such devices is yet to be fully evaluated, an evidence gap that this review aims to fill.

An anticipated limitation of this review is considerable heterogeneity amongst study characteristics and outcomes measured, making statistical comparison challenging. Such heterogeneity has been identified in a previous review, mostly due to differences in automated devices used and methods for manual ABPI measurements.[20] We plan to assess the impact of these sources of heterogeneity during our subgroup analyses.

Overall, this review aims to summarise the current evidence for the accuracy of automated ABPI devices. The results will be used to aid medical professionals in the diagnosis of PAD, altering the current clinical pathway and aligning it to what is recommended in NICE guidelines. The results may also assist in providing eligibility criteria framework for future trials designed to validate new automated ABPI devices.

Conflict of Interest: IC is the editor and chief of *JVSGBI*.

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Appendix 1 Draft systematic search strategy

		Embase	Medline	CINAHL
1	Peripheral Arterial Disease/	26132	10307	7,175
2	Peripheral Arter* Disease*.ab,ti.	25943	16317	5,110
3	Arterial Occlusive Diseases/	22529	28029	3,733
4	Arteriosclerosis/	24577	56745	6,760
5	Atherosclerosis/	161378	42443	10,557
6	"lower extremity arter* disease".ab,ti.	575	407	112
7	"lower limb arter* disease".ab,ti.	172	125	13
8	"atherosclero*".ab,ti.	227914	164467	27,678
9	"arteriosclero*".ab,ti.	16717	16236	927
10	PVD.ab,ti.	4876	2946	544
11	PAOD.ab,ti.	1357	814	122
12	Ankle Brachial Index/	12715	3824	2,281
13	ankle brachial ind*.ab,ti.	8611	5487	1,648
14	ankle brachial pressure ind*.ab,ti.	1342	999	329
15	ABPI.ab,ti.	760	466	220
16	ABI.ab,ti.	15326	7819	2,447
17	AAI.ab,ti.	2874	1978	558
18	Ankle ind*.ab,ti.	121	83	22
19	Arm ind*.ab,ti.	834	608	204
20	Brachial ind*.ab,ti.	9009	5750	1,706
21	Blood Pressure Determination/	46993	29440	11,150
22	Blood Pressure Determination*.ab,ti.	432	505	38
23	Oscillometr*.ab,ti.	5912	3558	1,017
24	Oscillometry/	7672	10039	0
25	Plethysmography/	14869	10729	2,657
26	Plethysmography, Impedance/	2949	5572	508
27	Photoplethysmography/	5079	2504	0
28	plethysmograph*.ab,ti.	19666	14438	2,153
29	photoplethysmograph*.ab,ti.	4558	3415	547
30	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	341527	252058	46,548
31	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	28608	15362	16,006
32	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	87167	67224	5,685
33	30 and 31 and 32	697	401	135

Appendix 2 QUADAS-C: risk of bias in comparative diagnostic accuracy studies

Comparative review question

Patients:	
Index test A:	
Index test B:	
Reference standard and target condition:	

Add rows for additional index tests if necessary

Comparative study design

Which of the following study designs does the primary study most strongly resemble?	*#1 Fully Paired* *#2 Randomized* *#3 Partially paired with random subset* *#4 Partially paired with nonrandom subset* *#5 Unpaired nonrandomized* *Other (please describe the study design):*

The QUADAS-C Guidance Document contains example flow diagrams for each design

Flow diagram

Draw a flow diagram for the primary study

Appendix 2 QUADAS-C: risk of bias in comparative diagnostic accuracy studies continued

Domain 1: Patient Selection			
Information to support judgment	*Describe methods of patient selection.* *Describe included patients (previous testing, presentation, intended use of index test, and setting).* *Describe how patients were allocated to receive each of the index tests. If randomization was used to assign individual patients (or clusters of patients) to index tests, describe the randomization process.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)***	**Answers for _____ (test B)***
Signaling questions	1.1 Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	Yes/No/Unclear
	1.2 Was a case-control design avoided?	Yes/No/Unclear	Yes/No/Unclear
	1.3 Did the study avoid inappropriate exclusions?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	1.4 Could the selection of patients have introduced bias?	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C1.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C1.2 Was a fully paired or randomized design used?	Yes/No/Unclear	
	C1.3 Was the allocation sequence random?†	Yes/No/Unclear/ Not applicable	
	C1.4 Was the allocation sequence concealed until patients were enrolled and assigned to index tests?†	Yes/No/Unclear/ Not applicable	
Risk of bias	C1.5 Could the selection of patients have introduced bias in the comparison?	Low/High/Unclear	

** Example when the comparison is between two index tests. Additional columns can be added for each additional test in the comparison.*

† Only applicable to randomized designs

See the QUADAS-C Guidance Document for more detailed explanations.

C1.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 1.4 in QUADAS-2) was 'low' for each index test.

C1.2: Answer 'yes' if one of the following methods was used for allocating patients to index tests: (1) each patient receiving all of the index tests (fully paired design) or (2) random allocation of patients to one of the index tests (randomized design).

C1.3: Answer 'yes' if the study generated a truly random allocation sequence, for example, computer-generated random numbers and random number tables.

C1.4: Answer 'yes' if the study used appropriate methods to conceal allocation, such as central randomization schemes and opaque sealed envelopes.

C1.5: Risk of bias can be judged 'low' if questions C1.1 to C1.4 were answered 'yes' (questions C1.3 and C1.4 are only applicable to randomized designs). If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic. If C1.2 was answered 'no', strongly consider 'high risk of bias'.

Appendix 2 QUADAS-C: risk of bias in comparative diagnostic accuracy studies continued

Domain 2: Index Test			
Information to support judgment	*Describe the index tests and how they were conducted and interpreted.* *For paired comparative studies, describe the order in which the index tests were performed.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)**	**Answers for _____ (test B)**
Signaling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/No/Unclear	Yes/No/Unclear
	2.2 If a threshold was used, was it prespecified?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias?	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C2.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C2.2 Were the index test results interpreted without knowledge of the results of the other index test(s)?‡	Yes/No/Unclear/ Not applicable	
	C2.3 Is undergoing one index test unlikely to affect the performance of the other index test(s)?‡	Yes/No/Unclear/ Not applicable	
	C2.4 Were the index tests conducted and interpreted without advantaging one of the tests?	Yes/No/Unclear	
Risk of bias	C2.5 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Low/High/Unclear	

‡ Only applicable if patients received multiple index tests (fully or partially paired designs)

C2.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 2.3 in QUADAS-2) was 'low' for each index test.
C2.2: Answer 'yes' if index test A was interpreted blind to the results of index test B and vice versa. Blinding is not necessary if none of the index tests involve subjective interpretation.
C2.3: Answer 'yes' if one index test cannot influence or interfere with the results of subsequently performed index test(s). Examples of such influence or interference include distortion of sampling area (biopsies) and patient fatigue (questionnaires).
C2.4: Answer 'yes' if there were no differences between the index tests that may unfairly benefit one of the tests. An example of such a difference is when index test A was performed by an expert and index test B by a nonexpert. Differences between tests that reflect clinical practice are acceptable, in which case 'yes' is appropriate.
C2.5: Risk of bias can be judged 'low' if signaling questions C2.1 to C2.4 were answered 'yes' (C2.2 and C2.3 are only applicable to fully or partially paired designs). If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic.

Appendix 2 QUADAS-C: risk of bias in comparative diagnostic accuracy studies continued

Domain 3: Reference Standard			
Information to support judgment	*Describe the reference standard, how it was conducted and interpreted, and whether any of the index tests were part of the reference standard.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)**	**Answers for _____ (test B)**
Signaling questions	3.1 Is the reference standard likely to correctly classify the target condition?	Yes/No/Unclear	Yes/No/Unclear
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	3.3 Could the reference standard, its conduct, or its interpretation have introduced bias?	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C3.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C3.2 Did the reference standard avoid incorporating any of the index tests?	Yes/No/Unclear	
Risk of bias	C3.3 Could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?	Low/High/Unclear	

C3.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 3.3 in QUADAS-2) was 'low' for each index test.
C3.2: Answer 'yes' if none of the index tests were part of the reference standard. Note that this issue is different from blinding (signaling question 3.2 in QUADAS-2).
C3.3: Risk of bias can be judged 'low' if signaling questions C3.1 and C3.2 were answered 'yes'. If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic.

Appendix 2 QUADAS-C: risk of bias in comparative diagnostic accuracy studies continued

Domain 4: Flow and Timing			
Information to support judgment	*Describe any patients who did not receive the index tests or reference standard or who were excluded from the analysis.* *Describe the time interval and any interventions between the index tests and the reference standard.* *Describe the time interval and any interventions between the index tests being compared.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)**	**Answers for _____ (test B)**
Signaling questions	4.1 Was there an appropriate interval between index tests and reference standard?	Yes/No/Unclear	Yes/No/Unclear
	4.2 Did all patients receive a reference standard?	Yes/No/Unclear	Yes/No/Unclear
	4.3 Did all patients receive the same reference standard?	Yes/No/Unclear	Yes/No/Unclear
	4.4 Were all patients included in the analysis?	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	4.5 Could the patient flow have introduced bias?	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C4.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C4.2 Was there an appropriate interval between the index tests?	Yes/No/Unclear	
	C4.3 Was the same reference standard used for all index tests?	Yes/No/Unclear	
	C4.4 Are the proportions and reasons for missing data similar across index tests?	Yes/No/Unclear	
Risk of bias	C4.5 Could the patient flow have introduced bias in the comparison?	Low/High/Unclear	

C4.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 4.5 in QUADAS-2) was 'low' for each index test.
C4.2: For many index tests, 'appropriate' would constitute performing the tests at the same time after patient enrolment. This excludes the possibility of disease progression or change in patient management. Some index tests have different 'diagnostic windows' and are ideally performed at different timepoints; subject-matter expertise is required to determine this.
C4.3: Answer 'yes' if either (1) a single reference standard was used in all patients or (2) multiple reference standards were used (e.g., either surgery or follow-up) and these reference standards were the same for patients receiving index test A and patients receiving index test B.
C4.4: Missing data occurs if test results are unavailable, invalid, inconclusive, or if patients are excluded from the analysis. Answer 'yes' if there is no missing data, or if the proportion and reasons for missing data are similar for index test A and index test B.
C4.5: Risk of bias can be judged 'low' if signaling questions C4.1 to C4.4 were answered 'yes'. If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic.