Automated measurement of ankle brachial pressure index for assessing the presence of peripheral arterial disease in people with leg ulceration

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Contribution of authors

Dwayne Boyers developed the economic model, conducted cost-effectiveness analyses, and interpreted their results. Moira Cruickshank (Research Fellow) selected relevant papers from the literature, performed data extraction and risk of bias assessment of all studies included in the review of clinical effectiveness evidence and synthesized their results; Lorna Aucott (Senior Statistician) conducted all statistical analyses for the review of clinical effectiveness evidence; Charlotte Kennedy (Research Assistant) reviewed the identified cost-effectiveness evidence and contributed to the acquisition of input data for the economic model under the supervision of Dwayne Boyers (Senior Health Economist); Paul Manson (Information Specialist) developed and ran the literature searches, retrieved full-text copies of the selected papers and provided information support throughout the project; Paul Bachoo (Consultant in Vascular Surgeon and Medical Director Acute Sector NHS Grampian) provided expert advice and guidance on the clinical aspects of this assessment. Miriam Brazzelli (Reader on Research) planned the systematic review of the clinical

evidence, contributed to interpreting the test accuracy results, and coordinated all aspects of this assessment. All authors contributed to the writing of this draft report.

Abstract

Background

Peripheral artery disease (PAD) is a common condition caused by narrowing/blockage of the arteries, resulting in reduced blood supply. PAD is associated with increased risk of vascular complications, but early treatment reduces mortality and morbidity. Leg ulcers are long-lasting wounds, usually treated by compression therapy. Compression therapy is not suitable for people with PAD, as it can affect the arterial blood supply. In clinical practice, people with PAD are identified by measurement of the ankle brachial pressure index (ABPI) using a sphygmomanometer and manual Doppler device. However, this method can be uncomfortable for people with leg ulcers and automated devices have been proposed as a more acceptable alternative. The objective of this appraisal was to summarise the clinical and cost-effectiveness evidence on the use of automated devices to detect PAD in people with leg ulcers.

Methods

Clinical effectiveness

To identify reports of relevant studies, we searched major electronic databases and scrutinised the information supplied by the manufacturers of the automated devices under investigation. Due to the lack of evidence on people with leg ulcers, we considered evidence from studies of any design assessing automated devices versus an acceptable reference device in any population receiving ABPI assessment. We summarised information on diagnostic accuracy of the automated devices and level of agreement with the reference device.

Cost effectiveness

An economic model, comprising a decision tree (24 weeks) and markov models to capture life-time costs and QALYs associated with venous, arterial, and mixed aetiology disease in leg ulcer patients. Analyses were conducted from a UK NHS and personal social services perspective. Costs and QALYs were discounted at 3.5% per year. Deterministic and several probabilistic analyses were used to capture uncertainty surrounding a range of optimistic and pessimistic assumptions about the

impact of automated tests on health outcomes (ulcer healing and requirement for invasive management of arterial disease).

Results

Clinical effectiveness

We included 24 studies evaluating five devices (BlueDop Vascular Expert, BOSO ABI-System 100, Dopplex Ability, MESI ABPI MD, and WatchBP Office ABI). Two studies assessing people with leg ulcers found that automated devices often gave higher ABPI readings than manual Doppler. In the 22 studies involving people without leg ulcers, automated devices generally demonstrated good specificity and moderate specificity. Meta-analysis of 12 studies showed a pooled sensitivity of 64% (95%CI 57%-71%) and a pooled specificity of 96% (95%CI 92%- 98%) for detection of PAD.

Cost effectiveness

Automated devices cost less than manual Doppler to deliver. However, increased risks of invasive treatment requirements for inappropriately compressed arterial/mixed ulcers due to FN results, and increased healing times due to delayed compression of FP test results mean that in most scenarios manual Doppler was less costly and had slightly higher QALYs than automated devices. Results are highly uncertain, dependent on many assumptions, and should be interpreted cautiously.

Discussion

The limited evidence identified for each automated device, especially in people with leg ulcers, and its clinical heterogeneity precludes any firm conclusions on the diagnostic performance and cost-effectiveness of these devices in clinical practice.

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List of abbreviations

ABPI	Ankle brachial pressure index
AUC	Area under the curve
CLI	Critical limb ischaemia
CKS	Clinical knowledge summary
CRD	Centre for Reviews and Dissemination
CT	Computerised tomography
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
EAG	External assessment group
EVRA	Early venous reflux ablation
F (2,3,4)	Fontaine stages of arterial disease (stage 2,3 and 4)
FN	False negatives
FP	False positives
GP	General practice
HES	Hospital episode statistics
HR	Hazard ratio
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
IC	Intermittent claudication
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial Haemorrhage
IQR	Interquartile range
KM	Kaplan Meier
LN	Log normal
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NWCSP	National Wound Care Strategy Programme

PAD	Peripheral artery disease
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal social services research unit
QALW	Quality-adjusted life week
QALY	Quality-adjusted life year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies - version 2
ROC	Receiving Operating Characteristics
SCM	Specialist committee members
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
THIN	The health improvement network
TN	True negatives
TP	True positives
VLU	Venous leg ulcer

Plain language summary

Leg ulcers are long-lasting wounds mostly caused by problems in blood flow in the veins, which are treated by applying bandages or stockings to create a ‘compression’ effect. However, compression should not be used in people with a condition called Peripheral Artery Disease (‘PAD’). To identify people with PAD who should not receive compression therapy, health professionals perform a test called ‘Ankle Brachial Pressure Index’ (ABPI), which involves taking blood pressure of the arms and ankles using a device called ‘Doppler ultrasound’. The procedure is time-consuming and people with leg ulcers often find it uncomfortable. Automated devices have been proposed as a more acceptable option for assessing leg ulcers. However, we need to know whether these devices produce reliable results and represent good value for money for the NHS.

We found 24 clinical studies that assessed five automated devices to measure ABPI. The type of patients and clinical setting varied between studies. Two studies assessed people with leg ulcers and showed that the automated devices tended to give higher readings than standard Doppler. Results of the 22 studies assessing people without leg ulcers showed that the automated devices could correctly identify people who did not have PAD but were less precise in identifying people with PAD. However, there was not enough evidence to confirm if these devices are reliable enough to be used in clinical practice.

Compared to manual Doppler, the automated devices were less costly to deliver in clinical practice but had increased costs due to potentially inaccurate results. Our evaluation required many assumptions about how the devices would be used in practice and there was no data on their impact on patient outcomes. Results are highly uncertain and should be interpreted cautiously. Given current evidence, it is unlikely that automated tests are a convenient option for the NHS.

Scientific Summary

Background

Peripheral artery disease (PAD) is a highly prevalent atherosclerotic condition characterised by the narrowing of the peripheral arteries resulting in restriction of blood supply to the affected limb. Although PAD is frequently asymptomatic, it can cause complications that can range from intermittent claudication (pain on walking which is relieved by rest) to critical limb ischaemia. Up to one-quarter of people with symptomatic PAD may require intervention and amputation may be necessary if it is left untreated. Leg ulcers are wounds on the lower leg (below the knee) or foot that takes time to heal. Compression treatment (bandages or stockings) is recommended to treat venous leg ulcers and there is a robust evidence base to support its effectiveness. However, compression therapy should be avoided in people with leg wounds and symptoms of arterial insufficiency as compression may cause damage by impairing the arterial supply to the ulcerated leg. To improve PAD diagnosis and decide the most suitable treatment, people with leg ulcers are assessed using ankle-brachial pressure index (ABPI) measurements. Ankle brachial pressure index is usually measured using a sphygmomanometer and manual Doppler device, which requires expertise from the relevant operator/healthcare professional. The procedure can be protracted and unpleasant for those with leg ulcers. Automated devices may be advantageous in reducing the length of time taken to assess ABPI and, thereby, any associated discomfort for the patient. In addition, automated devices may potentially be more accurate than manual processes in detecting PAD, thus conferring additional benefits such as reduced time to treatment and improved outcomes for people with leg ulcers.

Objectives

The specific objectives of this assessment were to:

- Determine the diagnostic performance and clinical utility of automated devices available in UK clinical practice (BlueDop Vascular Expert [BlueDop Medical], boso ABI-system 100 [BOSCH + SOHN], WatchBP Office ABI [Microlife], WatchBP Office Vascular [Microlife]), MESI ABPI MD [MESI], MESI mTABLET ABI (MESI), Dopplex Ability Automatic ABI System [Huntleigh Healthcare]) for assessing the presence of PAD in people with leg ulcers.

- Develop an economic model to assess the cost-effectiveness of the automated devices available in UK clinical practice for assessing the presence of PAD in people with leg ulcers.

Methods

Clinical effectiveness

Comprehensive electronic searches were conducted to identify relevant reports of published studies. Evidence was considered from studies of any design assessing the relevant automated devices versus standard clinical assessment using a manual Doppler device. Initially, the population of interest was people with leg ulcers requiring measurement of ABPI but, due to the dearth of available evidence, was broadened to any population receiving ABPI measurement. Data on the diagnostic performance of the automated devices including data on the level of agreement between ABPI readings from automated devices and those from the reference device were extracted from the included studies. Information on the use of the devices in clinical practice was also recorded.

A two-stage, *de novo* decision analysis model was developed to assess cost-effectiveness. The first part was a decision tree model, which used a linked-evidence approach to capture the impact of test diagnostic accuracy on expected costs and QALYs for the first 24-weeks following test use. This included delayed venous ulcer healing due to false positive test results (indicating PAD, when ulcer was venous) and increased risk of requiring invasive arterial treatment for inappropriately compressed arterial / mixed ulcers following a false negative test result (indicating venous when underlying disease was arterial / mixed). It was assumed that any inaccurate tests would be identified within the 24-week time horizon of the decision tree.

The surviving proportion of the cohort then entered arterial, mixed, or venous ulcer Markov models depending on their true underlying disease classification. The venous disease model included 5 mutually exclusive health states, centered around ulcer healing (Healed index ulcer, unhealed index ulcer, recurrence, healed post recurrence, and death). The arterial and mixed disease models included four health states, focusing on the long-term outcomes of the arterial component of disease (critical limb ischemia (CLI); healed post CLI; amputation, and death). The decision to structure the mixed Markov model similarly to the arterial only model

was based on discussion with clinical experts who explained that, in clinical practice, the arterial component of disease is likely to take priority in the patient's care pathway.

Costs were based on an NHS and PSS perspective costs (2021 values) and included:

- Micro-costing of the automated and manual Doppler devices.
- Costs of applying compression for the unhealed duration of a venous ulcer.
- Costs of referral to vascular services for test positive patients, including the additional costs of unnecessary referral for patients with a FP test result.
- Costs of treating arterial disease, including endovascular and bypass procedures as well as follow up nursing care.
- Long term follow-up costs in the Markov model included the cost of managing recurrent venous ulcers, recurrent CLI and long-term health and social care costs of amputation.

Health state utility values were obtained from the literature and were based on EQ-5D data, valued using the UK value set where possible. Utilities were combined with mortality estimates for each health state to calculate QALYs. In the decision tree, utilities were dependent on the duration of ulcer healing time for venous ulcers, and whether patients had critical limb ischemia for those with arterial / mixed disease. All utilities were adjusted for UK age- and sex-specific general population norms, allowing the cohort to experience reduced utility as they aged over subsequent model cycles.

Expected costs and QALYs were accumulated over a life-time horizon, in six-monthly cycles and an annual discount rate of 3.5% per annum was applied to future costs and QALYs. Probabilistic analyses were conducted (Monte-Carlo simulation with 1,000 draws for each parameter) were provided for a range of pessimistic and optimistic alternative base case scenarios. A full range of deterministic scenarios explored the impact of alternative sources of model inputs and assumptions on cost-effectiveness results.

Results

Nature, description and quality of the available evidence

Twenty-four studies, published in 26 papers, were included in the systematic review of clinical effectiveness. Two studies enrolled specifically people with leg ulcers (167

participants in total) whilst the remaining studies (4258 participants in total) included people from primary care practices, cardiovascular risk services, vascular services and from epidemiological/general population-based studies. All studies used an ABPI threshold of 0.9. Most of the studies assessed the performance of a single automated device with only one study comparing two devices (WatchBP and MESI ABPI MD). Regarding the type of automated devices, two studies provided data on the BlueDop Vascular Expert device, four studies on the BOSO ABI-System 100, six studies on the Dopplex Ability, eight studies on the MESI ABPI MD and five studies on the WatchBP Office. No studies assessed the performance of the WatchBP Office Vascular and the MESI mTABLET ABI devices. Apart from one study conducted in New Zealand, all included studies were conducted in Europe (six in the UK). The risk of bias of included studies was assessed using the QUADAS-2 tool. Most studies were judged at low risk for the index test domain and at unclear risk for the patient selection, reference standard and flow and timing domains. The risk of applicability concerns was low in most studies.

Summary of benefits and risks

The two studies assessing people with leg ulcers did not provide sensitivity and specificity estimates but reported that automated devices gave generally higher readings than manual Doppler. The results of the 22 studies assessing people without leg ulcers varied. Seventeen studies reported sensitivity and specificity estimates for the detection of PAD and showed that the automated devices had good sensitivity but only moderate sensitivity indicating that a proportion of people with PAD would be missed. Sensitivity of BlueDop Vascular Expert ranged from 66% to 95% and specificity from 90% to 94% in two studies; sensitivity of the BOSO ABI-System 100 ranged from 61% to 77% and specificity from 94% to 98% in three studies; sensitivity of Dopplex Ability ranged from 20% to 79% and specificity from 86% to 96% in four studies; sensitivity of the MESI ABPI MD ranged from 57% to 75% and specificity from 67% to 99% in five studies; sensitivity of the WatchBP Office ABI ranged from 44% to 83% and specificity from 97% to 100% in four studies;

We were able to combine results across 12 studies (2004 participants in total) and three automated devices. The pooled sensitivity and specificity for PAD diagnosis using automated ABPI were 64% (95% CI 57% to 71%) and 96% (95% CI 92% to 98%), respectively. Regarding the performance of individual devices, the pooled sensitivity for MESI ABPI MD was 67% (95% CI 59% to 74%) and the pooled specificity 94% (95% CI 83% to 98%); the

pooled sensitivity for WatchBP Office ABI was 53% (95% CI 37% to 69%) and the pooled specificity 98% (95% CI 96% to 99%). For the remaining devices, we could not conduct meaningful meta-analyses due to the limited number of available studies.

Summary of cost-effectiveness, including sensitivity analyses

The uncertainties in the diagnostic accuracy evidence base and the unclear link between test results and patient management mean it is difficult to draw any firm conclusions on cost-effectiveness. A lack of evidence on the impact of the tests on important patient outcomes, the extent to which inaccurate test results would be identified in practice, and the implications of acting on inaccurate test results contribute further uncertainty to the assessment of cost-effectiveness. Automated tests were less costly to deliver due to shorter testing times, but in most modelling scenarios, these cost savings were quickly offset by any additional risks and costs associated with withholding compression (false positive) or inappropriately applying compression (false negative). Given the current evidence base, it is unlikely that the automated tests would generate QALY gains or cost-savings, unless a high proportion of FP and FN tests could be reliably identified in clinical practice through holistic patient assessment, and automated tests could deliver improvements in patient referral over manual doppler testing.

Discussion

Strengths, limitations of the analyses and uncertainties

The methods used to conduct this assessment were detailed, thorough and in line with current methodological standards. We identified only two studies assessing the performance of automated devices in determining ABPI in people with leg ulcers. Given the current lack of evidence in people with leg ulcers, we decided to widen our target population to include studies assessing the use of the automated devices for measuring ABPI in different settings. We identified and summarised 22 studies focusing on people without leg ulcers.

The main limitations of the clinical effectiveness assessment are summarised below.

- Lack of evidence on people with leg ulcers to draw any meaningful conclusion about this clinical population;

- Considerable clinical heterogeneity - in terms of characteristics of the patient population, setting, and testing procedures - across studies that focused on people without leg ulcers;
- Suboptimal agreement between readings of the automated devices and those of the manual Doppler with a systematic tendency toward higher automated readings;
- Use of manual Doppler as the reference standard for detection of PAD;
- Variation in the prevalence of PAD across studies;
- Limited data on the performance of the automated devices in relevant subgroups of patients (e.g., diabetes patients);
- Uncertainty about the optimal threshold for automated ABPI measurement;
- Uncertainty about the potential role of automated devices in clinical practice (screening tool, alternative/adjuvant tool to current manual Doppler);
- Lack of data on the impact of the routine use of automated devices on health outcomes (e.g., the consequences of a delayed diagnosis because of false negative results);
- No data on the WatchBP Office Vascular and MESI mTABLET ABI devices

With regard to the economic modelling, we identified the following areas of uncertainties that complement those identified for the review of clinical effectiveness evidence and raise doubt about the robustness of the cost-effectiveness results:

- A lack of data regarding the impact of different tests on patient-relevant outcomes such as ulcer healing.
- It is unclear whether automated tests could achieve tangible benefits in terms of a reduced time to referral for compression therapy in patients with venous disease. Any benefits would rely on a lack of skills to complete manual Doppler assessment in the community, and it is unclear how widespread such a skill shortage might be.
- Uncertainty around whether inaccurate test results might be identified during clinical evaluation of patients during a testing appointment, and thus the extent to which inaccurate results would be acted upon in clinical practice (i.e., if tests would lead to inappropriate compression of arterial ulcers [false negatives], or delayed time to compression [false positives]).
- Limited data regarding the costs and outcomes specifically for mixed ulcer disease.

Generalisability of the findings

It is unclear how the results of studies assessing the accuracy of automated devices for measuring APBI in people without leg ulcers could be generalised to people with leg ulcers.

Conclusions

Future research is needed to evaluate the use of automated devices within specific populations (people with leg ulcers) and relevant settings. For the broader use of automated devices in clinical practice, more robust evidence is required to establish whether the use of automated devices is appropriate and cost-effective for the general screening of clinical populations with any vascular concerns. In addition, evidence is needed to support the use of automated devices as an alternative or adjunct to manual Doppler in people with symptoms of PAD.

Chapter 1. Objectives

The overall objective of this assessment was to summarise the current evidence on the clinical and cost-effectiveness of automated devices to help identify peripheral arterial disease (PAD) in people with ulcers of the lower limb. PAD can lead to serious complications including critical limb ischaemia and amputation. The early identification of PAD is important to determine prompt and optimal patient management at the community and primary care levels.

The specific objectives of this assessment are the following:

- To determine the diagnostic performance and clinical utility of automated devices available in UK clinical practice (BlueDop Vascular Expert [BlueDop Medical], boso ABI-system 100 [BOSCH + SOHN], WatchBP Office ABI [Microlife], WatchBP Office Vascular [Microlife]), MESI ABPI MD [MESI], MESI mTABLET ABI (MESI), Dopplex Ability Automatic ABI System [Huntleigh Healthcare]) for assessing the presence of PAD in people with leg ulcers.
- To develop an economic model to assess the cost-effectiveness of the automated devices available in UK clinical practice for assessing the presence of PAD in people with leg ulcers.

Chapter 2. Background and definition of the decision problem

2.1 Description of the health problem

Peripheral artery disease

Peripheral artery disease (PAD) is a common artherosclerotic condition caused by narrowing or blockage of the arteries by fatty deposits (known as atheroma), which results in a reduction of blood supply to the affected limb. PAD is associated with an increased risk of vascular complications such as myocardial infarction and stroke. Early treatment is known to reduce mortality and morbidity.[1] Although PAD is frequently asymptomatic, it can cause complications that can range from intermittent claudication (pain on walking which is relieved by rest) to critical limb ischaemia. Manifestations of critical limb ischaemia include ulceration and gangrene. People with critical limb ischaemia are at high risk of limb amputation and premature death.[2-4]

Leg ulcers

Leg ulcers are long-lasting wounds on the lower leg (below the knee) or foot that take several weeks to heal. Most leg ulcers (about 70%) are venous leg ulcers caused by blood accumulating in the legs due to problems in the veins, which tend to be chronic and recurring;[5] about 10% of leg ulcers are caused by peripheral arterial disease and about 20% are mixed aetiology leg ulcers (both arterial and venous).[5-8] Outbreaks of ulceration can last from weeks to years and ulcers can extend to a surface area greater than 25cm^2.[9-11]

Compression therapy (bandages or stockings) has historically been used to treat venous leg ulcers and there is a large evidence base to support its effectiveness.[12] However, using compression to treat ulcers may cause damage by impairing the arterial supply to the ulcerated leg. As compression therapy is unsuitable for people with PAD,[13, 14] it is recommended that people with leg ulcers are screened for arterial disease using the ankle-brachial pressure index (ABPI).[12, 13]

2.2 Incidence and/ or prevalence

Peripheral artery disease

Global prevalence of PAD of 10-15% has been estimated[3, 15, 16] and increases with age, especially in those aged in their 60s and 70s.[2, 17-20]

The incidence of PAD is similar between males and females and higher among black people compared to white people.[19] Hospital Episode Statistics for England for 2020-2021 reported 4,466 finished consultant episodes and 3,220 admissions with a mean length of stay of 6.9 days for peripheral vascular disease (code I73.9).

Leg ulcers

It has been estimated that around one million or 2% of adults in the UK have leg ulcers.[21] Records from The Health Improvement Network (THIN) database show that in 2017/18 the annual number of people with an arterial leg ulcer was 1% while the annual number of people with a venous ulcer was 15%. The observed percentage of change (increase) in the annual number of venous ulcers between 2012/13 and 2017/18 was 101%. More recently, the Hospital Episode Statistics for England for the period 2020-2021 have reported 20,555 finished consultant episodes and 11,423 admissions with a mean length of stay of 9.0 days for '*ulcer of lower limb, not elsewhere classified*' (code L97.X).[22]

2.3 Impact of health problem: significance for patients in terms of ill-health (burden of disease) and significance for the NHS

Peripheral artery disease

NICE guideline CG147 recommends that people are assessed for the presence of PAD if they:

- have symptoms suggestive of peripheral arterial disease or
- have diabetes, non-healing wounds on the legs or feet or unexplained leg pain or
- are being considered for interventions to the leg or foot or
- need to use compression hosiery.[23]

Leg ulcers

It has been shown that the quality of life in people with leg ulcers is affected negatively in terms of pain, impaired mobility, work and social life, anxiety and depression, activities of daily living, sleep disturbance and self-esteem.[24-26] Leg ulcers are also costly to healthcare providers.[12] It has been estimated that people with venous leg ulcers require a nursing visit/dressing change every 2 to 3 days and that all utilise GP office visits. The total annual cost to the NHS of managing people with healed venous leg ulcers has been estimated at

around £422,000,000 and unhealed venous leg ulcers at £2,781,000,000, with mean annual costs per patient as £2036 and £7886, respectively.[21]

2.4 Purpose and description of the technologies under assessment

Measurement of the ankle brachial pressure index (ABPI) is widely used in clinical practice, to help identify people with PAD who should not receive compression therapy. The current conventional method to measure ABPI consists of a sphygmomanometer and manual Doppler device. The procedure requires specific skills to be performed and can be protracted and unpleasant for those with leg ulcers.[13, 23] Automated devices, which have the advantage to reduce the time of ABPI measurement and, therefore, any associated discomfort for the patient, have been proposed as a potential alternative to manual Doppler. Moreover, if automated devices demonstrated a better accuracy than the conventional manual method in detecting the presence of PAD, could have the thus conferring benefits such as reduced time to treatment and improved outcomes for people with leg ulcers.[27] The technologies considered for this appraisal are devices that measure and calculate ABPI automatically, which are available to the NHS in England and have appropriate regulatory approval.

Characteristics of the technologies under assessment

These technologies include doppler, oscillometry and plethysmography-based devices. Doppler-based devices use a doppler probe and provide doppler waveforms signals as an output while oscillometry-based devices assess oscillations in the vessel wall and plethysmography-based devices assess blood volume changes. The signal measured by these methods is either directly used to estimate blood pressure or assist the measurement of this with a pressure cuff. Devices that do not provide doppler waveforms signals may provide information about the quality of arterial circulation in the ankles instead. However, it is unclear whether these alternative outputs can be considered equivalent to doppler waveform signals. Current technologies comprise the BlueDop Vascular Expert (BlueDop Medical); the boso ABI-system 100 (BOSCH + SOHN), WatchBP Office ABI (Microlife) and WatchBP Office Vascular (Microlife) oscillometry-based devices; the MESI ABPI MD (MESI) and MESI mTABLET ABI (MESI) oscillometry and plethysmography-based devices; and the Dopplex Ability Automatic ABI System (Huntleigh Healthcare), which is a plethysmography-based device. Table 1 illustrates the characteristics and features of the relevant devices.

Table 1 Summary of the characteristics of the devices considered for this appraisal

Test name	BlueDop Vascular Expert (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Components	• Hand-held egg-shaped Doppler ultrasound device and tablet computer with software	• 2 arm cuffs, 2 ankle cuffs • Control panel	• 2 cuffs • Blood pressure monitor • Can be used with PC	• 2 cuffs • Blood pressure monitor • Can be used with PC	• 3 cuffs • Control unit with results screen	• 4 wireless cuffs • Medical tablet computer • Can integrate with electronic health records	• 4 dual-chamber cuffs • Control unit with results screen • Options for integrated printer and USB cable
How is the test done?	• Blood pressure in arms taken with a conventional blood pressure cuff • Ankle pressure measurements taken without cuff • ABPI calculated automatically as ratio between mean ankle and arm blood pressure	• Cuffs attached to upper arms and lower legs • Simultaneous oscillometric measurement on all 4 limbs • ABPI calculated automatically	• Cuffs applied to arms and button pressed on monitor • Cuffs inflate and deflate automatically and simultaneously, sense oscillations in the artery wall, algorithm estimates systolic blood pressure • Cuff is left on the arm with the highest	• Cuffs applied to arms and button pressed on monitor • Cuffs inflate and deflate automatically and simultaneously, sense oscillations in the artery wall, algorithm estimates systolic blood pressure • Cuff is left on the arm with the highest	• Cuffs applied and button pressed on control unit • Cuffs inflate and deflate automatically and simultaneously sense change in artery volume (plethysmography) and oscillations in artery wall (oscillometry), algorithm estimates	• Same as MESI ABPI MD except blood pressure is first measured simultaneously in both arms and then both ankles together with re- measuring in the arm that had the highest pressure	• Cuffs applied and play button pressed on control unit • Cuffs automatically inflate and deflate and sense change in artery volume and estimates systolic blood pressure (pneumatic plethysmography) • ABPI automatically calculated

Test name	BlueDop Vascular Expert (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
			pressure, another cuff is applied to legs one at a time and blood pressure measured as before • ABPI calculated automatically	pressure, another cuff is applied to legs one at a time and blood pressure measured as before • ABPI calculated automatically	systolic blood pressure • ABPI calculated automatically		
Outputs	• ABPI • Doppler waveforms • Perfusion pressure • Vascular reserve • Can indicate whether the Doppler waveform signal is monophasic or multiphasic	• ABPI • Blood pressure • Difference s in blood pressure • Pulse • Pulse pressure • Indications of possible cardiac arrythmia disorders	• ABPI • Inter-arm difference • Atrial fibrillation (NICE MTG13)	• ABPI • Pulse wave velocity • Inter-arm difference • Atrial fibrillation (NICE MTG13)	• ABPI • Pulse waveforms • Pulse volume waveform (graph)	• ABPI • Pulse waveforms • Pulse volume waveform (graph) • Oscillations	• ABPI • Pulse waveforms • Pulse volume waveform (graph)
Time needed	• 1 minute to measure ABPI	• 1 minute to measure ABPI	• 10 to 15 minutes for whole procedure	• 10 to 15 minutes for whole procedure	• 1 minute to measure ABPI	• 1 minute to measure ABPI	• 3 minutes to measure ABPI

Test name	BlueDop Vascular Expert (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Patient resting and position for the test	• No need to rest before test • Sitting or lying down	• Need to lie quietly without talking	• At least 5 minutes rest before test • Need to lie flat and still for test	• At least 5 minutes rest before test • Need to lie flat and still for test	• No need to rest before test • Need to lie flat and still for test	• At least 5 minutes rest before test • Need to lie flat and still for test	• No need to rest before test • Need to lie flat and still for test
Indications for use	• Particularly beneficial for patients with heavily calcified arteries (for example, people with diabetes, people who smoke or renal patients) or patients who cannot tolerate a cuff at the ankle (for example, people with open wounds or lower extremity oedema) • Not suitable for paediatric or foetal use	• Suitable for people whose upper arm circumferences are between 22 cm and 48 cm and ankle circumferences are between 18 cm and 38 cm. • Should not be used in people with severe heart failure	• For adults and children aged 3 years or older. • Should not be used in people for whom the use of blood pressure cuffs is not suitable (for example in people with arm and leg stents).	• For adults and children aged 3 years or older. • Should not be used in people for whom the use of blood pressure cuffs is not suitable (for example in people with arm and leg stents).	• For people aged 10 years and over.	• For people aged 10 years and over.	• For people aged 18 years or older. • Should not be used in people with PAD (ankle systolic pressure<60m mHg) • Should not be used if the leg is affected by gangrene, recent skin graft, dermatitis, cellulitis, or untreated wounds. But it may be used on the unaffected leg. • Minimal training is

Test name	BlueDop Vascular Expert (BlueDop Medical)	boso ABI-system 100 (BOSCH +SOHN)	WatchBP Office ABI (Microlife)	WatchBP Office Vascular (Microlife)	MESI ABPI MD (MESI)	MESI mTABLET ABI (MESI)	Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
							needed to use the device.

2.5 Identification of important sub-groups

The following subgroups were considered relevant to the scope of this assessment.

- People with leg ulcers who require measurement of ABPI as part of their initial assessment.
- People with leg ulcers or healed leg ulcers who need re-assessment of ABPI as part of monitoring.
- People with diabetes, rheumatoid arthritis, systemic vasculitis, atherosclerotic disease advanced chronic renal failure or other conditions in which arterial calcification is common.
- People who have had lymph nodes removed or damaged, limb amputation or other conditions where blood pressure cannot be measured on both arms and legs.
- People with sickle cell disease who present with leg ulcers.

2.6 Comparators

In UK clinical practice, the current method for measuring ABPI as part of an initial clinical assessment for people with leg ulcers is a manual Doppler-based device: a hand-held Doppler ultrasound probe and a manually inflated blood pressure cuff (sphygmomanometer). The Doppler waveform output can identify health issues even if a person has an ABPI that does not indicate arterial disease. The procedure involves systolic pressure measurements on each limb and multiple measurements on the ankles. The Doppler probe is placed on the artery to assess the blood flow in the artery. The sound of the blood flow stops when the cuff is inflated around the artery and starts again when the cuff is deflated. The systolic blood pressure is then assessed by the sphygmomanometer for calculating the ABPI.

People are required to lie down and remain still before and during the test. The procedure may take between 30 min to 1 hour to be completed according to the expertise of the operator and may involve two operators. The assessment is typically carried out by district or community nurses at a person's home, care home or a leg ulcer clinic, or by practice nurses at GP practices. The healthcare setting depends on the person's ability to attend the assessment outside of their home and local service arrangements. Scarcity in the required skills and training to conduct ABPI

assessments may necessitate onward referral to specialist services after immediate care for the ulcer.

The NWCSP recommends a full clinical assessment of leg wounds within 14 days of initial presentation but there is variation in current clinical practice.[13]

2.7 Care pathways

Assessment and treatment of leg ulcers in the NHS is conducted according to the recommendations of the National Wound Care Strategy Programme (NWCSP).[13] Recommended immediate care for leg ulcers consists of cleansing and emollient, simple, low-adherent dressing with sufficient absorbency and mild graduated compression. People should be supported to self-care, if appropriate. If any of the following are present, immediate referral to the relevant clinical specialist is recommended: acute infection, symptoms of sepsis, acute or chronic limb threatening ischaemia, suspected deep vein thrombosis or suspected cancer. The NWCSP further recommends that assessment of leg wounds should take place within 14 days of original presentation.[13] The NWCSP and the NICE Guideline CG147 both recommend including vascular assessment of arterial supply by way of ABPI.[13, 23] The guideline recommends measuring the ABPI by recording systolic blood pressure in both arms and in the posterior tibial, dorsalis pedis and, where possible, peroneal arteries. It is recommended that measurements are taken manually using a Doppler probe of suitable frequency in preference to an automated system. The guideline also recommends documenting the nature of the Doppler ultrasound signals in the foot arteries (pattern of the Doppler waveforms). The type of waveform can provide information about the quality of arterial circulation and might identify issues even if a person has an ABPI that does not indicate arterial disease (e.g., people with arterial calcification). The index in each leg is calculated by dividing the highest ankle pressure by the highest arm pressure.

ABPI values are usually interpreted as follows:

- less than 0.8 suggest arterial disease
- less than 0.5 suggest severe arterial disease
- between 0.8 and 1.3 suggest no arterial disease and

- greater than 1.3 suggest arterial calcification.

Values above 1.5 indicate that the vessels are likely to be incompressible and the results are not reliable. Results may be misleadingly high in people with diabetes, rheumatoid arthritis, systemic vasculitis, atherosclerotic disease, and advanced chronic renal failure, and should be interpreted with caution. In addition, caution should be exercised in using compression therapy in people with diabetes due to potential arterial calcification and underlying sensory neuropathy.[28] The test can be uncomfortable for people with leg ulcers, due to both the need to lie still during the test and the placement and inflation of the blood pressure cuff near an ulcer.

Treatment of **venous leg ulcers** with an adequate arterial supply should include strong compression therapy that is intended to apply at least 40mmHg compression, according to NWCSP recommendations.[13] The SIGN Guideline 120 for management of chronic venous leg ulcers also indicates that compression of at least 40mmHg should be applied (this guideline was withdrawn in August 2020 and is currently being refreshed).[29] Strong multi-component compression bandaging should be offered to people with chronic ankle/leg oedema not reduced by elevation, abnormal limb shape, copious exudate or very fragile skin. Cardiac clinicians should be consulted regarding the balance of the cardiac burden and using compression in people with advanced, unstable cardiac failure.

People with **leg ulcers with signs of arterial disease** should be referred for vascular surgical/endovenous interventions and advice on compression and NICE clinical guideline CG147 on diagnosis and management of peripheral arterial disease should be followed.[23] Whilst awaiting vascular expertise, mild graduated compression is appropriate in oedematous legs with no signs of arterial insufficiency.

People with **leg ulcers of other or uncertain aetiology** should be referred to a dermatologist and mild graduated compression used in the meantime if there are no signs of arterial insufficiency. For treating leg ulcers in people with lymphoedema, People with lymphoedema and ABPI <0.5 should not receive compression. Those with ABPI of 0.5-0.8 should receive reduced compression of 15-25mmHG. In addition, all should be referred to a vascular specialist.[30]

People with **mixed aetiology ulcers** have both venous disease and arterial disease and, without intervention, the arterial disease will take priority in decision making about treatments. There is currently no consensus on the appropriate level of compression for treating mixed leg ulcers and various criteria have been implemented.[31] The European Wound Management Association position document on compression therapy makes the following recommendations for treating people with mixed arterial and venous ulcers:

- People with moderate arterial insufficiency with an ABPI 0.5-0.8: Reduced compression (15-25mg) if there is access to expert bandagers and teams with immediate access to vascular services; refer to vascular specialist particularly if continuing rest pain
- People with severe arterial insufficiency with an ABPI<0.5: Refer to vascular specialist. No compression. Many of these patients may benefit from either arterial surgery or interventional radiology.[32]

Other recommendations for treatment of mixed ulcers include referral to tissue viability in the first instance. People with mixed aetiology ulcers will require close monitoring and reassessment of vascular status every three months, or sooner if the ulcer deteriorates.[33]

Ongoing care of leg ulcers should continue with a review of the effectiveness of the treatment plan at each dressing change. Documentation by way of wound photography at least every 4 weeks is recommended and escalation to the local specialist service if the ulcer does not show significant improvement or deteriorates. Additionally, at 12 weeks, the local specialist service should be consulted for the same reasons. Ulcers that have improved but not healed at this stage should be reassessed.

To **prevent recurrence of leg ulcers**, advice should be offered on skincare, footwear, exercise and mobility, rest and limb elevation, nutrition and self-care and, if appropriate, smoking cessation and weight loss. For people with healed venous leg ulcers, the NWCSP guidelines recommend the continuation of compression therapy

and review every 6 months. Changes in symptoms or skin problems related to the compression hosiery should prompt a reassessment, including a vascular assessment of arterial supply.

The SIGN Guideline 120 for management of chronic venous leg ulcers indicated that compression of at least 40mmHg should be applied. The guideline was withdrawn in August 2020 and is currently being refreshed.[29]

Chapter 3. Assessment of clinical effectiveness

3.1 Systematic review methods

An objective synthesis of the evidence of the clinical effectiveness of devices for automated assessment of ankle brachial pressure index (ABPI) as compared to a manual Doppler device for assessing ABPI and peripheral artery disease in people with leg ulcers. The evidence synthesis was conducted in accordance with the general principles of the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in healthcare and the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[34, 35] The methods were pre-specified in a research protocol (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=327588).

Identification of studies

A sensitive literature search strategy was developed by an Information Specialist to identify published peer-reviewed studies. Major electronic databases were searched, including MEDLINE, Embase, Cochrane Library, Web of Science, and CINAHL. The initial focus of the search was the list of approved devices in the NICE final scope. There were no restrictions on the date or language of publication at the time of the search. The reference lists of studies selected for full-text appraisal were screened for additional studies. Websites of manufacturers, professional organisations, regulatory bodies and HTA organisations were searched to identify additional relevant reports. Any additional information on potentially relevant studies provided by the manufacturers of the devices of interest was also considered. All references were exported to Endnote for recording and deduplication. A draft MEDLINE search is detailed in Appendix 1.

Inclusion and exclusion criteria

Population

The NICE scope for this appraisal specified the population as people with leg ulcers who need assessment of ABPI. Initial screening of search results alongside material provided by the manufacturers of the respective devices suggested that there would be very few studies focusing on people with leg ulcers. Thus, the scope of this assessment was broadened to include studies with any population in which ABPI was measured using a suitable automated device, providing all other eligibility criteria were fulfilled.

Interventions

The interventions under investigation were the following automated devices for measuring ABPI:

- BlueDop Vascular Expert (BlueDop Medical)
- boso ABI-system 100 (BOSCH + SOHN)
- WatchBP Office ABI (Microlife)
- WatchBP Office Vascular (Microlife)
- MESI mTABLET ABI (MESI)
- MESI ABPI MD (MESI)
- Dopplex Ability Automatic ABI System (Huntleigh Healthcare)

Comparator

The current method for measuring ABPI as part of an initial clinical assessment for people with leg ulcers and/or PAD is a manual Doppler-based device: a hand-held Doppler ultrasound probe and a manually inflated blood pressure cuff (sphygmomanometer). The Doppler waveform output can identify health issues even if a person has an ABPI that does not indicate arterial disease. The procedure involves systolic pressure measurements on each limb and multiple measurements on the ankles. The Doppler probe is placed on the artery to assess the blood flow in the artery. The sound of the blood flow stops when the cuff is inflated around the artery and starts again when the cuff is deflated. The systolic blood pressure is then assessed by the sphygmomanometer for calculating the ABPI.

People are required to lie down and remain still before and during the test. The procedure may take between 30 min to 1 hour to be completed according to the expertise of the operator and may involve two operators. The assessment is typically carried out by district or community nurses at a person's home, care home or a leg ulcer clinic, or by practice nurses at GP practices. The healthcare setting depends on the person's ability to attend the assessment outside of their home and local service arrangements. Scarcity in the required skills/training to conduct ABPI assessments may necessitate onward referral to specialist services after immediate care for the ulcer.

Outcomes and study design

Relevant clinical outcomes and types of studies considered suitable for inclusion are reported in Tables 2 and 3 below.

Table 2 Eligibility criteria for research question 1 (performance of devices for automated assessment of ABPI for detecting the presence of PAD)

Population	**People who require ABPI measurement**
Devices under investigation	• BlueDop Vascular Expert (BlueDop Medical) • boso ABI-system 100 (BOSCH + SOHN) • WatchBP Office ABI (Microlife) • WatchBP Office Vascular (Microlife) • MESI mTABLET ABI (MESI) • MESI ABPI MD (MESI) • Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Current method for measuring ABPI and detecting PAD	Manual Doppler device: a hand-held Doppler ultrasound probe and a manually inflated blood pressure cuff.
Reference standard for detecting PAD	Imaging technologies including Duplex ultrasound, Angiography, Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA).
Outcomes	<u>Measures for consideration may include:</u> • Accuracy to detect peripheral arterial disease • Concordance between measurements by manual and automated devices • Concordance between measurements by different automated devices • Technical failure rate • Time required for using the device and calculating ABPI • Resources needed to do the test (for example, number of people or grade of staff needed to do the test) • Acceptability and experience of using the device

Study design	• Any cross-sectional study investigating the diagnostic performance of a single automated device as an alternative to a manual Doppler method for the measurement of ABPI and detection of PAD. • Any fully paired direct comparison in which one automated device is compared with either a manual Doppler method or another automated device in the same study population against an acceptable reference standard (e.g., Duplex ultrasound, Angiography, CTA, MRA). • Studies that assess the agreement between ABPI measurements obtained from an automated device with those obtained from a manual Doppler method or between 2 (or more) automated devices. • Studies of any design providing information on the use of the test (time to do test, technical failure rate, resources needed).
Healthcare setting	• Primary care (GP practice) • Community care (people's homes, care homes, community hospitals, leg ulcer clinic) • Secondary care

Table 3 Eligibility criteria for research question 2 (impact on clinical outcomes)

Population	**People who require ABPI measurement**
Devices under investigation	• BlueDop Vascular Expert (BlueDop Medical) • boso ABI-system 100 (BOSCH + SOHN) • WatchBP Office ABI (Microlife) • WatchBP Office Vascular (Microlife) • MESI mTABLET ABI (MESI) • MESI ABPI MD (MESI) • Dopplex Ability Automatic ABI System (Huntleigh Healthcare)
Comparator	Measuring ABPI and assessing arterial circulation using a handheld Doppler probe and manual blood pressure sphygmomanometer.

Outcomes	Clinical outcomes for consideration may include: • Morbidity (including any adverse events caused by assessment or treatment) • Mortality Patient-reported outcomes for consideration may include: • Health-related quality of life • Acceptability of using the device (including for example the position during the testing procedure) and patient experience. Intermediate measures for consideration may include: • Time to ulcer treatment • Time to ulcer healing • Number of referrals to specialist services (for example for ulcers that are not healing) • Number of hospitalisations • Number of leg amputations • Other healthcare resource use • Impact of test result on clinical decision-making • Rate of testing
Study design	• Randomised controlled trials • Single arm trials • Prospective and retrospective cohort studies
Healthcare setting	• Primary care (GP practice) • Community care (people's homes, care homes, community hospitals, leg ulcer clinic) • Secondary care

Study selection and data extraction

Two reviewers (MC, MB) independently screened the citations identified by the search strategies. This strategy differed from that detailed in the protocol, which specified that the results of the searches would be screened by one reviewer with a random sample of 20% of citations independently screened by a second reviewer. Potentially relevant articles were retrieved in full and independently screened by the same two reviewers for eligibility based on the pre-specified inclusion criteria. One reviewer (MC) screened all documents which had

been submitted by the companies with an interest in the respective interventions using the same criteria as used on the results of the search strategies. Potentially relevant studies were selected and checked for relevance by a second reviewer (MB).

Disagreements were resolved by discussion. Multiple publications of the same studies were linked and considered together.

One reviewer (MC) extracted data from each eligible study using a customised form developed for the purpose of this assessment. A second reviewer (MB) cross-checked the extracted data. This strategy, which differs from that specified in the research protocol, (i.e., two independent reviewers involved in data extraction), was adopted due to time constraints. Any disagreements were resolved by discussion or consultation with a third reviewer (LA).

The following information was recorded from each study:

1. Characteristics of studies: first author, year of publication, country, language, setting, objectives, inclusion and exclusion criteria, type of enrolment, source of funding and conflicts of interest.
2. Characteristics of study participants: age, sex, comorbidities, number of enrolled participants, numbers of limbs and participants included in the analysis, numbers and reasons for withdrawal.
3. Skills of the operator performing the measurement of ABPI using the devices under investigation or the reference device (i.e., years of experience).
4. Characteristics of the automated devices under investigation (BlueDop Vascular Expert [BlueDop Medical], boso ABI_system 100 (BOSCH + SOHN); WatchBP Office ABI [Microlife]; WatchBP Office Vascular [Microlife]; MESI ABPI MD [MESI]; MESI mTABLET ABI [MESI]; Dopplex Ability Automatic ABI System [Huntleigh Healthcare]).
5. Characteristics of the reference standard device (i.e., manual Doppler method, Duplex ultrasound, angiography, CTA, MRA)
6. The reported number of true positives, false positives, false negatives and true negatives and, when available, the area under the receiver-operating characteristic curve (AUC) for each device for each relevant outcome.
7. Measures assessing agreement between devices' measurements (correlation and reliability measures).

8. Relevant patient-reported, clinical and intermediate outcome measures, and information related to the use of the devices.

Assessment of risk of bias

Tools were used to assess the risk of bias of included studies according to their study design. QUADAS-2 criteria were used to assess the quality of included diagnostic studies.[36] QUADAS-2 consists of four domains: patient selection, index test, reference standard and flow and timing. Each domain is assessed in terms of 'low', 'high' or 'unclear' risk of bias, and the first three in terms of concerns regarding 'low', 'high' or 'unclear' applicability. The QUADAS-C tool was used to assess the methodological quality of comparative diagnostic accuracy studies.[37] The following decision rules were applied to these assessments. The patient selection domain was judged to be at an 'unclear' risk of bias in studies that did not report the study exclusion criteria. For the purposes of this assessment, the results of the automated devices of interest (i.e., index tests) are considered to be objective measurements (as they are automatically calculated by the respective devices) and not subject to interpretation. Thus, in the 'index test' domain, the item '*Were the index test results interpreted without knowledge of the results of the reference standard?*' was answered 'yes', indicating a low risk of bias. For the corresponding item regarding the reference standard, the response was 'yes' if the reference standard test had been conducted prior to the index test or was conducted after the index text but the operator was explicitly blinded to the automated test result. If both sets of measurements were conducted by the same operator, then the interpretation of the reference standard was classed as 'high' risk of bias if the automated device was utilised before the manual device or the order of devices was random, or 'unclear' risk of bias if the order of devices utilised was not reported, unless the operator had been explicitly blinded to results of the automated device. In the 'flow and timing' domain, the item 'was there an appropriate interval between index test and reference standard' was classed as 'no' if the resting period before testing was considered insufficient (i.e., less than 10 minutes) or was not reported. The item 'were all patients included in the analysis' was assessed as a 'no' response where at least 10% of participants were not included in the analysis.

For assessing the quality of non-randomised evidence reporting quantitative data on the clinical utility of the devices we used the checklist developed by the HSRU, University of

Aberdeen, in partnership with the NICE Review Body for Interventional Procedures (ReBIP). The ReBIP checklist was adapted from several sources and comprises 17 items, which assess the following aspects: generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow-up, and performance of the analysis.[34, 38-40] Individual items were rated as 'yes', 'no' or 'unclear'. A rating of 'yes' indicated a low risk of bias.

One reviewer (MC) extracted the data, and a second reviewer (MB) checked the data extracted. Any disagreements were resolved by consensus.

Data synthesis and analysis

Analyses were performed using the methods recommended by Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[41] For each automated device we extracted data to populate 2x2 contingency tables (TP, FP, FN, and TN) of test results cross-classified against those of the manual Doppler method or any other acceptable reference standard. If not reported in the included studies, we back calculate the number of TP, FP, FN, and TN cases using sensitivity and specificity estimates, the total number of patients and the prevalence of PAD. Back calculation of data was not always precise due to the rounded of available published data. This impacted also on the precision of the confidence intervals and where these were out-with the plausible range they were truncated to be between 0 and 1.

Where appropriate, we used the Hierarchical Summary ROC (HSROC) with random effects model implemented in STATA® (using the METANDI command) to assess the overall performance of each device. This statistical model provides summary estimates of sensitivity and specificity with their corresponding 95% confidence region and 95% prediction region. In accordance with the STATA requirements, we performed meta-analyses only when diagnostic data from four or more studies were available.[42]

Heterogeneity was assessed by visual inspection of the forest plots of sensitivity and specificity and of the prediction region in the summary ROC plots, when meta-analyses were performed. There were insufficient data, to allow investigation of sources of heterogeneity in estimates of test accuracy by adding covariates to the statistical model.

We initially planned to conduct sensitivity analysis to assess the impact of studies' methodological quality on the meta-analyses results by restricting analyses to studies at low risk of bias; however, due to the limited number of studies available for each automated device this proved unfeasible.

Measurements of agreement between the manual and automated devices or between measurements by different automated devices (e.g., Pearson's correlation coefficient, intraclass correlation coefficient, Cohen's kappa coefficient, Bland Altman analysis) were tabulated and described narratively.

Statistically significant was considered for P values of less than 0.05. Stata® software version 17.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.[43] Graphs were made using either Stata or Review Manager software version 5.3 (Nordic Cochrane Centre, Copenhagen).

Patient and public involvement

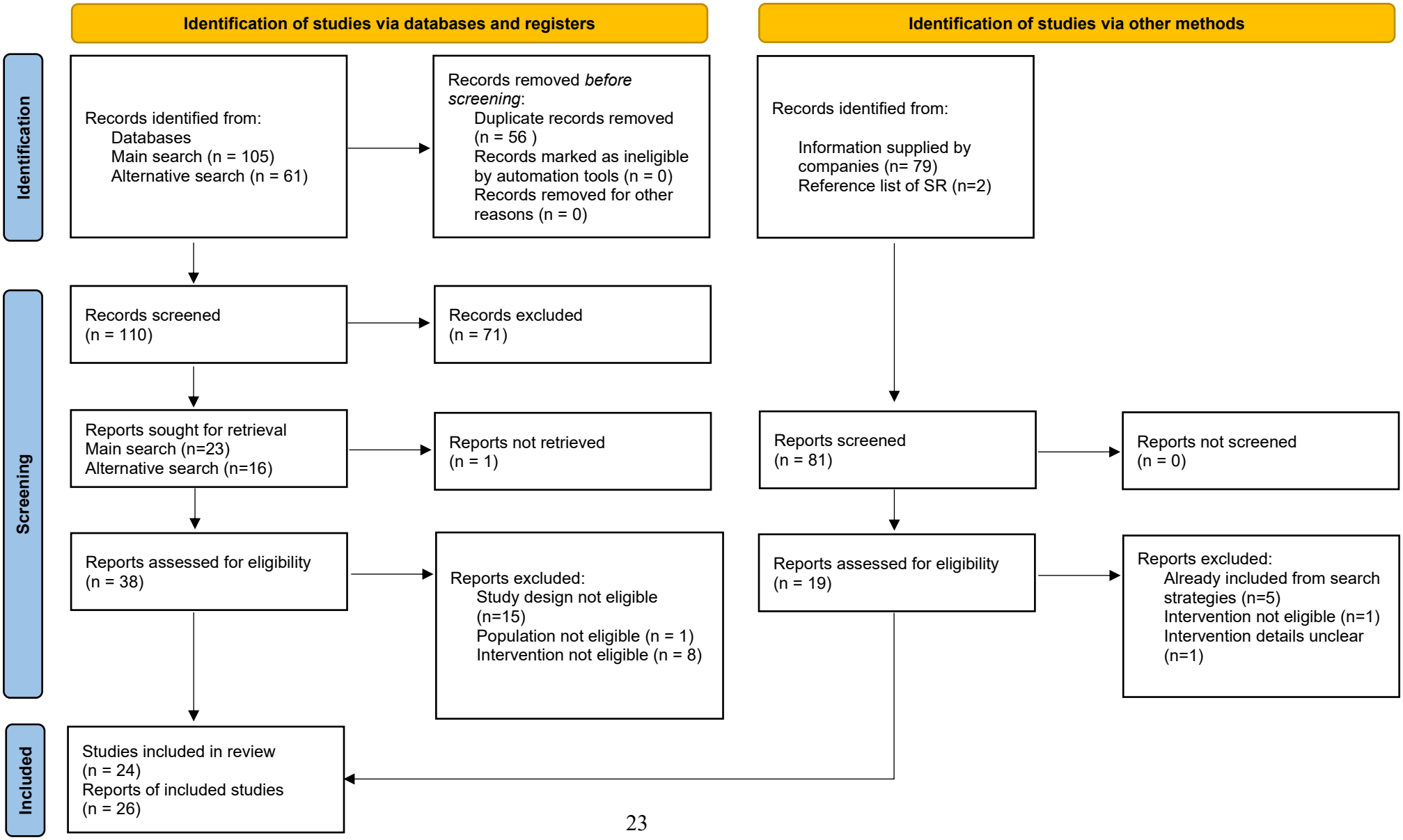
This assessment was conducted as part of the NICE Diagnostics Programme (DAP), in which a range of stakeholders such as members of the public and national groups representing patients or carers are involved in the interpretation of the identified evidence. Thus, it was not considered necessary to involve further patient representatives or lay people.

3.2 Results of the assessment of clinical effectiveness

Results of the literature searches

166 records were retrieved by the database searches. In addition, 78 records were supplied by the respective companies, giving a total of 244 records. After de-duplication, 110 abstracts and all 79 records from the companies were screened for relevance. Two records were identified from the reference list of an existing systematic review. Of these, 57 reports were selected for full text assessment from which 25 met our inclusion criteria, detailing a total of 23 studies. Reports detailing interim results of one further eligible study were submitted by the respective company after the screening process, resulting in a total of 24 studies reported in 26 publications (see Figure 1).

Figure 1 PRISMA 2020 flow diagram



Characteristics of included studies

A total of 24 studies published in 26 reports were included in the review of clinical effectiveness. Characteristics of the included studies are presented in Table 4. Two studies focused on assessment of ABPI in people with leg ulcers,[44, 45] whilst the populations of the remaining studies were either people with symptoms of PAD,[46-53] people with risk factors for PAD,[54-56] people otherwise requiring assessment of ABPI,[57-65] or people taking part in an epidemiology study.[66, 67] Six studies were conducted in the UK,[44, 45, 48, 49, 51, 57] two studies in each of Czech Republic[58, 66] and France,[52, 62] three in Spain[46, 64, 67] and one each in Hungary,[59] Switzerland,[47] Iran,[54] New Zealand,[60] Sweden,[50] Netherlands,[61] Italy,[63] Slovenia,[53] India,[55] Poland,[65] and Greece.[56] The studies by Boilley et al. and Catillon et al. appear to have been conducted by the same research group with overlapping recruitment periods.[52, 62] While it is unclear whether the same participants may have been included in both studies, it is worth noting that the two studies report different outcome measures.

One study assessed the performance of two automated devices (WatchBP Office and MESI ABPI MD) for measuring ABPI whilst the remaining studies assessed only the performance of one automated device.[64] The BlueDop Vascular Expert device was assessed by a published study and an ongoing study for which the sponsor provided confidential interim results,[46, 57] the BOSO ABI-System 100 device by four studies,[47, 58, 59, 66] the Dopplex Ability by six studies,[44, 48, 49, 51, 54, 60] the MESI ABPI MD by seven studies,[45, 50, 52, 53, 61-63] and the WatchBP Office ABI device by four studies.[55, 56, 65, 67] We did not identify any study assessing the performance of WatchBP Office Vascular or MESI mTABLET ABI for measuring ABPI in people with leg ulcers or symptoms of PAD. The reference standard was manual Doppler in 20 studies[44, 45, 47-53, 55, 56, 59-67] and duplex ultrasound in four studies.[46, 54, 57, 58] Two of these four studies also assessed the performance of the manual Doppler. All studies were published in English except for the studies by Jarai et al. and Raya et al. that were published in Hungarian and Spanish, respectively.[59, 64] Google Translate was used to facilitate screening and data extraction of these studies.

Characteristics of the automated devices under investigation and the reference standard device for each included study are reported in Appendix 2. The healthcare professional assessing ABPI was reported in 17 studies: six studies reported the involvement of a vascular

specialist,[44, 46, 52, 57, 60-62] five involved trained nurses,[48, 54, 59, 64, 67] three studies an experienced physician or technician,[47, 65, 66] two studies involved a podiatrist,[49, 51] and one study involved general practice staff.[45]

Baseline characteristics of participants in the included studies are reported in Appendix 3. Mean age of participants ranged from 27.5 years[55] to 72.5 years[63] and the proportion of male participants ranged from 39.8%[54] to 100%.[55]

Table 4 Characteristics of included studies

Study ID, country [secondary study]	Study design/ consecutive enrolment?	Automated device/ Reference device	Population	Main exclusion criteria	Funding source	N analysed: Participants/ Limbs
PEOPLE WITH LEG ULCERS						
Welsh 2016, UK[44]	Cross-sectional/NR	Dopplex Ability/ Manual Doppler	People with leg ulcers who need assessment of ABPI.	• Marked oedema or lymphoedema • Signs of severe ischaemia or arterial disease	NR	22/NR
Green 2020, UK[45] [Boast 2019][68]	Cross-sectional/NR	MESI ABPI MD/ Manual Doppler	People with leg ulcers who need assessment of ABPI.	NR	NHS Executive's Estate and Technology Transformation Fund	145/NR
NOT PEOPLE WITH LEG ULCERS						
NCT05073510 2022, Spain[46]	Prospective cohort/NR	BlueDop Vascular Expert/ Duplex ultrasound	People with suspected or history of PAD.	• Lower extremity wound or compromised skin of the legs that prevents access to the studies arteries • Presence of anatomic or comorbid conditions that could limit ability to fully participate in the study	BlueDop Medical Ltd	[redacted]
Kordzadeh 2018, UK[57]	Prospective cohort/Yes	BlueDop Vascular Expert/ Duplex ultrasound	People referred to vascular outpatient services (one-stop clinic).	NR	NR	166/276

Study ID, country [secondary study]	Study design/ consecutive enrolment?	Automated device/ Reference device	Population	Main exclusion criteria	Funding source	N analysed: Participants/ Limbs
Homza 2019, Czech Republic[58]	Cross-sectional/Yes	BOSO ABI-System 100/ Duplex ultrasound	People with diabetes presenting to a cardiovascular outpatient clinic.	• Critical limb ischaemia • Limb amputation • Renal failure grade 5 • Active cancer	NR	62/NR
Jarai 2018, Hungary[59]	Cross-sectional/Yes	BOSO ABI-System 100/ Manual Doppler	People enrolled in the Hungarian Hypertension Society's ERV Registration Program	NR	NR	397/793
Wohlfahrt 2011, Czech Republic[66]	Cohort/ NR	BOSO ABI-System 100/ Manual Doppler	General population (1% random sample of Czech population).	NR	Internal Grant Agency of the Ministry of Health of the Czech Republic	839/1678
Diehm 2009, Switzerland[47]	Cross-sectional/ Yes	BOSO ABI-System 100/ Manual Doppler	People with chronic symptomatic PAD.	• Major amputations • Open wounds or ulceration in lower limbs • Previous bypass surgery or angioplasty • Marked oedema • BMI>40 • Atrial fibrillation	NR	50/98

Study ID, country [secondary study]	Study design/ consecutive enrolment?	Automated device/ Reference device	Population	Main exclusion criteria	Funding source	N analysed: Participants/ Limbs
Babaei 2020, Iran[54]	Cross-sectional/ NR	Dopplex Ability/ Ultrasound duplex scan	People with diabetes and symptoms of PAD.	• Cellulitis • Lymphoedema • Thrombophlebitis • DVT in past 6 months • Congestive heart failure • Wound preventing Doppler probe or ankle cuff placement	None	303/606
Millen 2018, New Zealand[60]	Cross-sectional/ NR	Dopplex Ability/ Doppler air plethysmography-based Parks Flo-Lab system	People attending for standard non-invasive vascular assessment	• Lower limb ulcers • Oedema • Upper limb arteriovenous fistulas	None	66/129
Davies 2016, UK[48] [Davies 2014][69]	Prospective observational and cross-sectional/NR	Dopplex Ability/ Doppler ultrasound	People with CV risk factors but no known CV disease or diabetes.	NR	Huntleigh Healthcare and European Knowledge Economy Skills Scholarship	380/724
Lewis 2016, UK[49]	Cross-sectional/ Yes	Dopplex Ability/ Duplex ultrasound	People referred for lower limb arterial assessment.	• Lymphoedema • Thrombophlebitis • Cellulitis • DVT • Bilateral limb amputation • Mastectomy	Health and Care Research Wales, and Huntleigh Diagnostics	189/109

Study ID, country [secondary study]	Study design/ consecutive enrolment?	Automated device/ Reference device	Population	Main exclusion criteria	Funding source	N analysed: Participants/ Limbs
Lewis 2010, UK[51]	RCT cross-over/ NR	Dopplex Ability/ Manual Doppler	People with symptoms of PAD.	• Bilateral limb amputation	NR	NR/295
Zebari 2022, Sweden[50]	Prospective cohort/Yes	MESI ABPI MD/ Manual Doppler	Patients attending a vascular surgery outpatient clinic.	• Extensive ulceration at ankle level	Swedish state, ALF agreement, Swedish Heart-Lung Foundation and Hjart-Lungfonden	153/306
Hageman 2021, Netherlands[61]	Cross-sectional/ Yes	MESI ABPI MD/ Manual Doppler	Patients referred to vascular laboratory for ABI measurement.	• Major limb amputation • Marked oedema in one or both feet • Upper extremity arteriovenous fistulas • Axillary lymphadenectomy	No relevant financial relationships	201/402
Boilley 2020, France[52]	Cross-sectional/ Yes	MESI ABPI MD/ Manual Doppler	Patients referred to vascular medicine unit for suspected PAD based on exertional limb symptoms.	NR	None	102/NR
Catillon 2020, France[62]	Cross-sectional/ NR	MESI ABPI MD/ Doppler ultrasound	Patients with a scheduled Doppler ultrasound appointment	• Wounds	None	43/NR

Study ID, country [secondary study]	Study design/ consecutive enrolment?	Automated device/ Reference device	Population	Main exclusion criteria	Funding source	N analysed: Participants/ Limbs
			assessed either by medical students or vascular specialists.			
Varetto 2019, Italy[63]	Cross-sectional/ Yes	MESI ABPI MD/ Manual Doppler	Patients undergoing vascular consultation.	NR	NR	185/370
Span 2016, Slovenia[53]	Cross-sectional/ NR	MESI ABPI MD/ Manual Doppler	People with symptoms of PAD.	• Known arrhythmia • Upper extremity • Arteriovenous fistulas or symptomatic critical limb ischaemia • Ulcers or major lower leg amputation	NR	136/NR
Verma 2022, India[55]	Cross-sectional/ NR	WatchBP Office ABI/ Vascular Doppler device	Construction workers (described as a "high-risk population").	• Major amputation in upper or lower limbs • Open wounds or ulceration in lower limbs • Marked oedema of one or both feet	None	200/NR
Raya 2019, Spain[64]	Cross-sectional/ Yes	WatchBP Office, MESI ABPI MD/ Manual Doppler	People attending a primary care centre (for any reason).	• Injuries • Phlebitis • Lymphangitis • Venous thrombosis	Catalan Society of Family and Community Medicine	202/404

Study ID, country [secondary study]	Study design/ consecutive enrolment?	Automated device/ Reference device	Population	Main exclusion criteria	Funding source	N analysed: Participants/ Limbs
Rodriguez-Roca 2014, Spain[67]	Cross-sectional/ NR	WatchBP Office ABI/ Manual Doppler	People without PAD seen in primary care	NR	Governmental grant from the Socio-Sanitary Foundation of Castile-La Mancha	322/NR
Sinski 2013, Poland[65]	Cross-sectional/ Yes	WatchBP Office ABI/ Ultrasound Doppler	People with known coronary artery disease.	• Peripheral oedema • Atrial fibrillation	Medical University of Warsaw	80/158
Kollias 2011, Greece[56]	Cross-sectional/ NR	WatchBP Office ABI/ Manual Doppler	People with cardiovascular risk factors attending a hypertension or diabetes outpatient clinic.	• Atrial fibrillation • Incompressible ankle arteries • Excessive ankle oedema • Inflammatory ankle lesions	Microlife, Widnau, Switzerland	93/186

Note. PAD, peripheral artery disease; CAD, coronary artery disease; CV, cardiovascular; NR, not reported

Risk of bias assessments

Twenty-one studies were assessed using the QUADAS-2 tool,[46-63, 65-67] one study using QUADAS-C[64] and two using the ReBIP checklist.[44, 45]

Of the 21 studies assessed with the QUADAS-2 criteria, five studies were at unclear risk of bias for the patient selection domain due to lack of reporting exclusion criteria.[52, 57, 63, 66, 67] Risk of bias was low across all studies for the index test domain but unclear for nine studies in the reference standard domain [redacted] and/or whether the operator was blinded to the results of the automated device measurement.[55, 56, 58-61] In the study by Boilley (2020), all measurements were conducted by one operator, with the manual Doppler measurement taken after the automated device measurement.[52] Thus, risk of bias was assessed as high for the reference standard domain. The flow and timing domain was judged to be at high risk of bias in seven studies due to either insufficient resting time prior to testing[54, 66, 67] or [redacted] The risk of bias in the flow and timing domain was assessed as unclear in six studies due to the lack of information about either the number of participants included in the analysis[51] or the resting period before the actual testing procedure.[49, 55, 57, 59, 60] In general, applicability concerns were low across studies.

The one study assessed using QUADAS-C was assessed as low risk of bias across all domains except reference standard and flow and timing due to lack of information regarding the resting period before testing and the order of administration of the automated devices.[64]

Two studies - Welsh 2016 and Green 2020 - were assessed using the ReBIP tool.[44, 45] The study by Welsh included a representative sample, clearly defined inclusion and exclusion criteria and participants at a similar point in disease progression. The study by Green did not report inclusion and exclusion criteria and information on the representativeness of the sample was limited. Both studies involved prospective data collection, with clearly defined interventions delivered in an appropriate setting, and important and objective outcomes. Information on withdrawals was not reported by either study and there was insufficient information to assess whether participants who dropped out were similar to those who completed the study or whether important prognostic factors had been identified.

Full details of risk of bias assessments are reported in Appendix 4.

3.3 Clinical effectiveness results

Diagnostic outcomes

People with leg ulcers

A summary of key findings of the two studies involving people with leg ulcers is presented in Table 5.[44, 45] These studies did not report the sensitivity and specificity of the automated devices for diagnosing PAD.

Table 5 Summary of key findings of studies recruiting people with leg ulcers

Study ID	Automated device/ Reference device	Population setting	Patients analysed, n	Summary of findings
Welsh 2016 (UK)[44]	Dopplex Ability/ Manual Doppler	People with leg ulcers attending a community leg ulcer clinic for ABPI assessment	22	• 56% of Dopplex Ability readings were higher than manual Doppler readings, 9% were lower and 34% were equal • Mean (SD) difference between methods: 0.068 (0.175) • Mean Dopplex readings when given first: 1.04 • Mean Dopplex readings when given second: 1.20
Green 2020 (UK)[45]	MESI ABPI MD/ Manual Doppler	People with leg ulcers who need assessment of ABPI in general practice	145	• 17% of readings with the MESI ABPI MD device were accurate according to manual Doppler measurement

Acceptability and experience of using the device

The two studies that assessed ABPI in people with leg ulcers both reported information on the acceptability of the respective automated devices and experience of their use.[44, 45] The study by Welsh et al. reported that the Dopplex Ability was easier to use than the manual Doppler and more convenient in terms of testing time.[44] This study reported also that the majority of patients found the automated device to be acceptable, but some felt discomfort when the cuff was fully inflated. The study by Green et al. acknowledges some issues related to the use of the automated device including the length of time and complexity of the initial setting up of the software; the insufficient general practice personnel, and the fact that GPs may not refer patients for ABPI assessments due to limited availability of appointments.[45]

They also reported that several GP practices felt that wound care was not within the remit of their practice and would be better managed by leg ulcers services.[45] The reported benefits of the MESI ABPI MD include speed, simplicity of use, accuracy and printouts of the assessment, as well as enhanced patient management and appropriate referral to more specialised services. Half of the staff involved in the study expressed the intention to continue using the MESI ABPI MD device but pointed out that additional resources such as staff, time and funding would be needed.

People not with leg ulcers

Given the lack of studies enrolling people with leg ulcers and the fact that ABPI measurement in people with leg ulcers is used to identify patients with peripheral arterial disease who should not receive compression therapy, we considered it relevant to summarise the evidence on the ability of the automated devices to detect PAD in people with no leg ulcers who required ABPI measurement.

A summary of the key findings for the 22 studies assessing patients without leg ulcers is presented in Table 6. A total of 4258 people were analysed. Most people were referred to a vascular service or had cardiovascular risk factors. The prevalence of PAD was 100% in one study that focused on people with a previous diagnosis of PAD[47] and ranged from 2%[54, 66] to 80%[52] across the remaining studies. Seventeen studies reported sensitivity and specificity estimates of the automated device for detecting PAD with either manual Doppler or Duplex ultrasound used as the reference device.[46, 48-50, 52-61, 64-66]. Across studies, sensitivity estimates ranged from 20% for the Dopplex Ability[54] to 95% for the BlueDop Vascular Expert[57] device; specificity estimates ranged from 67%[50] to 100%.[55]

Results according to the type of automated device are reported below.

BlueDop Vascular Expert device

Data on the BlueDop Vascular Expert device were provided by a published study[57] and an ongoing study[46] for which the company provided confidential interim results. Both studies assessed people who were referred to a vascular service and compared the performance of the BluDop Vascular Expert device with that of Duplex ultrasound (255 participants in total). The study by Kordzadeh et al. reported a sensitivity of 95% and a specificity of 90%.[57] The

interim results of the ongoing study show a moderate sensitivity ([redacted]) and good specificity ([redacted]).[46] Prevalence of PAD was not reported.

BOSO ABI-System 100 device

The BOSO ABI-System 100 device was assessed by four.[47, 58, 59, 66] The patient population varied across studies (see Table 6). Three studies (1298 participants in total) provided sensitivity and specificity estimates.[58, 59, 66] Sensitivity of the BOSO ABI-System 100 device ranged from 61% in a sample of diabetic people[58] to 77% in the general population or people enrolled in a hypertension programme.[59, 66] Specificity estimates were higher across studies and ranged from 94%[58, 59] to 98%.[66] Prevalence of PAD was not consistently reported across studies (see Table 6) and as expected varied according to the characteristics of the enrolled patient population (e.g., 2% among a random sample derived from the general population and 100% among a sample of patients with an established PAD diagnosis).

Dopplex Ability

The Dopplex Ability device was assessed by five studies that enrolled people with symptoms of PAD or at risk of cardiovascular events.[48, 49, 51, 54, 60] Four studies (938 participants in total) provided estimates of accuracy.[48, 49, 54, 60] The reference device was either manual Doppler[48, 60] or Duplex ultrasound.[49, 54] Sensitivity varied considerably across studies and ranged from 20% in a sample of diabetic people[54] to 79% in people referred for lower limb arterial assessment;[49] specificity ranged from 86%[60] to 96%.[48, 54] Prevalence of PAD ranged from 2%[54] to 63%.[49]

For the BlueDop Vascular Expert, BOSO ABI-System 100, and Dopplex Ability devices there were too few studies to conduct a meaningful meta-analysis.

MESI ABPI MD device

The MESI ABPI MD device was assessed by seven studies enrolling people who had been referred to a vascular service or to a primary care centre, and people presenting with symptoms of PAD.[50, 52, 61-64, 67] Five studies provided estimates of accuracy;[50, 52, 53, 61, 64] sensitivity ranged from 57%[53] to 75%[50] and specificity estimates from 67%[50] to 99%[53]. Prevalence of PAD ranged from 6%[64] to 80%.[52] Sample size ranged from 102 to 202 participants.

We were able to combine the results of five studies (742 participants in total; 243 (33%) with PAD), which provided relevant diagnostic data. The pooled sensitivity of MESI ABPI MD for detection of PAD was 67% (95% CI 59% to 74%) and the pooled specificity was 94% (95% CI 83% to 98%). Figures 2 and 3 below show the forest plot and summary ROC plot depicting the accuracy of MESI ABPI MD measurement versus manual Doppler measurement for detection of PAD.

Figure 2 Forest plot of MESI ABPI MD measurement versus manual Doppler measurement for PAD diagnosis.

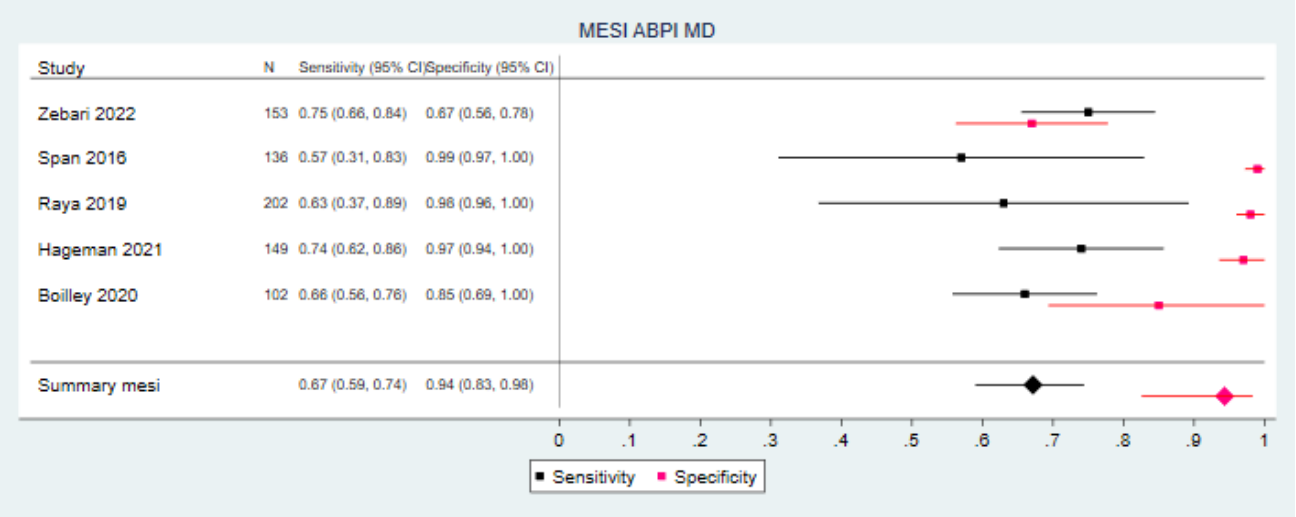
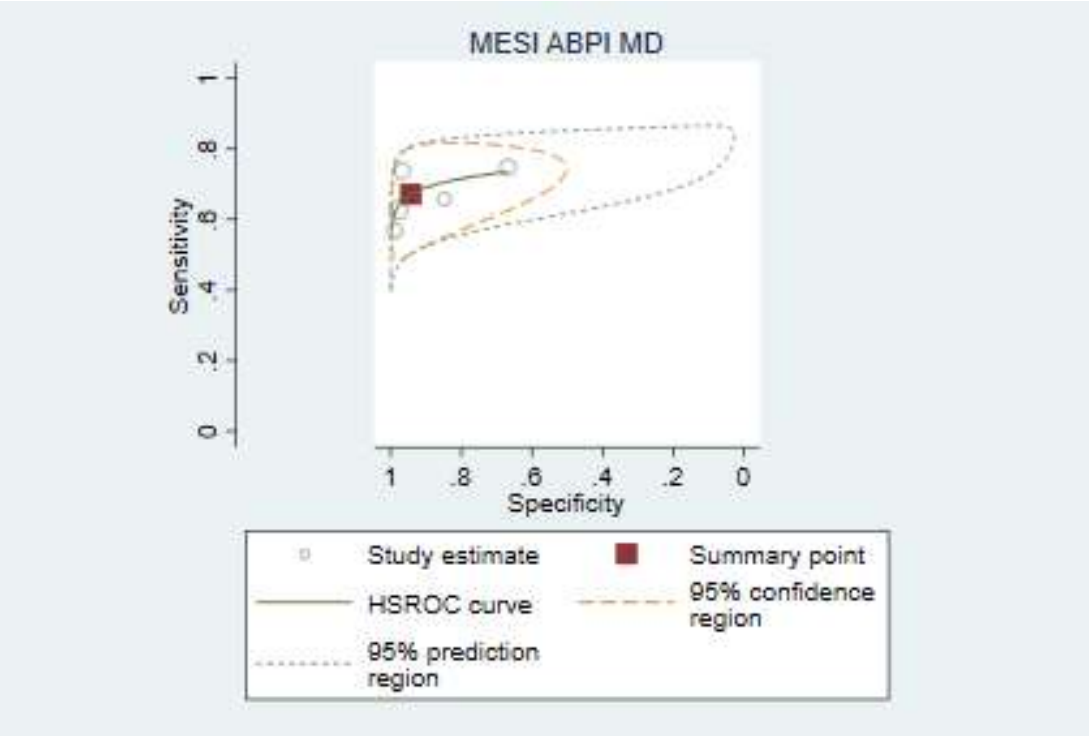


Figure 3 Summary ROC plot for ABPI measurement using the MESI ABPI MD device



WatchBP Office ABI device

The WatchBP Office ABI device was assessed by five studies enrolling people with cardiovascular risk factors or established coronary artery disease, people seen in primary care and people sampled from the general population.[55, 56, 64, 65, 67] Four studies provided estimates of accuracy.[55, 56, 64, 65] Sensitivity estimates ranged from 44 %[64] to 83%[56] and specificity estimates from 97%[56] to 100%[55] Prevalence of PAD ranged from 6%[55, 64] to 40%.[65] Sample size ranged from 80 to 202 participants.

We were able to combine the results of four studies (575 participants in total; 73 (13%) with PAD), which provided relevant diagnostic data. The pooled sensitivity of WatchBP Office ABI for detection of PAD was 53% (95% CI 37% to 69%) and the pooled specificity was 98% (95% CI 96% to 99%). Figures 4 and 5 below show the show the forest plot and summary ROC plot depicting the accuracy of WatchBP Office ABI versus manual Doppler ABPI for detection of PAD.

Figure 4 Forest plot of WatchBP Office ABI measurement versus manual Doppler measurement for PAD diagnosis

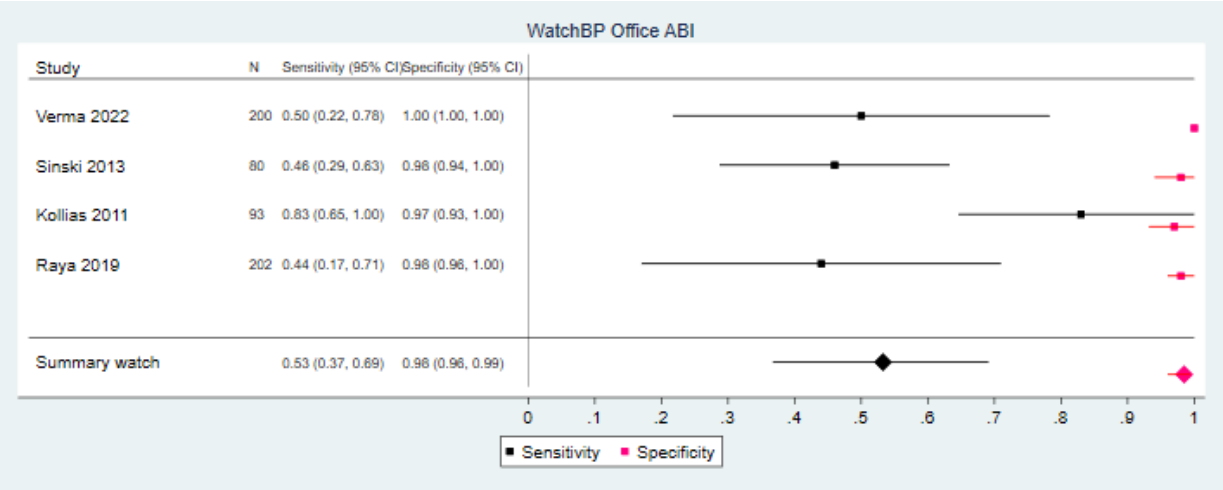
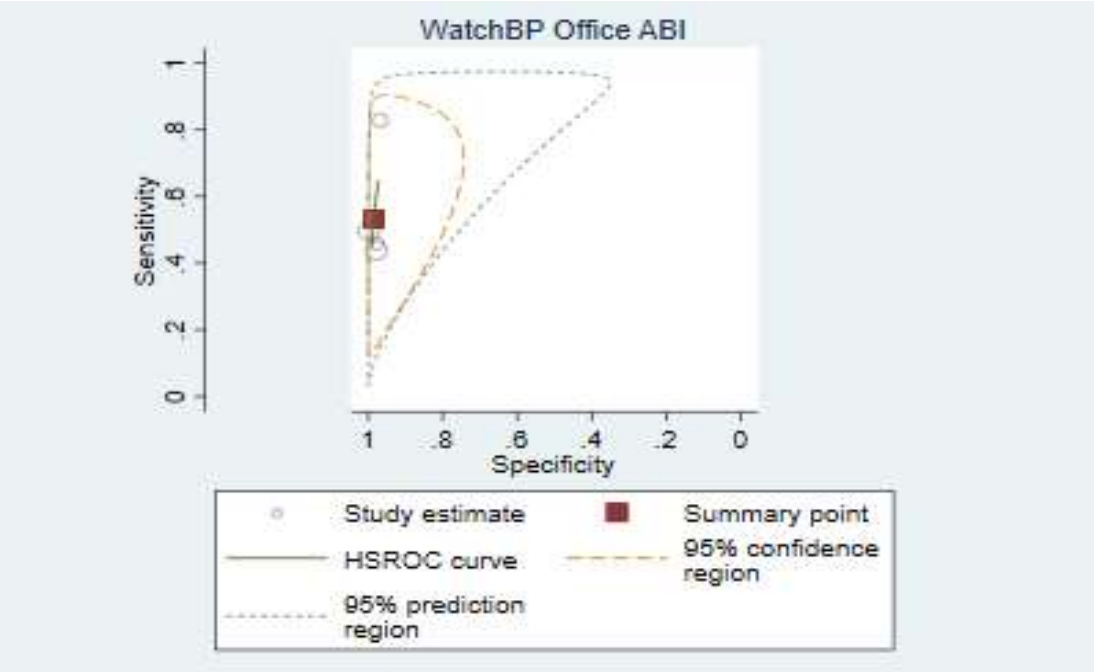


Figure 5 Summary ROC plot for ABPI measurement using the WatchBP Office ABI device



Figures 6 and 7 below show the forest plot and summary ROC plot for all studies, irrespective of the type of automated device, for which accuracy data to a construct 2x2 contingency table (i.e., true positives, false positives, false negatives, and true negatives) were available or could be calculated from the information provided in the included studies (12 studies). Across included studies, the pooled sensitivity for the diagnosis of PAD using automated devices was 0.64% (95% CI 57% to 71%) and the pooled specificity 96% (95% CI 92% to 98%). Sample size ranged from 66 to 696 participants.

Figure 6 Forest plot of automated ABPI measurement versus manual Doppler measurement for PAD diagnosis

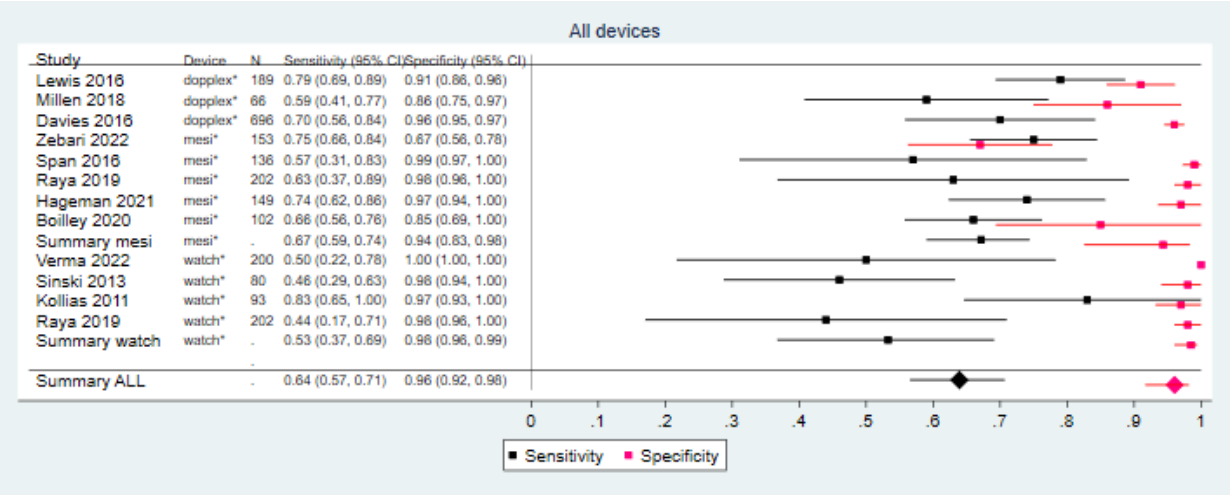
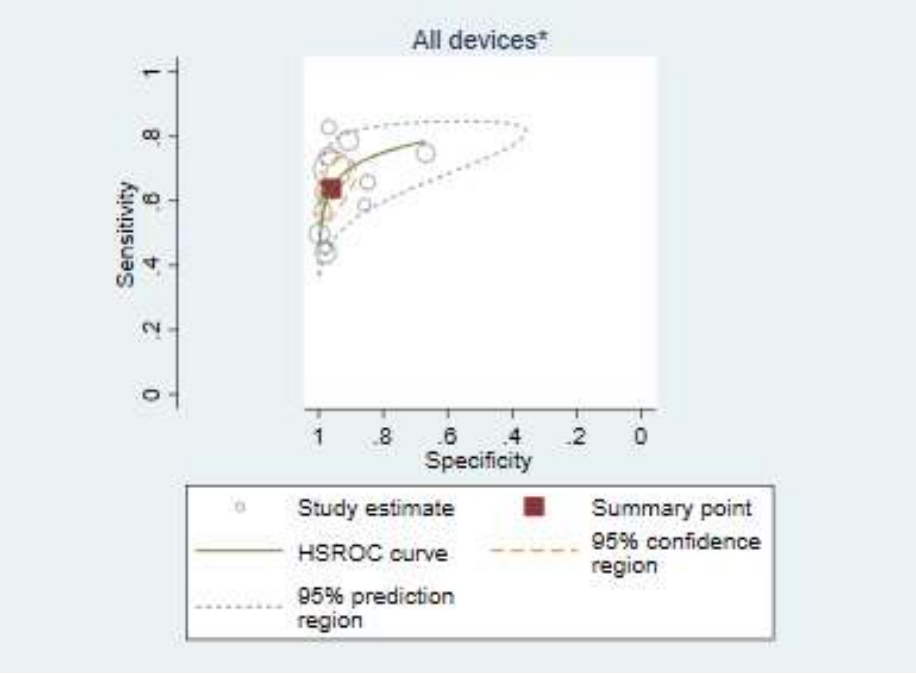


Figure 7 Summary ROC plot for ABPI measurement using automated devices



*Three studies used Dopplex Ability, five studies MESI ABPI MD and four studies WatchBP Office ABI.

Table 6 Summary of key diagnostic outcomes for studies assessing people without leg ulcers

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
NCT05073510 Interim results to May 2022 (Spain)[46]	BlueDop Vascular Expert/ Duplex ultrasound	People referred for Duplex ultrasound of lower limb(s) with suspected or previous history of PAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kordzadeh 2018 (UK)[57]	BlueDop Vascular Expert/ Duplex ultrasound	People referred to vascular outpatient services.	166	Median (IQR) 73 (65-81) 62.0	NR	DPA NR	0.92 (0.88, 0.95)	95	90	NR	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
Homza 2019 (Czech Republic)[58]	BOSO ABI-System 100/ Duplex ultrasound	People with diabetes at a cardio-vascular outpatient clinic.	62	67.6 (min, max 41.8, 83.2) 74.2	NR	NR DPA or ATA	NR	61	94	NR	NR
Jarai 2018 (Hungary)[59]	BOSO ABI-System 100/ Manual Doppler	People enrolled in Hungarian Hypertension Society's ERV Registration Program	397	63.9 (11.5) 44.6	NR	NR NR	0.94 (0.92, 0.95)	77	94	r=0.689** Kappa statistics: 0.7 Bland-Altman plot (difference between ABI measurements): r=0.01 (limits of agreement: -0.29, 0.32)	7.7/ <1

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
Wohlfahrt 2011 (Czech Republic)[66]	BOSO ABI-System 100/ Manual Doppler	General population (1% random sample of Czech population).	839	54.3 (13.8) 46.8	2	↑DPA or PTA/R BA NR	NR	77	98	Pearson's correlation coefficient: r=0.45 Bland-Altman plot (difference between ABI measurements): mean 0.1 (limits of agreement: -0.11, 0.30)	NR
Diehm 2009 (Switzerland)[47]	BOSO ABI-System 100/ Manual Doppler	People with chronic symptomatic PAD.	50	65 (6) 62.0	100	DPA and PTA/↑BA NR	NR	NR	NR	Pearson product-moment correlation: r=0.76	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
										Bland-Altman plot (difference between ABI measurements; non-diabetic patients): Low Doppler ABI: r=0.05 (95% CI -0.02, 0.11), p>0.1 High Doppler ABI: r=-0.02 (95% CI -0.08, 0.04), p>0.1	
Babaei 2020 (Iran)[54]	Dopplex Ability/ Duplex ultrasound	People with diabetes and symptoms of PAD.	303	60.1 (0.3) 39.8	2 (according to Duplex ultrasound)	↑PT or DP/↑BA NR	0.48 (0.44, 0.52)	20	96	NR	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
Millen 2018 (New Zealand)[60]	Dopplex Ability/ Manual Doppler	People attending for non-invasive vascular assessment	66	69.5 (12) 77.3	43	BA, PTA and DPA NR	NR	59	86	Pearson's correlation coefficient: R^2=0.17	2.3/ NR
Davies 2016 (UK)[48]	Dopplex Ability/ Manual Doppler	People with CV risk factors but no known CV disease or diabetes.	380	64 (9) 57.0	6	NR NR	0.96 (0.94, 0.98)	70	96	Bland-Altman plot (difference between ABI measurements): mean 0.016±0.1	3.9/ 0.0
Lewis 2016 (UK)[49]	Dopplex Ability/ Duplex ultrasound	People referred for lower limb arterial assessment.	189	67 (12) 65.1	36 (according to Duplex ultrasound)	Distal CFA, SFA and PA (Duplex ultrasound) NR	0.88 (0.83, 0.93)	79	91	NR	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
Lewis 2010 (UK)[51]	Dopplex Ability/ Manual Doppler	People with symptoms of PAD.	NR	NR NR	NR	NR NR	NR	NR	NR	r=0.89**	NR
Zebari 2022 (Sweden)[50]	MESI ABPI MD/ Manual Doppler	Patients attending a vascular surgery outpatient clinic.	153	72 (10) 63.4	52	NR NR	NR	75	67	Spearman rank correlation: r=0.552 Bland-Altman plot (difference between ABI measurements): mean -0.067 (limits of agreement: -0.52, 0.38)	n=28 (%NR)/ NR
Hageman 2021 (Netherlands)[61]	MESI ABPI MD/ Manual Doppler	Patients referred to vascular laboratory for	201	67 (11) 55.7	31	↑ankle/↑BA	0.96 (0.93, 1.00)	74	97	Pearson correlation coefficient: r=0.87	15.7/ 0.0

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
		an ABI measurement.				↑BA and ankle				Bland-Altman plot (difference between ABI measurements): mean 0.05 (limits of agreement: -0.20, 0.29)	
Boilley 2020 (France)[52]	MESI ABPI MD/ Manual Doppler	Patients referred to vascular medicine unit for suspected PAD based on exertional limb symptoms.	102	63 (11) 84.3	80	NR NR	NR	66	85	Kappa coefficient=0.35 (0.15) Correlation coefficient=0.63 ** Bland-Altman plot (difference between ABI	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
										measurements): mean 0.12 ±0.26	
Catillon 2020 (France)[62]	MESI ABPI MD/ Manual Doppler	Patients with a scheduled Doppler ultrasound appointment assessed either by medical students or vascular specialists.	43	66 (14.4) 67.4	11	PTA and ATA/↑BA and ankle NR	NR	NR	NR	Pearson correlation coefficient: r=0.2	NR
Varetto 2019 (Italy)[63]	MESI ABPI MD/ Manual Doppler	Patient who underwent vascular consultation	185	72.5 (13.6)	NR	↑TBA & PDA/ ↑BA ↑TBA & PDA/↑BA	NR	NR	NR	Kendall's Tau=0.63 Bland-Altman plot (difference	19%/ 11%

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
										between ABI measurements): mean 0.07 (95% CI 0.05, 0.09)	
Span 2016 (Slovenia)[53]	MESI ABPI MD/ Manual Doppler	People with symptoms of PAD.	136	64 (7.8) NR	10	↑DPA or PTA/↑BA NR	NR	57	99	Pearson correlation coefficient: r=0.61 Bland-Altman plot (difference between ABI measurements): mean 0.06 (limits of agreement: -0.21, 0.33)	9.3 [total for automated and Doppler failures]
Verma 2022 (India)[55]	WatchBP Office ABI/	Construction workers	200	27.5 (4.1)	6	BA and PTA	0.98 (0.96, 1.0)	50	100	Pearson correlation	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
	Manual Doppler	(described as a “high-risk population”). People with ulceration in the lower limbs and marked oedema were excluded.		100.0		↑Arm and ankle				coefficient: r=0.96 (95% CI 0.99, 1.07) ICC (agreement between methods): 0.98 (95% CI 0.97, 0.99) Bland-Altman plot (difference between ABI measurements): mean 0.07 (95% CI -0.03, 0.12)	

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
Raya 2019 (Spain)[64]	WatchBP Office, MESI ABPI MD/ Manual Doppler	People attending a primary care centre (for any reason).	202	63 (7) 44.1	6	Pedal and tibial arteries NR	WatchBP: 0.80 MESI: 0.78	WatchBP: 44 MESI: 63	WatchBP: 98 MESI: 98	WatchBP ICC: 0.27 (95% CI 0.0, 0.5) MESI ICC: 0.20 (95% CI 0.0-0.4)	WatchBP: 13 MESI: 14/ 4
Rodriguez-Roca 2014 (Spain)[67]	WatchBP Office ABI/ Manual Doppler	People without PAD seen in primary care.	322	47.7 45.7	17	↑PTA or pedal artery/↑SBP NR	NR	NR	NR	Pearson correlation coefficient: r=0.7 ICC: 0.7 (95% CI 0.6, 0.8) Bland-Altman plot (difference	NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
										between ABI measurements): mean -0.03 (limits of agreement: -0.21, 0.15)	
Sinski 2013 (Poland)[65]	WatchBP Office ABI/ Manual Doppler	People with known coronary artery disease.	80	70.1 (9.4) 66.3	40	PTA/↑BA NR	NR	46	98	Pearson correlation coefficient: r=0.51 Bland-Altman plot (difference between ABI measurements): mean -0.15 (limits of agreement: -0.58 to 0.28)	2.5/ NR

Study ID	Automated device/ Reference device	Population Setting	Patients analysed, n	Age, y, mean (SD) Male sex (%)	PAD prevalence according to Doppler (%)	Doppler ABI Automated ABI	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Agreement between automated device and reference standard	Technical failure rate, % Automated device/ Reference device
Kollias 2011 (Greece)[56]	WatchBP Office ABI/ Manual Doppler	People with cardiovascular risk factors attending a hypertension or diabetes outpatient clinic.	93	62.5 (11.1) 62.4	17	↑DPA or PTA/↑BA NR	0.98	83	97	Pearson correlation coefficient: r=0.80, p<0.001 Bland-Altman plot (difference between ABI measurements): mean 0.03 ±0.11	1.6/ NR

ATA, anterior tibial artery; PTA, posterior tibial artery; DPA, dorsal pedal artery; TBA, tibial pedal artery; PT, posterior tibialis; DP, dorsalis pedalis; SBP, systolic blood pressure; CFA, common femoral artery; SFA, superficial femoral artery; PA, popliteal artery, CV, cardiovascular; NR, not reported; ↑, highest value; *for all 103 enrolled participants; ** method not reported

Agreement between devices and threshold for diagnosis PAD

Correlation coefficients for ABPI measurements varied across studies but in most cases showed a moderate or good relationship between the automated devices under investigation and the reference devices (see Table 6). However, the Bland-Altman plot was often suboptimal, and most studies reported a systematic tendency for the automated device to overestimate ABPI values with larger differences observed in the lower range of ABPI values. These differences could translate in a potential risk for the automated devices of underestimating the presence of PAD when the common 0.9 threshold is applied.

It is worth noting that even though all included studies used the common ABPI threshold of 0.9 for the detection of PAD, some studies calculated a ROC curve to determine the optimal threshold for PAD diagnosis.[48-50, 54, 58, 59, 61] Table 7 presents the sensitivity and specificity of automated ABPI measurement according to the best-identified threshold for diagnosing PAD. As expected, modification of the ABPI threshold resulted in higher sensitivity estimates and slightly lower specificity estimates.

Table 7 Optimal threshold for diagnosing PAD using an automated device

Study ID	Automated device/ Reference device	Patients analysed, n	Optimal ABPI threshold for PAD diagnosis using the automated device	Sensitivity, %	Specificity, %
Homza 2019[58]	BOSO ABI-System 100/ Duplex ultrasound	62	1.0*	84	75
Jarai 2018[59]	BOSO ABI-System 100/ Manual Doppler	397	0.96	NR	NR
Babaei 2020[54]	Dopplex Ability/ Duplex ultrasound	303	1.2	40	80

Davies 2016[48]	Dopplex Ability/ Doppler ultrasound	380	1.04	98	75
Lewis 2016[49]	Dopplex Ability/ Duplex ultrasound	189	0.98	87	80
Zebari 2022[50]	MESI ABPI MD/ Manual Doppler	153	1.0*	77	62
Hageman 2021[61]	MESI ABPI MD/ Manual Doppler	201	Diabetic patients: 1.00	96	91
			Non-diabetic patients: 1.02	91	90
Span 2016[53]	MESI ABPI MD/ Manual Doppler	136	1.0*	85	96
Raya 2019[64]	WatchBP Office, MESI ABPI MD/ Manual Doppler	202	WatchBP: 1.12	84	86
			MESI: 1.16	88	70
Kollias 2011[56]	WatchBP Office ABI/ Manual Doppler	93	0.97	92	92

Note. *Sensitivity analysis rather than optimal threshold

People with diabetes

Table 8 presents key diagnostic outcomes of people with diabetes in studies that enrolled solely people with diabetes[54, 58] or those that reported results separately for diabetic and non-diabetic patients.[46, 56, 60, 61] Apart from Babaei et al. who reported a very low sensitivity (20%) for automated ABPI measurement in people with diabetes, there was not a clear indication that the accuracy of the automated devices was much different in diabetic patients.[54]

Time of ABPI measurement using the automated device and the reference device

The time required to assess ABPI using the respective devices was not consistently reported across studies. Often it was not clearly reported what 'timing' entailed (e.g., resting period, fitting of cuffs, resting plus testing period) making challenging to compare findings across studies. Apart from the study by Raya et al., in all remaining studies that reported this information, the assessment with the automated device required less time than that with the manual Doppler, mainly due to shorter resting time before starting the automated measurement.[64] In the study by Raya 2019 measurement of ABPI with the WatchBP Office ABI device required longer time (mean 14.4 minutes) than that with the MESI ABPI MD device (mean 10.7 minutes) or the manual Doppler (mean 12.1 minutes) because of the time needed to identify the arm with the highest systolic blood pressure.[64]

Table 8 Diagnostic outcomes for people with diabetes

Study ID (geographical location)	Patients analysed	Automated device/Reference device	People with diabetes		People not with diabetes	
NCT05073510 (Spain)[46]	[redacted] diabetic patients	BlueDop Vascular Expert/ Duplex ultrasound	Sensitivity [redacted]	Specificity [redacted]	Sensitivity [redacted]	Specificity [redacted]
Homza 2019 (Czech Republic)[58]	62 diabetic patients	BOSO ABI-System 100/Duplex ultrasound	Sensitivity 61%	Specificity 94%	N/A	N/A
Babaei 2020 (Iran)[54]	303 diabetic patients	Dopplex Ability/Duplex ultrasound	Sensitivity 20%	Specificity 96%	N/A	N/A
Millen 2018 (New Zealand)[60]	66 18 diabetic patients	Dopplex Ability/Manual Doppler	The presence of diabetes had no significant effect on the ABI accuracy			
Hageman 2021 (Netherlands)[61]	201 61 diabetic patients	MESI ABPI MD/Manual Doppler	Sensitivity 68%	Specificity 95%	Sensitivity 76%	Specificity 97%
Kollias 2011 (Greece)[56]	93 42 diabetic patients	WatchBP Office ABI/Manual Doppler	The mean difference between the manual Doppler and automated ABI measurements was similar in diabetics and non-diabetics			

Note. N/A, not applicable; *the number of diabetic patients refers to the total number of people enrolled in the ongoing trial [redacted] up to [redacted] the exact number of diabetic patients analysed in not available.

Technical failures

Some studies reported the occurrence of technical failures in the measurement of ABPI. Millen (2018) and Davies (2016) reported failed Dopplex Ability measurements in 2.3% and 3.9% of limbs, respectively.[48, 60] Davies et al. further explained that the failures were caused by hypertension in the limbs and that there were no failed manual Doppler measurements. Hageman et al. reported measurements errors relating to the use of the MESI ABPI MD device in a total of 15.7% of limbs - with a higher proportion in limbs with PAD (28%) compared with limbs without PAD (7%).[61] Similarly, Varetto et al. reported a higher proportion of measurement failures related to the use of the MESI ABPI MD (19%) compared with the manual Doppler (11% of failures).[63] Zebari et al. reported 28 error codes produced by the MESI ABPI MD device in 306 legs, with 6/28 error codes being considered technical failures.[50] In general, across studies assessing the use of the MESI ABPI MD device, failed measurements occurred in people with critical limb ischaemia/incompressible arteries (9.3%),[53] arterial calcifications (4.8%),[61] values consistent with PAD (71.4%),[61] or normal values (23.8%).[61] ABPI measurements failures after the use of the WatchBP Office ABI device were reported in a low number of participants (2.5% of patients[65] and 1.6% of limbs[56]). More errors were observed in limbs with PAD (35.2%) than in limbs without PAD (5.7%).[56] One study reported that zero values were returned by the BOSO-ABI System 100 in 7.7% of limbs and by the manual Doppler in 3.3% of limbs.[59] The confidential interim results of the ongoing study assessing the use of the BlueDop Vascular Expert device show that 'device deficiencies' incidents

[redacted].[46]

Chapter 4. Assessment of cost-effectiveness

4.1. Systematic review of existing cost-effectiveness evidence

Objective

The objective of the cost-effectiveness review was to identify, summarise and critically appraise existing economic evaluations of devices for automated assessment of ABPI for diagnosing PAD in people with leg ulcers.

Search strategies

A per protocol search was carried out, first using Ovid MEDLINE (See Appendix 1), which generated zero results for economic evaluations of the different approaches to measure ABPI in people with leg ulcers. The search was broadened to include any economic evaluations of the candidate tests, and similarly no results were identified.

Inclusion and exclusion criteria

Inclusion and exclusion criteria with regards to population, intervention and comparators were as per those included described in Section 3.1. With regards to study type, we sought full economic evaluations, defined as comparative analyses of costs and outcomes in the framework of cost-utility, cost-effectiveness, cost-benefit, or cost-minimisation analyses. Economic evaluations conducted alongside single effectiveness studies (for example randomised controlled trials or cohort studies), or decision analysis models were deemed eligible for inclusion.

Quality assessment of included studies

It was anticipated that included studies would be appraised against the NICE reference case for the assessment of the cost-effectiveness of diagnostic tests.[70]

Evidence synthesis of cost-effectiveness studies

It was intended that detailed summary tables of study methods and results would be provided alongside a narrative assessment of cost-effectiveness results across studies.

Results

The per protocol search identified no studies of the cost-effectiveness of the candidate tests for the assessment of PAD in people with leg ulcers. We therefore conducted further

literature searches with the aim of informing the development of a *de novo* decision analysis model for the assessment.

Additional literature searches

Methods for additional literature searches

Two supplementary, sensitive literature searches using database index terms and free text were carried out by an Information Specialist to find additional peer-reviewed literature relevant to development of the model structure and / or population of the economic model. Search 1 focused on the cost-effectiveness decision analysis models evaluating any method for the diagnosis / detection of peripheral arterial disease (PAD). Search 2 focussed on identifying cost-effectiveness decision analysis models for either the diagnosis or treatment of leg ulcers. The resources included in both searches were Medline, Embase, EconPapers, EconLit, and the journal *Value in Health*. There were no restrictions on date or language of publication at the time of the search. The reference lists of studies selected for full text appraisal were screened for additional studies. All references were exported to Endnote for recording and deduplication. A draft MEDLINE search is provided in Appendix 6.

Cost-effectiveness models for the diagnosis of peripheral arterial disease (PAD)

The PAD diagnostic model search identified 239 possibly relevant titles and abstracts after de-duplication. For the PAD search, a systematic review (Moloney et al) was identified which summarised the literature up until 2018.[71] Therefore, further detailed screening of the literature was undertaken for the period 2018 – 22 only, to identify additional studies not already captured in the Moloney et al systematic review.[71] The search identified 80 potentially relevant titles and abstracts of papers published between 2018 and 2022, of which 6 full texts were retrieved and read and only 1 included as it was a decision analysis model for the diagnosis of PAD. The methods of the identified decision analysis model are summarised briefly in Table 9 below. The single identified study, Itoga et al. is of limited relevance to the current assessment as it relates to the use of ABI for general population screening, and the setting in the USA may not be directly transferrable to the UK setting in terms of model parameterisation.[72]

Table 9 Summary of PAD detection models, published between 2018 and 2022.

Study	EE type	Intervention, comparator	Population	Country. Perspective	Currency. Price year	Model type (cycle length, time horizon)	Model states	Outcome measures	Sensitivity analysis	Results	Relevance for this assessment
Itoga, 2018[72]	CUA	ABI screening / no screening	65-year-olds general population, asymptomatic of PAD	USA, healthcare system perspective	USD; 2016/17	Markov cohort (1 month; 35 years)	Symptomatic PAD; Asymptomatic PAD +/- meds; amputation; post-amputation; stroke; MI; death	Cost, QALY, Cost per QALY	Varied starting PAD prevalence, medication costs, adherence to medications.	Inc. Cost: $338; Inc QALY: 0.0038; ICER: $88,758.	Partial: Earlier stage than current scope, general population screening. Downstream health states, including amputation potentially relevant but parameters outside UK setting.

CUA = cost-utility analysis; ICER = Incremental cost-effectiveness ratio; PAD = peripheral arterial disease; QALY = Quality adjusted life years;

Cost-effectiveness models for the treatment and management of leg ulcers

The leg ulcers search identified 520 studies after removal of non-English language studies and duplicates. The search identified a recent systematic review (Layer et al) which summarised the leg ulcer modelling literature up until 2018.[73] Therefore, assessment of studies was undertaken only for the period between 2018 and 2022 to identify any studies not captured in that review which may be useful for the current assessment. This process included screening of 114 abstracts, of which 21 full texts were retrieved and read and 8 included as they were decision analysis models for the treatment or management of leg ulcer patients. These studies are summarised briefly in Table 10 below.

Table 10 Summary of leg ulcer models, published between 2018 and 2022.

Study	EE type	Intervention, comparator	Population	Country. Perspective	Currency. Price year	Model type (cycle length, time horizon)	Model states	Outcome measures	Sensitivity analysis	Results	Relevant parameters for this assessment
Cheng et al. 2018[74]	CUA	Electric stimulation therapy (Accel-Heal) plus dressings and compression bandaging, dressings and compression bandaging alone	Venous leg ulcers	Australia, payer	AUD ($), 2015	Markov (2 weeks, 5 years)	No VLU, unhealed VLU, healed, complicated VLU, death	Total costs, total QALYs, expected cost of compression therapy	Univariate deterministic, probabilistic	Total cost intervention/comparator: $68,78,106/$37,875,018 Total QALY intervention/comparator: 504,431/476,090 Expected cost of compression over 5 years: $270,000,000	QALY source: Iglesias et al. 2005[75] Probability of healing – usual care (3 months): 0.2281[76] Probability of recurrence – usual care (annual): 0.5574[77]
Guest et al. 2018[78]	CUA	Collagen-containing dressings plus compression therapy followed by SoC, SoC	Venous leg ulcers	UK, NHS	GBP (£), 2015/16	Decision tree (1 month, 6 months)	Healed or unhealed at 6 months	Total QALY, total cost, probability of healing	Univariate deterministic, probabilistic	Total QALY intervention/comparator:0.373/0.331 Total management costs per patient intervention/comparator: £3789/£6328 Probability of healing – intervention/comparator: 0.49/0.11	Utility soured from Clegg & Guest, 2007[79] All healing rate and cost parameters were sourced from Guest et al. 2017.[80]
Health Quality Ontario. 2019[81]	CUA	Compression stockings, usual care (no compression stockings)	Healed venous leg ulcers	Canada, payer	CAD ($), 2018	Markov (1 month, 5 years)	Healed ulcer, recurred ulcer, infected ulcer, dead	Average total cost, average total effects (QALYs), ICER	Univariate deterministic, probabilistic	Average total cost intervention/comparator: $1518/$971 Average total QALY intervention/comparator: 4.060/4.040	Utility parameters – recurred/healed: 0.77/0.87 Pham et al. 2012[82] Probability of recurrence (monthly)

										ICER: £27,300	– compression bandages: 0.163[82]
Rognoni et al. 2020[83]	CUA	Stenting, standard medical treatment	Deep venous outflow obstruction and leg ulcers	Italy, payer	EUR (€), 2019	Markov (1 month, 3 years)	Active ulcer, healed ulcer, recurred ulcer	ICER	Univariate deterministic, probabilistic	ICER: €2,388	Utility parameters – active/recurred/healed: 0.73/0.64/1.00 [79] Metanalysis of 8 studies from China, Poland, Canada, UK and USA for healing and recurrence estimates. Healing rate (3 months) = 0.62 (95% CI: 0.49, 0.74) Ulcers recurred (1 year) = 0.10 (95% CI: 0.07, 0.13)
Veličković et al. 2020[84]	CUA	Super absorbent wound dressing (Zetuvit plus silicone), standard of care dressing mix as defined by Atkin et al, 2020[85]	Moderate-to-highly exuding leg ulcers	UK, NHS	GBP (£), 2019	Time invariant state-transition microsimulation model (1 week, 24 weeks)	HS1 (healed-skin intact) HS2 (unhealed grade 1 – progressing) HS3 (Unhealed grade 1: static) HS4 (Unhealed grade 1 – deteriorating) HS5 (Unhealed grade 2 – severe)	Total costs, total QALWs, ICER, NMB	Univariate deterministic, probabilistic	Total costs – intervention/comparator: £2887/£3109 Total QALWs – intervention/comparator: 15.933/15.852 ICER: Intervention dominant NMB: £1841	Utility soured from Clegg & Guest, 2007[79] Costs sourced from Harding et al. 2013[86]

Ontario Health (Quality). 2021[87]	CUA, CEA	Skin substitute dressings as an adjunct to standard care, standard care alone	Uninfected, difficult-to-heal neuropathic diabetic foot ulcers or uninfected difficult-to-heal venous leg ulcers	Canada, payer	CAD ($), 2020	Markov (1 week, 26 weeks)	Healed, Unhealed, Dead	Mean cost, mean QALY, mean ulcer free weeks, ICER, cost per ulcer free week	Univariate deterministic, probabilistic	Mean cost – intervention/comparator: $19,415/$7,148 Mean QALYs – intervention/comparator: 0.330/0.324 Mean ulcer free weeks – intervention/comparator: 10.12/6.33 ICER: $1,868,850 Cost per ulcer free week: $3,235	Utility soured from Clegg & Guest, 2007[79]
Guest et al. 2021[88]	CUA	Thigh administed Intermittent pneumatic compression (IPC) in addition to standard care, standard care	Hard-to-heal venous leg ulcers	UK, NHS	GBP (£), 2019/20	Markov (1 week, 24 weeks)	Uninfected ulcer, infected ulcer, improved ulcer, healed ulcer	Total costs, total QALY, probability of healing, ICER	Univariate deterministic, probabilistic	Total cost (if IPC stopped after 6 weeks) – intervention/comparator: £3,020/£3,037 Total QALY – intervention/comparator: 0.34/0.32 Probability healing – intervention/comparator: 0.38/0.24 ICER: Intervention dominant	Utility soured from Clegg & Guest, 2007[79] Costs sourced from Guest et al. 2017[89] and Guest et al. 2018.[80]
Veličković et al. 2022[90]	CUA	Super absorbent wound dressing, standard of care dressing mix as defined	Moderate-to-highly exuding leg ulcers	Germany, payer	EUR (€), 2020	Microsimulation state-transition model (1 week, 6 months)	HS1 (healed-skin intact) HS2 (unhealed grade 1 – progressing) HS3 (Unhealed grade 1: static) HS4 (Unhealed grade 1 –	Total cost, total QALW, healing rate.	Univariate deterministic, probabilistic	Total cost – intervention/comparator: €4528/€5299 Total QALW – intervention/comparator: 17.229/17.077 Healing rate – intervention/comparator: 34.27%/31.70%	

		by Atkin et al, 2020[85]					deteriorating) HS5 (Unhealed grade 2 – severe)				

4.2 Independent assessment of cost-effectiveness

The systematic review did not identify any cost-effectiveness studies involving the candidate tests for this assessment. The EAG has therefore developed a *de novo* decision analysis model to assess the cost-effectiveness of automated ABPI devices, compared to standard care (manual doppler testing) to assess peripheral arterial disease amongst adults with leg ulcers.

Modelled population

The population for the model base case analysis is adults with leg ulcers presenting to healthcare professionals in the community setting, in whom ABPI testing is required to identify or rule out peripheral arterial disease (PAD). By community setting, the base case analysis refers to a leg ulcer clinic setting, where sufficient skills to assess the patient's condition are available. It does not refer to screening in a GP / nurse setting. Scenario analyses explore the potential for different costs and time to ulcer healing parameters in other settings, for example where the skills to complete manual doppler testing are not accessible in the community. We model a cohort of adults, average age 70, 30.46% female, in accordance with the data reported from Callam et al.[6] (quoted in SIGN and NICE CKS guidelines).[29, 91] We use data from Callam et al. because, to our knowledge, it is the largest study that reports prevalence of arterial insufficiency, alongside the age and sex profile of leg ulcer patients in UK clinical practice. Despite the study being over 30 years old, the EAG's clinical expert confirms that the demographics of the modelled cohort are consistent with those that would be seen in current UK clinical practice.

Interventions and comparators

The model compares the cost-effectiveness of seven automated ABPI measurement devices, compared to standard care (manual doppler testing). Full details and characteristics of each test are provided in Chapter 3. Briefly, the tests under consideration for this assessment are:

1) BlueDop Vascular Expert (BlueDop medical)
2) Boso ABI-system 100 (Bosch and Sohn)
3) Watch BP Office ABI (Microlife)
4) Watch BP Office Vascular (Microlife)
5) MESI ABPI MD (Mesi)
6) MESI mTABLET ABI (Mesi)
7) Dopplex Ability Automatic ABI system (Huntleigh)

Where a company has more than one test included in the scope for this assessment (for example Mesi), we include both in the model as separate strategies. Where parameters for one of a company's tests are missing (e.g., where no diagnostic accuracy data are available), it is assumed that the model parameters for the other test can be imputed directly. The assumption was deemed reasonable following discussion with the EAG's clinical expert and is consistent with submissions from the relevant companies (Microlife and Mesi).

4.3. Modelling Methods

A two-stage model (decision tree followed by markov cohort state transition) was developed to evaluate the cost-utility of the candidate tests. The model was developed using Treeage Pro 2021.[92] Model development, parameterisation and reporting was conducted in accordance with the NICE reference case for diagnostic test evaluations.[70]

As outlined in the assessment of clinical effectiveness (see Chapter 3), there is no direct evidence to inform the consequences of the tests for clinical or patient outcomes (e.g., ulcer healing rates / time). The model therefore uses a linked evidence approach to quantify a range of potential consequences of test accuracy for ulcer healing times, risk of requiring invasive pad treatment and subsequent outcomes that might be observed in UK clinical practice.

The model structure was informed by an assessment of existing leg ulcer economic evaluation models (See Table 10) and was developed to be consistent with the recommendations of national guidance on the management of leg ulcers (NCWSP), NICE guidance on peripheral arterial disease (PAD) - CG147 and SIGN guidance (SIGN 2010)[13,23,29] NICE specialist committee members (SCMs) provided feedback on how inaccurate test results (FP or FN) would be identified in clinical practice and the associated consequences for patient outcomes. The final model structure was adapted following SCM feedback and EAG clinical expert advice.

Model structure and assumptions

Decision tree phase

The initial decision tree (diagnostic) phase of the model implements the linked evidence approach to capture the costs and consequences (advantages and disadvantages in terms of

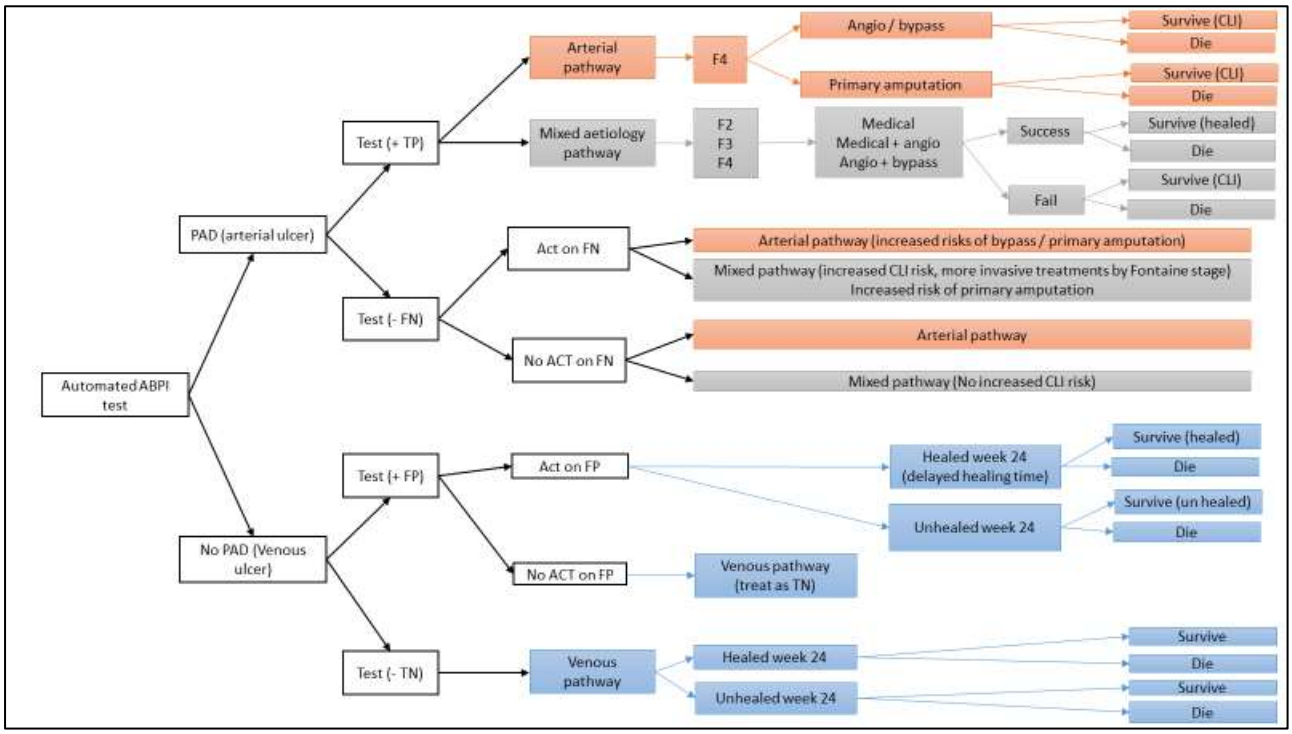
clinical and patient outcomes) of the diagnostic accuracy (sensitivity and specificity) of automated ABPI measurement compared to manual doppler testing.

The initial time horizon for the decision tree phase of the model was chosen as 24 weeks post initial presentation to healthcare services with a leg ulcer. 24-weeks was chosen to be consistent with the primary outcome of existing leg ulcer RCTs in this field (e.g., EVRA trial[93]). Discussion with several clinical experts confirmed that 24 weeks would be sufficient to identify false positive and false negative testing errors in clinical practice and to assign the patient to correct treatment pathways and is consistent with guidelines for treating arterial disease and management of arterial ulcers.[13, 23, 29] It would also be sufficient to capture urgent PAD referrals from the community and to initiate appropriate surgical management in secondary care if appropriate. It is therefore assumed that after 24 weeks, all patients would be allocated to the correct diagnosis, and the surviving cohort would then enter the appropriate Markov model to assess long-term costs and outcomes.

The cohort are initially assigned to the venous or arterial disease pathway, according to the underlying PAD prevalence (i.e., ABPI <0.9) amongst leg ulcer patients. The PAD proportion of the cohort is then further split into the proportion with purely arterial, and the proportion with mixed (arterial / venous) aetiology. Splitting the cohort into purely arterial and mixed aetiology allows for the application of different parameters and treatment pathways in the model, based on the severity of the underlying arterial component of the disease (defined using Fontaine stage). Costs and outcomes (QALYs) are then accrued depending on the sensitivity and specificity of the test result, depending on whether the underlying disease is arterial (including mixed) or venous.

Figure 8 illustrates the decision tree phase of the model, up to the point where the surviving cohort are allocated to appropriate starting states in the Markov model.

Figure 8 Diagnostic phase, simplified decision tree model pathway



*Simplified decision tree structure: Blue, salmon, and grey highlighted boxes reflect the venous, arterial, and mixed pathways respectively.

Angio = angioplasty; CLI = critical limb ischemia; F2, F3, F4 = Fontaine stage 2,3 and 4 respectively; FP = False positive; FN = False negative; PAD = peripheral arterial disease; TN = True negative; TP = True positive

Arterial ulcers: For the proportion of the cohort where the automated test accurately reports an ABPI output indicative of PAD (i.e., a true positive test - sensitivity), the cohort enter the arterial disease pathway, where they are referred to vascular services for further assessment and treatment of the arterial ulcer in accordance with NWSCP recommendations.[13] Using PAD classification (Fontaine system), ulcerated PAD patients are classed as Fontaine stage 4 (F4), because of the presence of the ulcer in a patient with arterial disease. All F4 patients with purely arterial disease are therefore assumed to have critical limb ischemia (CLI) meaning that arterial ulcers will not heal with conservative or medical management alone and thus require surgical treatment to restore blood flow (e.g., angioplasty or surgical bypass) to enable successful healing. A proportion may require primary amputation, but this would generally be avoided where possible. The cohort receive their first arterial treatment within the decision tree phase of the model, because a positive ABI test in the presence of other symptoms will trigger an urgent referral to vascular services. Based on the EAG's clinical expert opinion, it is assumed that in UK clinical practice, urgent referrals will receive treatment within approximately six weeks. Patients receiving intervention for CLI are

assumed to be at an increased risk of mortality, dependent on the treatment received. The surviving cohort are then allocated to the appropriate Markov model health state depending on whether their procedure was successful (enter the healed post-CLI state, assumed similar in terms of costs and outcomes to intermittent claudication) or unsuccessful (enter the CLI state where repeat treatments are provided, and an increased risk of amputation and mortality). Success of the initial treatment is defined as no further procedure required within the hospital admission.

It is assumed that purely arterial ulcers (F4) will have multiple signs of arterial disease, and that, in the context of a FN automated test result, a comprehensive and holistic assessment of the patient's condition would identify the FN result promptly and inappropriate compression would not be applied. This is captured in the decision tree through the parameter "act on test result". The base case analysis therefore assumes that a FN test result in an arterial only patient, would not be acted upon in clinical practice, and that a FN test alone would be unlikely to lead to long-term negative patient consequence, regardless of the setting in which the patient was seen (community or secondary care).

Mixed aetiology ulcers:

For the proportion of the cohort with mixed aetiology ulcers, impact on patient outcomes is likely to depend on the severity of the underlying arterial disease. Unlike purely arterial disease, a patient with mixed ulceration could have an ulcer primarily caused by venous disease. The mixed ulcer proportion of the cohort are therefore assumed to include Fontaine stages 2,3 and 4. Patients with mixed aetiology disease would not be classified as Fontaine stage 1 (asymptomatic) because F1 patients would typically have a higher ABPI >0.9. Table 11 summarises Fontaine stages, descriptions, and an approximate map to Rutherford stages (which is used for some model parameters).[94] It should be noted that whilst the Fontaine system may not be adopted universally in UK clinical practice for patient management, it is a useful approach to categorise the underlying severity of arterial disease that can be used to explore disease severity specific implications of FN results.

Table 11 Summary of Fontaine stages.

Fontaine stage	Description	Rutherford approximation
Stage I	Asymptomatic	Stage 0
Stage II (IIA & IIB)	Intermittent claudication (IIA pain after >200m walking; IIB: pain after <200m walking)	Stage 1,2
Stage III	Rest pain / sever claudication	Stage 3,4
Stage IV	Ischemic ulceration / gangrene	Stages 5,6

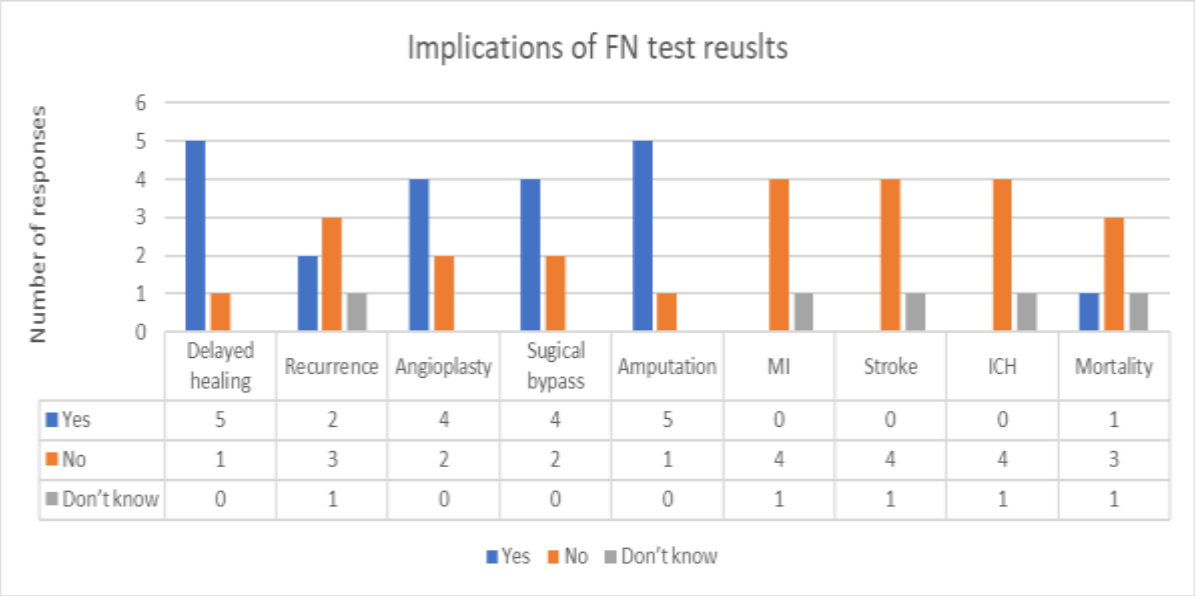
Whilst a mixed ulcer may heal within 24 weeks using conservative treatment (e.g., modified compression), under close monitoring to ensure no adverse events, in a manner similar to those for purely venous disease, this is unlikely to represent the management of mixed ulcers in UK clinical practice. The EAG clinical expert view is that, in UK practice, the arterial component of the ulcer takes priority for clinical management because the health gain forgone associated with non-treatment or delayed treatment of arterial disease is substantially greater than for venous disease. Therefore, in most cases, strong compression would not be applied to a PAD patient (ABPI <0.9), regardless of the Fontaine staging, even for moderate F2 disease. The EAGs clinical expert notes that it is more difficult to detect arterial disease amongst patients with mixed aetiology ulcers, especially for those with less severe arterial disease, as the underlying arterial disease may be less symptomatic, and the ulcer may present primarily with its venous component. Therefore, false negative test mistakes may be more likely to be missed in clinical practice for mixed aetiology compared to solely arterial disease.

We conducted a survey with NICE SCMs to better understand the implications of FN test results that are acted upon (i.e., where an ABPI test indicates that an ulcer is venous, when it has an arterial component, and inappropriate compression is applied). Five clinical experts responded. The majority felt that a FN test, leading to inappropriate compression of an arterial ulcer, could feasibly lead to delayed ulcer healing, increased risks of requiring invasive treatment (angioplasty or bypass) and potentially an increased risk of ultimately

requiring limb amputation. These outcomes and risks are all explicitly included within the model structure.

It was generally felt however that a FN would not directly lead to MI, stroke or ICH, hence these PAD outcomes have not been explicitly included in the model. One respondent felt that there would be an increased mortality risk. The additional risk of mortality due to a FN test result is captured indirectly in the model through increasing mortality following more invasive surgery due to the FN test result. Figure 9 summarises the implications of FN test results that are acted upon (i.e., strong compression inappropriately applied to an ulcer with arterial disease) as stated by the NICE SCMs:

Figure 9 Implications of FN test results



	Delayed healing	Recurrence	Angioplasty	Sugical bypass	Amputation	MI	Stroke	ICH	Mortality
Yes	5	2	4	4	5	0	0	0	1
No	1	3	2	2	1	4	4	4	3
Don't know	0	1	0	0	0	1	1	1	1

FN: False negative; ICH: Intracranial haemorrhage; MI: myocardial infarction.

Two clinical experts (one NICE SCM and the EAGs expert) commented that the extent to which these additional risks may be realised in clinical practice depends on the severity of the underlying arterial disease, and the extent to which a full and complete holistic assessment of the patient's condition was undertaken to identify a test result error (i.e., whether the test result is acted upon). If a FN is identified at the initial comprehensive patient assessment, implications would be minimal because the FN would not be acted upon.

For the base case analysis, we therefore assume that the implications of acting on a FN test result are Fontaine stage dependent. Based on the EAG's clinical expert advice, FN test results that are acted upon are modelled to affect patient outcomes through the need for more invasive treatments on a spectrum of treatment options for PAD ranging from mild (medical management), moderate (mix of angioplasty and bypass) and highly invasive (bypass and amputation) for patients in whom a mixed aetiology ulcer is inappropriately treated with strong compression. The increased risks applied in the model base-case analysis are detailed in the "parameters" section of the report. Whether the additional risks of treatment escalation are realised is dependent on whether the test is acted up on in the first place. The base case analysis assumes that all FN tests in mixed ulcer patients would be acted upon, but uncertainty surrounding this is explored in scenario analyses. FN, mixed aetiology ulcers may also be subject to consequences of delayed healing time due to a lack of clinical certainty around wound treatment, though the exact delay is unclear, with substantial variability across UK clinical practice.

Venous ulcers: Where a test is highly sensitive and accurately identifies absence of arterial disease (i.e., a true negative test result), the cohort enter the venous pathway, with the ulcer treated using strong compression and follow-up patient management in accordance with the NWCSP and SIGN guidance for venous ulcers. [13, 23, 29]

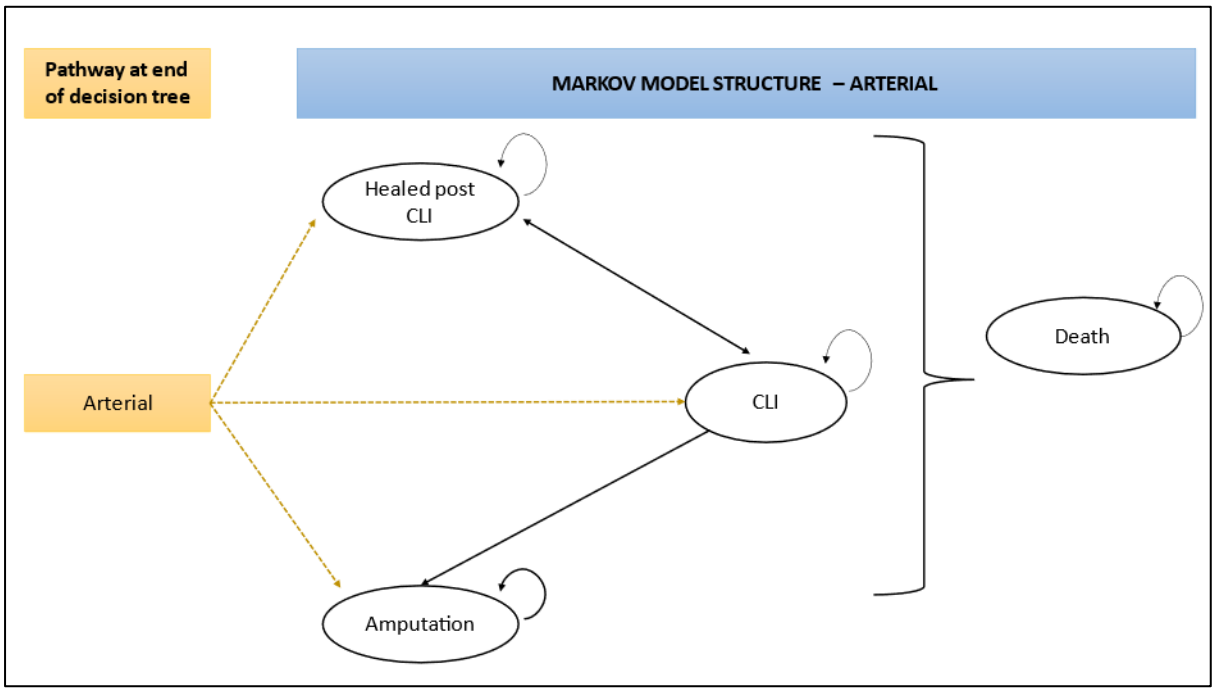
With regards to false positive (1-specificity) automated ABPI test results, clinical experts (N=4 NICE SCMs) explained that a false positive test result (i.e., an ABI that indicates arterial disease, compression withheld) would be identified in UK clinical practice primarily due to a failure of the ulcer to progress towards healing. Re-examination / review might identify a lack of history of claudication, previous venous disease or varicose veins or previous venous ulcers healed with compression. One expert noted that again, an effective holistic assessment should identify the absence of PAD, for example due to identifying the signs associated with chronic venous disease, and they note that the absence of PAD on doppler / ABPI alone does not lead to a diagnosis of venous disease. There was broad agreement that the main consequence of a FP test result that was acted upon would be delayed ulcer healing time for the venous, due to unnecessarily withholding compression. All SCMs agreed that a false positive would not lead to amputation of a venous ulcer as amputation in modern clinical practice is extremely rare.

Expected costs and benefits (utilities) are accrued within the decision tree phase of the model, dependent on the average duration of time that the cohort spends with healed / unhealed ulcers over the first 24 weeks. This allows the model to flexibly incorporate time advantages due to earlier testing in clinical practice if feasible, as well as time delays to ulcer healing due to compression treatment decisions driven by a test result. The base case analysis assumes that a FP test result would be acted upon, and initiation of appropriate compression therapy would be delayed until a definitive diagnosis was reached, thereby increasing ulcer healing times for the venous ulcer.

Markov model pathways – Arterial

The surviving cohort at the end of the decision tree phase of the model (24 weeks) enter the Markov model in either the "healed post CLI" state (if initial surgery from the decision tree phase was successful), the "CLI" state (if initial surgery was unsuccessful and further treatment required) or the "Amputation" state (if primary amputation was required or if bypass surgery was not successful). The arterial Markov model is described in Figure 10.

Figure 10 Markov model structure (arterial ulcers)



CLI: Critical limb ischemia

For the proportion entering in the CLI state, (those whose initial surgery was unsuccessful), the cohort receive either a repeat angioplasty or bypass procedure for limb salvage or may

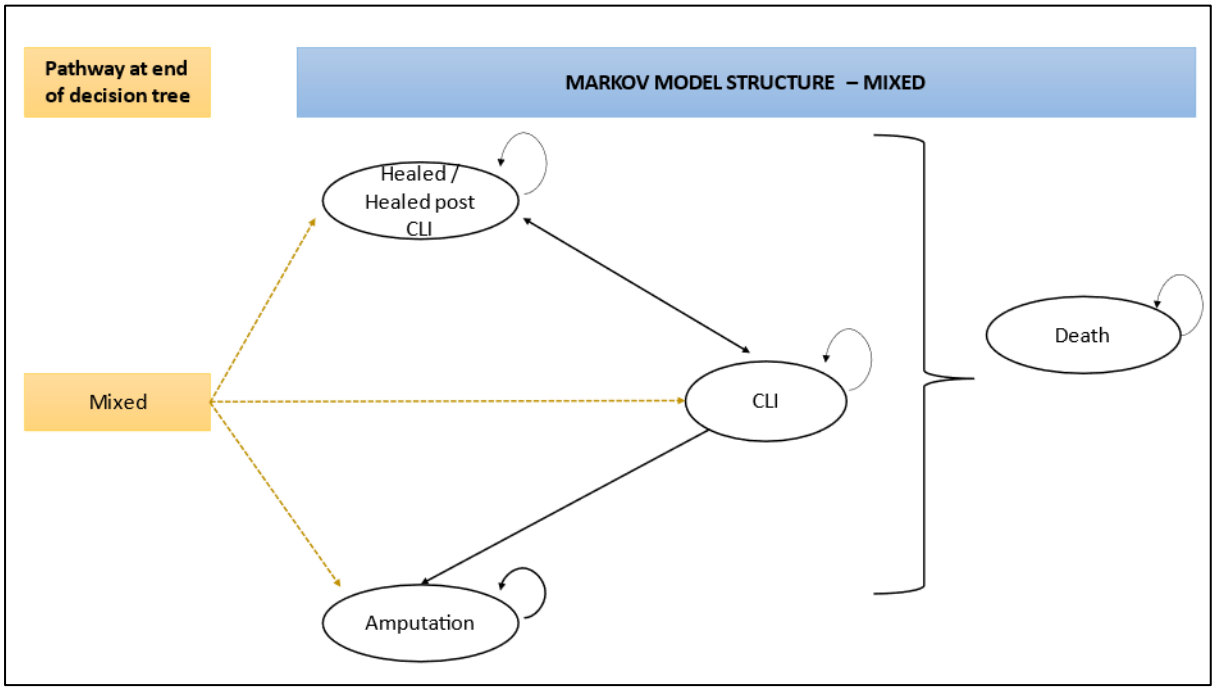
require amputation. Those who have successful treatment (obtained from national vascular registry data, defined as no further procedure required) enter a "healed post CLI" state, where they are exposed to a risk of recurrence, after which it is assumed, they re-enter the CLI state and start the treatment cycle again. Any further recurrences are thus assumed to be CLI. Patients whose initial treatment was unsuccessful at restoring blood flow within a single model cycle (6 months) re-cycle through the CLI state and receive subsequent treatments, increasing in intensity up to bypass and amputation. CLI patients with unhealing ulcers are subject to a risk of amputation, that increases following each subsequent round of surgical treatment (e.g., those with a failed bypass are all assumed to enter the amputation state).

The cohort can enter the "death" state from all other model health states, with an excess risk of mortality applied for underlying arterial disease in all model states. Further additional risks of mortality are applied in the CLI state reflecting the excess mortality risk compared to less severe stages of arterial disease.

Model pathways – Mixed aetiology

The mixed pathway is assumed to be very similar to that of the arterial pathway, given that in clinical management, arterial disease is the primary focus of treatment, even when ulcers are of mixed aetiology. The model pathway for mixed ulceration is described in Figure 11.

Figure 11 Markov model structure (Mixed venous / arterial ulcers)



CLI: critical limb ischemia.

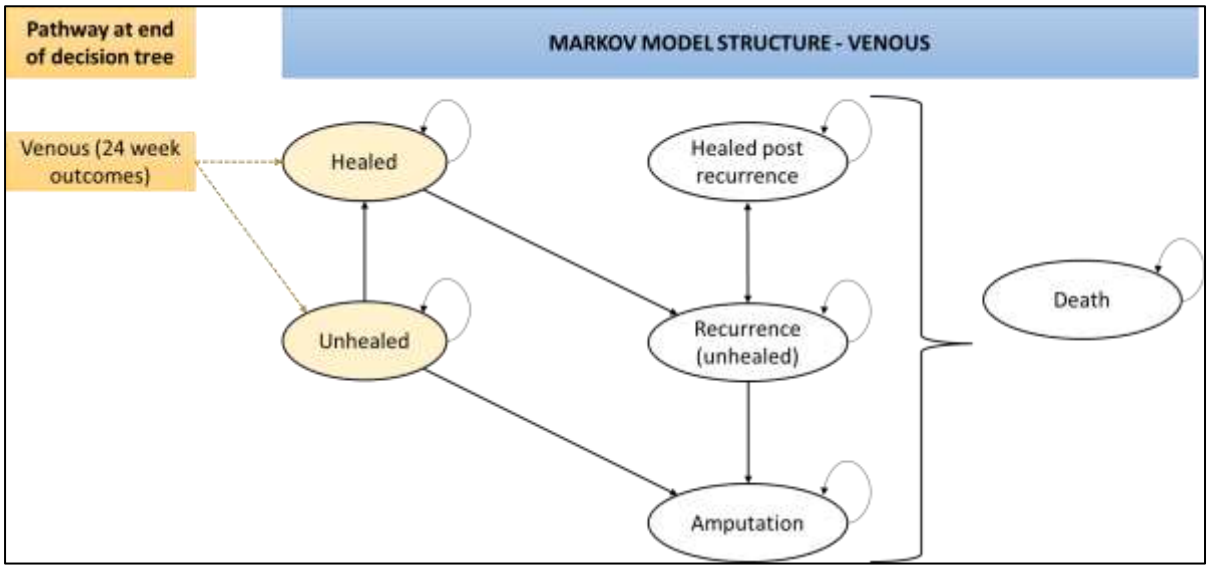
Prior to entering the Markov model, the mixed arterial ulcer proportion of the cohort are split according to severity of the arterial component of disease (Fontaine stage 2, 3 or 4). This staging, and the success of initial treatment processes is used to assign the cohort to the initial "healed" state (assumed equivalent in terms of costs and consequences to the "healed post CLI" state. This simplifying assumption was made due to a lack of alternative evidence to assign separate costs and utilities to "healed" and "healed post CLI" states for patients with mixed ulceration.

The proportion of the mixed cohort entering each Markov state depends on the Fontaine staging of the arterial component of disease, distribution of initial treatments (medical management for F2 / angioplasty or bypass for F3 and F4), and the success of those initial procedures. Those with successful treatment enter in the "healed" state, failed treatment in the "CLI" state and those who have a primary amputation, or amputation following failed bypass surgery enter the "amputation" state. It is assumed that primary amputation would be very rare for mixed ulcer patients and would only ever occur for F4 disease.

Markov model pathways – Venous

The proportion of the cohort with venous ulcers enter the pathway in the healed or unhealed ulcer states, depending on the surviving proportion of the cohort with healed / unhealed ulcers respectively at the end of the decision tree phase of the model (24- weeks). Figure 12 illustrates the model pathway for venous ulcers.

Figure 12 Markov model structure (venous ulcers)



Unhealed ulcers can continue to heal in subsequent model cycles, and a small proportion may remain unhealed longer term. Once an ulcer heals, it can remain healed or experience a recurrence (assumed equivalent in terms of costs and utilities to the "unhealed" state). Multiple rounds of healing and recurrence are allowed within the model accounting for the chronic recurrent nature of venous ulcers. The model structure also allows for a risk of amputation for venous ulcers, but this parameter is set to zero in the base case, reflecting clinical expert advice sought by the EAG that in modern clinical practice, amputation is extremely rare in a patient with purely venous disease. The cohort are exposed to a risk of mortality in all model cycles, assumed equal to that of the UK age and sex adjusted general population mortality risks. Mortality is not dependent on whether a venous ulcer heals or not.

Model parameters – prevalence and diagnostic accuracy

Prevalence parameters

To maintain consistency with the modelled cohort age and sex profile, the underlying prevalence of PAD (including purely arterial and mixed aetiology disease) of 22% was obtained from Callam et al., 1987,[6] quoted in both SIGN guidance, 2010 and NICE CKS (2021).[29, 91] The study was based on an assessment of 600 participants with leg ulcers in Scotland. It is assumed that each patient has one leg ulcer only. For the purposes of our model, the prevalence of arterial disease encompasses both patients with solely arterial involvement and mixed aetiology (i.e., predominantly venous ulcers, but with some evidence of arterial insufficiency, such as an ABPI<0.9). This prevalence estimate was used in

preference to an average prevalence from the diagnostic accuracy studies included in the review, because none of those studies were conducted in patients with leg ulceration specifically (See Section 3.3). Prevalence from the diagnostic accuracy studies is considered in a scenario analysis. Our prevalence estimate is also consistent with Guest, Fuller and Vowden, 2020 who conducted an analysis of the THIN database of over 2.4 million UK adult patients in 2017/18 (mean age 57.9; proportion female: 56%), of which 174,569 had ulcers identified within that year.[21] Of the 174,569 ulcers identified, 15% (scaled 79%; N=26,185) were venous, 3% mixed venous / arterial (scaled: 16%; N=5,237) and 1% (scaled 5%; N=1,746) arterial only.[21] The THIN database was thus used to parameterise the proportion of arterial ulcers that were of mixed aetiology, as 5237/6983 (75%). Prevalence parameters are entered in the model probabilistically using beta distributions as described in Table 12.

Table 12 Prevalence and other decision tree pathway parameters used in the economic model.

Parameter	Mean value n/N (%)	Dist. (alpha, beta)	Source / Notes
Prevalence of PAD	176/827 (21.3%)	Beta (α: 176; β: 651)	Callam, 1987;[6] SIGN 2010;[29] NICE 2021[91]
Proportion of PAD patients with mixed aetiology ulcers	5,237/6,983 (75.0%)	Beta (α: 5,237; β: 1,746)	Guest, Fuller and Vowden, 2020[21]

PAD, peripheral arterial disease

Diagnostic accuracy parameters (Sensitivity and specificity)

Diagnostic accuracy (i.e., sensitivity and specificity) parameters for automated compared to manual doppler tests were obtained from the diagnostic accuracy review (Section 3.3). Data were incorporated into the decision tree phase of the model to determine the proportion of PAD patients with a TP (sensitivity) or FN (1-sensitivity) test result, and the proportion of venous patients with a true negative (specificity) or FP (1-specificity) result.

The base case analysis considers manual Doppler to be the reference standard in primary care and, therefore, implicitly assumes perfect diagnostic accuracy (sensitivity and specificity equal to 1) for the base case analysis. The EAG acknowledges that the manual Doppler test is an imperfect reference standard and that better existing techniques such as angiography, CT angiography or MRI angiography would be required to generate a definitive diagnosis of PAD. However, it was not possible to adjust diagnostic accuracy estimates for the automated tests for several reasons. First, none of the studies included in this assessment compared automated versus manual readings against an acceptable reference standard that would enable direct estimation of diagnostic accuracy parameters. Secondly, the evidence base comparing manual Doppler with an acceptable reference standard was sparse. A recent systematic review[95] identified only one such study that compared manual Doppler testing with CT angiography,[96] and any comparisons about accuracy against automated tests would be purely naïve and across heterogenous studies. Finally, none of the included studies provided any further investigation or arbitration of disagreements between manual and automated devices, meaning that the correlation in testing errors is unknown. Any analyses that attempt to correct the estimates without knowledge of the correlation in testing errors may introduce further bias of unknown direction and magnitude.

It should also be noted that all but three of the included studies in the clinical effectiveness systematic review treated manual Doppler as the reference standard, with the remaining studies using Duplex ultrasound as the reference device. Where available, we have used data for a comparison against manual Doppler in our base case analyses. There were no comparisons of diagnostic accuracy of the BlueDop Vascular Expert device versus manual Doppler. To include the BlueDop Vascular Expert device within the economic model, it was therefore required to assume that the diagnostic accuracy of manual Doppler testing and Duplex ultrasound were equivalent. This assumption clearly adds substantial further uncertainty to the cost-effectiveness estimates, but was a requirement given a lack of information / studies comparing Duplex ultrasound and manual Doppler in the literature.

As noted in Section 3, study populations were highly heterogenous, raising serious concerns about the validity of pooling diagnostic accuracy studies. Our base case analysis therefore uses single studies for each test, with the most appropriate study selected based on similarity of population to the scope (more similar preferred), country (UK preferred) and sample size (larger studies preferred). The approach was taken to apply data from a population as close as possible to that of the assessment scope but acknowledging that there remain no diagnostic accuracy studies that report sensitivity and specificity in a population with leg ulcers. Whilst this base case approach chooses the most appropriate evidence available, it does not account for the overall uncertainty in the evidence base. Therefore, we apply several scenario analyses which vary sensitivity and specificity parameters as follows:

- Scenario 1: uses data from the study with the lowest diagnostic accuracy (average of sensitivity and specificity) for each test
- Scenario 2: uses data from the study with the highest diagnostic accuracy (average of sensitivity and specificity) for each test
- Scenario 3: uses data pooled across all available studies for each test, where there are at least 4 studies to enable a meta-analysis to be conducted. This was applicable only for MESI ABPI MD and WatchBP Office ABI. For this scenario, it was not possible to obtain pooled estimates for BlueDop, BOSO ABI-System 100 and Dopplex Ability. Whilst this approach has the limitation of pooling data where there is substantial heterogeneity, it has the advantage of capturing the uncertainty in the evidence base across all available studies for MESI ABPI MD and WatchBP Office ABI.

- Scenario 4: Several studies reported an optimal cut-off value for automated test results to generate the best diagnostic accuracy compared to manual doppler testing. This scenario applies the sensitivity and specificity parameters derived from studies that reported optimal cut-offs. None of the studies assessing the BlueDop Vascular Expert device reported optimal cut-off thresholds.
- Scenario 5: is a subgroup analysis, applying diagnostic accuracy data from studies that provided information for diabetes patients separately either because a subgroup analysis was available, or where the study was conducted in a diabetic population.

For scenarios 1 and 2, where we vary the source of a parameter between maximum and minimum available values across studies, we assume the base case value is retained where the min / max is equal to the base case parameters. For scenarios 3-5, where the scenario specific diagnostic accuracy parameters are not available for a test, we exclude that test from the cost-effectiveness calculations. For example, pooled meta-analysis estimates are only available for MESI ABPI MD and WatchBP Office ABI devices; therefore, the other automated tests are excluded from this scenario.

Sensitivity and specificity parameters are incorporated in the model using multi-normal distributions, with correlations between sensitivity and specificity obtained from the meta-analysis for MESI ABPI MD and WatchBP Office ABI studies. For the remaining studies, the correlation was assumed equal to the average correlation across all studies where this information could be calculated. The resultant correlations for MESI ABPI MD and WatchBP Office ABI were -1.00 and -0.99, respectively, whereas the correlation across all available studies (including available dopplex studies) was -0.84. The value of -0.84 was therefore applied to obtain correlated draws of sensitivity and specificity for all studies assessing the BlueDop Vascular Expert and BOSO ABI-System 100 devices, where this information could not be derived. Table 13 summarises the diagnostic accuracy parameters used in the model for the base case and each of the described scenario analyses.

Table 13 Diagnostic accuracy data used in the economic model.

		Sensitivity		Specificity		Corr.[B]	Notes / Source
	Scenario[F]	Mean	SE[A]	Mean	SE[A]		
Manual	Base case	1.00	0.00	1.00	0.00	1.00	Assumes perfect reference standard
Bluedop	Base case	0.95	0.155	0.9	0.021	-0.84	Kordzadeh, 2017[57]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	High value	0.95	0.155	0.9	0.021	-0.84	Kordzadeh, 2017[E57]
	Pooled estimate	--	--	--	--	--	Insufficient number of studies to conduct meta-analysis
	Optimal cut-off	--	--	--	--	--	No studies reporting optimal threshold
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Boso	Base case	0.77	0.125	0.94	0.022	-0.84	Jarai, 2018[59]
	Low value	0.61	0.099	0.94	0.022	-0.84	Homza, 2019[58]
	High value	0.77	0.102	0.98	0.005	-0.84	Wohlfahrt 2011[66]
	Pooled estimate	--	--	--	--	--	Insufficient number of studies to conduct meta-analysis
	Optimal cut-off	0.84	0.137	0.75	0.017	-0.84	Homza, 2019 - optimal threshold = 1.0[D58o]
	Diabetes subgroup	0.61	0.099	0.94	0.022	-0.84	Homza 2019[58]
Dopplex	Base case	0.7	0.073	0.96	0.008	-0.84	Davies, 2016[48]
	Low value	0.59	0.093	0.86	0.056	-0.84	Millen, 2018[C60]
	High value	0.79	0.049	0.91	0.026	-0.84	Lewis, 2016[49]
	Pooled estimate	--	--	--	--	--	Insufficient number of studies to conduct meta-analysis
	Optimal cut-off	0.98	0.022	0.75	0.017	-0.84	Davies, 2016 (optimal = 1.04)[48]
	Diabetes subgroup	0.2	0.033	0.96	0.022	-0.84	Babaei 2020[54]

		Sensitivity		Specificity		Corr.[B]	Notes / Source
	Scenario[F]	**Mean**	**SE[A]**	**Mean**	**SE[A]**		
MESI[G]	Base case	0.74	0.06	0.97	0.018	-1.00	Hageman, 2021[61]
	Low value	0.75	0.048	0.67	0.055	-1.00	Zebari, 2022[50]
	High value	0.74	0.06	0.97	0.018	-1.00	Hageman, 2021[E61]
	Pooled estimate	0.67	0.038	0.94	0.038	-1.00	Pooled across N=5 studies
	Optimal cut-off	0.91	0.039	0.9	0.031	-1.00	Hageman, 2021 (optimal = 1.02, non-diabetic)[61]
	Diabetes subgroup	0.68	0.063	0.95	0.082	-1.00	Hageman 2021[61]
WatchBP[H]	Base case	0.83	0.094	0.97	0.019	-0.99	Kollias, 2011[56]
	Low value	0.44	0.138	0.98	0.01	-0.99	Raya, 2019[64]
	High value	0.83	0.094	0.97	0.019	-0.99	Kollias, 2011[E56]
	Pooled estimate	0.53	0.082	0.98	0.008	-0.99	Pooled across N=4 studies
	Optimal cut-off	0.92	0.068	0.92	0.031	-0.99	Kollias, 2011 (optimal =0.97)[56]
	Diabetes subgroup	0.83	0.135	0.97	0.022	-0.99	Kollias 2011[56]

[A] Where sufficient data are available from within the source studies, standard errors are calculated as SE (sens) = sqrt(sens x (1-sens)/PADPx); SE (spec) = sqrt(spec x (1-spec)/(totPx - PADPx)). Where sufficient data are not available, the standard error is calculated as a proportion of the mean, with the proportion of the mean obtained from studies where the above formulae could be applied. The derived parameter values for both sensitivity and specificity are capped at 1 in the model.

[B] Correlation parameters obtained from meta-analysis for MESI ABPI MD and WatchBP Office ABI; correlation across all studies applied to studies not meta-analysed.

[C] For Dopplex Ability, Babaei et al reported lower sensitivity = 0.2, but is not included for this scenario as the study was solely in a diabetic population. [54]

[D] Optimal cut-off considered as part of a scenario analysis, where a threshold value of 1.0 was pre-determined rather than selected based on the data.

[E] The chosen base case study and study providing best diagnostic performance are the same

[F] High and low values are selected according to the average of sensitivity and specificity.

[G] Assumes that MESI ABPI MD and MESI mTABLET ABI have the same diagnostic accuracy parameters.

[H] Assumes that WatchBP Office ABI and WatchBP Office Vascular have the same diagnostic accuracy parameters.

Model parameters – decision tree treatments and outcomes for arterial (and mixed aetiology) disease

Characterisation of disease

Due to the presence of an ulcer, the proportion of the cohort with solely arterial disease are classified as Fontaine stage 4. The proportion of mixed ulcer patients across the disease stages is uncertain, and there is limited published evidence on the disease categorisation for mixed ulceration. We identified one study which is a retrospective analysis of 180 patients with suspected or known PAD and chronic venous insufficiency, median age 69 at a single centre in Germany between 2012 and 2018.[97] Assessment of clinical notes was used to determine Fontaine stage and the distribution is used to categorise disease stage for mixed ulceration in the model. We assume that there are no Fontaine stage I cases among prevalent arterial disease due to this proportion of the cohort having an ABPI reading <0.9.

Treatment for PAD

The economic model assumes that most PAD patients will first be treated with limb salvage. This reflects clinical practice where clinical teams would always attempt to save the limb first and attempt to avoid primary amputation where possible. Clinical expert opinion sought from the EAG's expert, and one NICE SCM indicates that primary amputation is rare, and would only ever occur in patients with Fontaine stage 4 arterial disease. Approximately 90% -95% of limbs will be amenable to some form of revascularisation / surgical bypass, and this would be the preferred option in clinical practice. The base case model includes the costs and outcomes of angioplasty and / or bypass for treating F3 and F4 disease and the costs of medical management for F2 disease (intermittent claudication). Information on initial treatment probabilities is sourced from the national vascular registry data where possible and includes both elective and non-elective procedures to calculate the proportion of treatments in each Fontaine stage that are endovascular (angioplasty), with the remainder assumed to be bypass. Whilst the data show that angioplasty may also be conducted for F2 disease, the EAG's clinical expert opinion was that, for a mixed ulcer, this would usually be managed with medical management initially. Therefore, the decision tree proportion of the model assumes that all stage 2 mixed ulcer patients are initially managed medically.

For those in whom limb salvage is not possible, primary amputation may be indicated. This may occur, for example, where there is a non-functional lower extremity, arteries that cannot be re-constructed, where there is massive tissue loss and bone exposure meaning bypass is

not possible, and where there are significant co-morbidities. The base case analysis applies a conservative estimate of the proportion of F4 arterial disease patients requiring primary amputation of 5%. Clinical experts explain that primary amputation in people with mixed ulceration is less likely, and the probability is therefore assumed to be 0%. It is assumed that F2 and F3 disease would never proceed directly to primary amputation.

The probability of treatment success for endovascular treatment and bypass is also obtained from the national vascular registry annual report and is defined as no further unplanned lower limb procedure prior to hospital discharge. The probability of treatment success is not available specifically for each Fontaine stage of disease. However, information is available according to whether the procedure is elective or non-elective, with a lower probability of success, higher probability of amputation and death following non-elective procedures compared to elective. Because non-elective procedures are more commonly required for more extensive arterial disease (higher Fontaine stage), the model indirectly calculates the probability of success in each Fontaine stage by weighting the outcomes by the proportion of procedures in each stage that were elective / non-elective.

Detailed probability parameters applied in the decision tree phase of the model for arterial and mixed aetiology disease are summarised in Table 14. These include the disease characterisation (Fontaine staging), treatment options by Fontaine stage where data allow this to be derived, and treatment success probabilities. Probability data are primarily sourced from the national vascular registry, 2021 annual report and supplemented with clinical expert opinion for primary amputation.[98] All probabilities are incorporated as beta distributions with alpha and beta parameters obtained from published event counts.

Table 14 Treatment and outcomes of arterial and mixed ulcer disease

Parameter	n/N (%)	Alpha	Beta	Dis.	Source / notes / assumptions
Disease classification					
Mixed – F2	77/152 (50.7%)	--	--	Remainder	Ammerman et al., 2020[97]
Mixed – F3	15/152 (9.9%)	15	137	Beta	
Mixed – F4	60/152 (39.5%)	60	92	Beta	
Proportion of stage specific surgeries that are angioplasty vs. bypass (remainder)					
Stage F2	4,204 / 6,160 (68.3%)	4,204	1,956	Beta	National vascular registry annual report 2021[98]
Stage F3	2,128 / 4,926 (43.2%)	2,128	2,798	Beta	
Stage F4	6,821 / 10,963 (62.2%)	6,821	4,142	Beta	
Elective vs. non-elective procedures (remainder non-elective):					
Proportion angio-elective (F2)	4,009 / 4,204 (95.4%)	4,009	195	Beta	Table A3.3, National vascular registry annual report 2021[98]
Proportion angio-elective (F3)	1,599/2,128 (75.1%)	1,599	529	Beta	
Proportion angio-elective (F4)	3,552 / 6,821 (52.1%)	3,552	3,269	Beta	
Proportion bypass elective (F2)	1,860 / 1,956 (95.1%)	1,860	96	Beta	Table 5.4, National vascular registry annual report 2021[98]
Proportion bypass elective (F3)	1,939 / 2,798 (69.3%)	1,939	859	Beta	
Proportion bypass elective (F4)	1,714 / 4,142 (41.4%)	1,714	2,428	Beta	
Treatment outcomes					
P success angioplasty (elective)	4061 / 4221 (96.2%)	4,061	160	Beta	Table 5.5A and 5.5B, National vascular registry annual report 2021[98]
P success angioplasty (emergency)	1805 / 2169 (83.2%)	1,805	364	Beta	
P success bypass (elective)	2428 / 2642 (91.9%)	2,428	214	Beta	

Parameter	n/N (%)	Alpha	Beta	Dis.	Source / notes / assumptions
P success bypass (emergency)	1980 / 2429 (81.5%)	1,980	449	Beta	
P die angioplasty (elective)	34 / 4221 (0.8%)	34	4,187	Beta	
P die angioplasty (emergency)	104 / 2169 (4.8%)	104	2,065	Beta	
P die bypass (elective)	42 / 2642 (1.6%)	42	2,600	Beta	
P die bypass (emergency)	119 / 2429 (4.9%)	119	2,310	Beta	

Abbreviations: F (2,3,4): Fontaine stages 2, 3 and 4 respectively.

Implications of false negative results for treatment of arterial and mixed aetiology disease

The model structure has been developed to incorporate the implications of FN test results through an increased requirement for treatment escalation to more invasive procedures to treat arterial ulcers. The base case assumes that those with purely arterial disease will not be acted upon because the test error will be identified through other patient symptoms. The additional risks of FN tests impacting on treatment escalation are only applied to mixed aetiology ulcers and are modelled to be dependent on disease severity (Fontaine stage).

The base case modelled consequences for a mixed aetiology ulcer where a FN test result is acted upon are as follows:

- Fontaine stage II, relatively mild disease, a patient with strong compression would experience extreme pain, would usually return within one week at which point the mistake would be identified. Most people at this stage would have no long-lasting negative consequences once the compression was removed and would continue to have their arterial disease managed medically, with monitoring and eventual reflux surgery for the venous disease.

- Fontaine stage III patients are more likely to require escalation of treatment to more invasive procedures and would be unlikely to be managed medically. Whilst highly uncertain, the EAG's clinical expert's best guess estimate is that approximately 70% (sampled probabilistically to account for uncertainty) of stage III patients (managed with angioplasty in the absence of a FN result) would require escalation to bypass, with the remaining having no longer term implications and retaining the initial procedure distribution.

- Fontaine stage IV: A FN test for a Fontaine stage IV patient would require escalation in all patients, directly to a bypass procedure. We assume an additional 5% would require a primary amputation (i.e., RR=2, total 10%) if a purely arterial ulcer (F4) was inappropriately treated with strong compression (although proportion acted upon assumed 0 in base case, some scenarios vary this assumption). Inappropriate compression of a F4 mixed ulcer case could increase the risk of requiring primary amputation in a patient who would otherwise have been suitable for revascularisation. We therefore assume that a FN result, that is acted upon by applying strong

compression to a F4 mixed aetiology ulcer would require primary amputation in 2.5% of cases. We assume there are no primary amputations for F2 or F3 disease, regardless of whether an arterial ulcer was compressed or not. Scenario analyses are explored where all risks of primary amputation are removed from the model, and it is assumed that all initially receive limb salvage.

Model parameters - ulcer healing probabilities and healing times

Probability of achieving successful ulcer healing:

Baseline venous ulcer healing probabilities were obtained from the delayed ablation arm of the UK EVRA RCT, per protocol analysis, showing a 24-week healing probability of 0.826 (0.768 to 0.876), sampled from a beta distribution.[93] For arterial ulcers it was assumed that all ulcers remained unhealed at 24 weeks. For mixed-aetiology ulcers, the analysis focuses on the arterial pathway, but also accounts for the utility gains and losses associated with different ulcer healing times over the first 24 weeks. Average healing times for a mixed aetiology ulcer were obtained from Humphreys et al, which was a prospective study of leg ulcer patients, treated with modified compression and assessed for revascularisation at 3 months if no improvement or worsening symptoms.[8] The sample were mean age at baseline: 81, treated at a specialist centre in Cheltenham from 1998 to 2003. A total of 193 patients with moderate arterial insufficiency (i.e., ABPI 0.5-0.85) achieved a 36-week ulcer healing probability of 0.676. The Humphreys et al study was chosen because it was a large UK study, provided parameters suitable for the model (healing probabilities and times in a single source), and was one of the few that categorised and defined mixed arterial ulcers in a manner that appeared somewhat transferrable to the parameterisation of the model.[8] Given that measures of uncertainty were not reported in the study, it was assumed that the SE was 20% of the mean, probabilities were parameterised using a beta distribution and converted to a 24-week probability for application in the decision tree phase of the model, assuming a constant rate over time.

Ulcer healing times

The average duration of time to healing for an ulcer that ultimately heals by week 24 is calculated in the model as a function of the baseline healing time (assumed for manual doppler testing, obtained from the literature[8, 93]), adjusted for time gains due to potential early diagnoses, and time delays due to inaccurate diagnoses associated with the automated tests. The following equation is used to calculate healing time:

$$T_{heal\_test} = T_{heal\_baseline} - T_{early\ diagnosis} + T_{excess\ healing\ time\ due\ to\ diagnostic\ delay}$$

Eq. 1

Baseline healing times

Baseline ulcer healing times were obtained from the EVRA trial, with a median, (IQR) healing time of 82 (69 to 92) days.[93] The median healing time was converted a mean for use in the economic model as 82/ln(2)=118.30 days. A LN distribution was then parameterised using the median and the approximated mean value. The median baseline healing time for mixed-aetiology ulcers was obtained from the KM curve in Humphries et al. was approximately 13 weeks (91 days), converted to a mean of 91/ln(2)=131 days and parameterised using a LN distribution. The detailed model parameters derived from the EVRA and Humphries studies are provided in Table 16.

Time gains due to early disease detection or improved referral pathways

It is unclear whether automated tests could lead to tangible reductions in ulcer healing time. For this to be the case, it would require automated tests to enable more efficient referrals to appropriate community or vascular services. For any improvements in referral pathways to be tangible, it would require automated tests to be used in settings where staff do not have the skill sets required to complete manual Doppler testing. This would not be the case in community leg ulcer clinics or vascular services. The EAG's clinical expert believed most GP practices would also have access to ABPI measurements in the community, either from a nurse at the GP practice, or within a group of practices, and that referrals to vascular services purely for an ABPI assessment to be completed would be unusual. This would suggest that it is unlikely automated tests could lead to more efficient triage of patients to community or vascular services in most settings. The EAG base case analysis therefore assumed there are no time gains from the use of automated tests.

There may however be a very small number of settings where automated devices could lead to more efficient referrals where access to healthcare professionals with the skills to complete manual doppler assessment are not readily accessible in the primary care setting. This might include, for example, some small rural GP practices or district nurses who may not have been trained in manual doppler assessment). In such scenarios, a TN automated test may lead to

referrals direct to community leg ulcer services rather than to outpatient vascular clinics. Any time gains might then be approximated as the difference in waiting times for vascular services compared to community leg ulcer clinics. These too are uncertain parameters. Waiting time information for community leg ulcer clinics are not readily available, but one clinical expert suggested waiting times for community leg ulcer clinics may be as low as 2 weeks (*Personal communication, Kate Donovan).* Patients in England are guaranteed to receive an outpatient consultation within 18 weeks (non-urgent), so this could be considered the usual maximum waiting time, though some trusts may struggle to meet these targets post pandemic. Applying these assumptions would suggest a maximum possible time saving to initiation of strong compression for a venous ulcer of 16 weeks, in a setting where manual Doppler assessment is inaccessible. This optimistic scenario analysis is provided for the committee's information. For arterial ulcers, it is even less likely that time gains could be realised, because the patient should present with other indications of arterial disease that would prompt urgent referral to vascular services.

Delayed healing times due to inaccurate results

Delays in healing time are modelled to depend on the diagnostic accuracy of the test, and whether the underlying cause of the ulcer is arterial, mixed, or venous. Time delays due to inaccurate test results are plausible but are likely to be highly variable in UK clinical practice and will depend on the setting, the expertise of the staff conducting the test, whether the test is used as a screening tool or conducted as part of a holistic patient assessment (i.e. whether a false reading is acted up on), how long it takes to identify the error, to what extent best practice guidelines are followed in clinical practice, and how patients present to clinical services when ulcers do not heal adequately. The uncertainty associated with multiple different assumptions makes it difficult to select a single base case parameter value that adequately reflects variability in clinical practice across and within settings.

To characterise the uncertainty around the impact of test results on healing times, the EAG survey asked NICE SCMs to provide a 'best guess' estimate alongside a range of plausible values for the time to detect FN and FP results, and the associated related delay in ulcer healing times for arterial and venous ulcers. These 'best guess' estimates were used as the base case values for Equation 4.1. The time to recognition and delayed healing time for false negative / false positive results provided by each clinical expert is provided in Table 15.

Uncertainty in each of the modelled time parameters is incorporated into the model probabilistically, assuming a gamma distribution to allow for a left-skewed distribution. Mean and SD parameters for the distribution are calculated using the clinical expert's best guess estimates to each timing question, converted to days. All available data from each question posed to the clinical experts are used to parameterise the distribution and we attach equal weight to each experts' response. All timing parameters were incorporated into the model probabilistically using gamma distributions to account for left skewed data. Table 16 describes all timing parameters in the model.

Table 15 Clinical expert survey responses to timing parameters

	Expert 1; best guess (min-max)	Expert 2; best guess (min-max)	Expert 3; best guess (min-max)	Expert 4; best guess (min-max)	Expert 5; best guess (min-max)
Time to recognise FP result	120 (NR) days	NR	28 (14 – 180 days)	42 (7-84 days)	NR
Delay in healing due to FP result	180 (NR) days	NR	90 (60 – 180 days)	84 (NR)	NR
Time to recognise FN result	42 (7-112 days)	14 (1-30 days)	3(1-7 days)	NR	7 (3-7 days)
Delay in healing due to FN result	84 (42-NR) days	NR	84 (14-360 days)	NR	180 (90-180)

Abbreviations: FN: False negative; FP: False positive; NR: Not reported

Table 16 Healing probabilities and times for venous and arterial ulcers applied to the decision tree model:

Parameter	Mean value	SE[B]	alpha	Beta / lambda [C]	Dist.	Notes / source
Venous ulcers						
24 weeks healing rate [D]	0.826	0.028	150.6	31.72	Beta	Deferred ablation arm of EVRA RCT (per protocol analysis)[93]
Baseline healing time (days)	Mean: 118.30[A] Median: 82	--	Mean of logs: 4.41	SD logs: 0.86	LN	EVRA RCT[93]
Time gains due to early testing	0 Days	--	--	--	Fixed	Base case assumption, varied in scenario analyses
Time delay to recognise FP results	63 Days	29 Days	4.72	0.075	Gamma	Clinical expert survey (See Table 15)
Time delay to ulcer healing due to FP results	118 Days	31 Days	14.49	0.123	Gamma	Clinical expert survey (See Table 15)
Arterial ulcer						
Probability of healing by 24 weeks (n/N)	0	--	--	--	Fixed	Assumption that purely arterial ulcers will not heal with conservative management alone
Baseline healing time	>24 weeks	--	--	--	Fixed	Assumption that purely arterial ulcers will not heal within the 24-week decision tree phase.
Time gains due to early testing	0 Days	--	--	--	Fixed	Base case assumption, varied in scenario analyses

Time delay to recognise FN results	0 Days	0 Days			Fixed	Assumes that a purely arterial ulcer would be unlikely to be missed in the context of a holistic patient assessment
Arterial ulcers (with mixed aetiology)						
36-week ulcer healing probability [D]	0.676	0.135	7.45	3.57	Beta	Humphreys et al., 2007[8]
Baseline healing time	Mean: 91[A] Median: 131	--	Mean of logs: 4.51	SD logs: 0.851	LN	Humphreys et al., 2007[8]
Time gains due to early testing	0 Days	--	--	--	Fixed	Base case assumption, varied in scenario analyses
Time delay to recognise FN results	17 Days	9 Days	3.57	0.210	Gamma	Assumption base on clinical expert survey (See Table 15)
Time delay to ulcer healing due to FN results	116 Days	32 Days	13.14	0.113	Gamma	Assumption base on clinical expert survey (See Table 15)

[A] Median healing time of 82 days converted to mean assuming exponential distribution (82/ln (2) = 118.30); [B] Assumption that standard error is 20% of the mean, applied where SE data are unavailable; [C] Lambda for LN distributions. [D] Converted to a 24-week probability for application in the model.

Abbreviations: dist.: Distribution; FN: False negatives; FP: False positives; LN: Log-Normal distribution; SE: standard error (standard deviation of the distribution)

As described in this section, potential time delays due to inaccurate results and potential time gains due to more appropriate referrals of true negative cases are highly uncertain, and the potential consequences (positive and negative) of the automated diagnostic tests are unclear. The EAG have conducted a range of scenario analyses to explore the impact of uncertainty in test timings on cost-effectiveness results, ranging from optimistic (where tests provide time gains, but no delays because inaccurate results are not acted upon) to pessimistic (where tests provide no time gains, but inaccurate results lead to ulcer healing delays and negative consequences of inappropriate compression). The key base case assumptions around the impact of test results on healing times, and a range of optimistic and pessimistic assumptions are detailed in Table 17.

Table 17 Assumptions around the impact of diagnostic accuracy on ulcer treatments and healing times

Parameter	Base case	Scenario analyses
Timing consequences for venous ulcers		
Reduced time to applying compression to a venous ulcer due to automated tests	Assume that in a community leg ulcer setting, there would be no gains in time to compression because all required skills to provide automated or manual doppler testing and to apply compression would be available in this setting. Automated doppler may reduce test times, but would not consistently shorten appointments (*Personal communication, Kate Donovan).* We have therefore not modelled any time gains for the base case scenario.	It could be argued that automated testing could improve referral pathways if easier to deliver as a screening tool in settings without access to manual doppler testing, to inform prompt referral to leg ulcer services. We therefore explore the impact of an optimistic scenario where the difference in waiting times between leg ulcer clinics and vascular outpatient clinics could be considered a reduction in ulcer healing time through ensuring prompt compression applied to the venous ulcer. Whilst this time saving is speculative and based on the assumption that an automated test could feasibly alter primary care referral behaviors, the optimistic scenario assumes a 16-week time saving might be achievable based on assumed wait times for community leg ulcer services = 2 weeks, and for vascular services = 18 weeks (NHS guaranteed time to consultation).

Delay in recognition of a false positive result and thus delayed time to ulcer healing.	Delayed ulcer healing time based on clinical expert opinion survey	Optimistic scenario: Assume no delay as mistake would be picked up in a holistic assessment of the patient, especially in leg ulcer clinics. Pessimistic scenario: Assume no false positive test results are healed by 24 weeks (broadly consistent with upper end of clinical expert delay in ulcer healing times).
Implications for mixed and arterial ulcers		
Probability that a FN test result is acted upon (and inappropriate compression applied)	Arterial = 0% (fixed) Mixed = 100% (fixed)	Optimistic: 0% arterial; 0% mixed Pessimistic: 100% arterial; 100% mixed
Additional risk of requiring treatment escalation, among those in whom a FN test is acted upon.	Highly uncertain parameter, based on escalation of treatment according to underlying disease severity (approximated using Fontaine stage), implications based on EAG clinical expert opinion, include increased risk of requiring bypass surgery (F3/4) and increased risk of primary amputation (F4)	Optimistic: Remove the risk of primary amputation and assume no consequences because all FNs identified in routine clinical practice through a holistic clinical assessment. Pessimistic: Assume all FNs that are acted upon require non-elective surgery.

Model parameters – Transition probabilities for Markov model.

At the end of the decision tree phase of the model, the surviving cohort enter the Markov model. Patients with venous ulcers enter the healed / unhealed states depending on whether their ulcer healed by week 24. Patients with arterial disease, are assumed to have CLI, due to the presence of an arterial ulcer (Fontaine Stage 4) and enter the CLI state where they receive invasive treatment (angioplasty or bypass surgery). Patients with mixed ulcers follow a pathway according to disease severity defined using the Fontaine stages of disease.

Venous ulcers

Those who are unhealed at 24 weeks entered the "unhealed" model state, but can continue to transition to the healed state over the longer term, following long-term follow up data from the EVRA RCT.[99] These data show that 194/224 (85.8%) of venous ulcer patients have achieved healing of the primary index ulcer by one year.

The proportion of the cohort with a healed ulcer are then subject to an ongoing risk of recurrence. Two sources were deemed potentially relevant for parameterising venous ulcer recurrence risk, with long term data available from both the ESCHAR and EVRA long-term follow up studies. The ESCHAR study showed a recurrence rate of 56% for the compression only arm of the trial at 4 years follow-up.[100] The EVRA study showed that, at one year of follow up, 32/194 (16.49%) patients in the deferred ablation arm of the study had a recurrent ulcer.[93] Long term follow-up of EVRA showed that 2- and 3-year cumulative recurrence rates were 0.239 (95% CI: 0.1852, 0.3053) and 0.2995 (95% CI: 0.2392, 0.3710) respectively.[99] Four-year data were also available, but the numbers at risk were small (N=32) and considered insufficient to populate the model. 3-year recurrence probabilities are then extrapolated over the remaining lifetime horizon of the model. The data from EVRA are applied in the base case analysis because 1) it provides a consistent source to populate multiple model parameters, 2) data are obtained from a large UK sample, and 3) granular data across multiple timepoints, including confidence intervals to derive distributions for the probabilistic analysis are available for several parameters.

The probability of healing for a recurrent ulcer was also obtained from the EVRA long-term follow up data. The probability of healing and subsequent recurrence risks for second and subsequent recurrences were assumed equal to the first given a lack of data beyond the first venous ulcer recurrence. This is likely to be a conservative estimate of future long-term

recurrence risk, based on clinical expert opinion that recurrence risk is likely to be higher for greater number of previous ulcer healing cycles. Whilst the model allows for a transition to amputation, EAG clinical expert advice was that amputation for venous leg ulcers in the UK is extremely rare, therefore the base case assumes a transition probability equal to 0. Venous ulcers are not assumed to be fatal, and therefore transition to the death state is assumed equal to UK age and sex adjusted all-cause mortality. The transition probabilities for the venous ulcer pathway are summarised in Table 18.

Table 18 Model transition probabilities (venous pathway)

Transition from:	To:	Source time	n/N (%)	Mean (SE)	6-monthy cycle prob	Alpha	Beta	Dist.	Source / Notes
Unhealed [A]	Healed	1 yr. prob	170/195 (87.2%)		64.2%	170	25	Beta	EVRA study[93]
		2 yr. prob		0.954 (0.047) [A]	53.7%	18.0	0.868	Beta	EVRA long term follow-up[99]
		3 yr. prob		0.962 (0.048) [A]	42.0%	14.3	0.565	Beta	EVRA long term follow-up[99]
Unhealed	Amputation	--	--		0	--	--	Fixed	Assumption
Unhealed	Death	--	--		ACM	--	--	Fixed	Assumption
Healed	Recurrence	1 yr. prob	38 / 154 (24.7%)		13.2%	38	116	Beta	EVRA long term follow-up[99]
		2 yr. prob	9 / 132 (6.8%)		3.5%	9	123	Beta	EVRA long term follow-up[99]
		3 yr. prob	10 / 93 (10.8%)		5.5%	10	83	Beta	EVRA long term follow-up[99]
Healed	Amputation	--	--		0	--	--	Fixed	Assumption
Healed	Death	--	--		ACM	--	--	Fixed	Assumption
Recurrence	Healed	1 yr. prob		0.884 (0.044) [A]	0.659	45.94	6.03	Beta	EVRA long-term follow up[99]

		2 yr. prob +		0.927 (0.046)[A]	0.480	28.72	2.26	Beta	EVRA long-term follow up[99]
Recurrence	Amputation	--	--		0	--	--	Fixed	Assumption
Recurrence	Death	--	--		ACM	--	--	Fixed	Assumption

[A] Data obtained from digitised KM curves – SE set = 5% of the mean.

ACM: All-cause mortality; prob.: Probability; SE: Standard error

Mixed and arterial ulcer transition probabilities

Table 19 describes the transition probabilities applied in the arterial (and mixed) disease model. The arterial and mixed proportion of the cohort enter the model in the CLI, healed or amputation state, depending on the outcomes achieved during CLI treatment (angioplasty or bypass surgery) in the decision tree phase of the model. Mixed (venous / arterial) and arterial ulcers follow similar pathways. For mixed ulcers, where Fontaine stage dependent transitions are available in the literature, these are applied in the model. However, for several parameters, it has not been possible to source stage dependent transition probabilities. Where this is the case, we assume that transition probabilities are independent of the underlying stage of disease severity.

The proportion of the cohort that enters the CLI state are treated with angioplasty or surgical bypass as it is assumed that medical management will be unsuccessful. The cohort are exposed to the same probabilities of success as defined for the decision tree pathways. For the proportion of patients who have a successful CLI procedure (no further procedure required), they enter the 'healed post CLI' state. Healed arterial and mixed ulcers (post CLI) then remain at risk of recurrence. The transition probability from healed post CLI back to the CLI state was assumed equal to the transition from symptomatic PAD to CLI as reported in a meta-analysis of N=7 studies of symptomatic PAD, conducted by Sigvant 2016.[101] The study published a recurrence rate at 1 year of 0.046, converted to a probability of 2.3% per cycle for application in the model, leading to a cumulative probability of CLI recurrence at 5 years equal to 21%. Each cycle of recurrence of CLI is assumed to carry the same event probabilities given a lack of evidence on the treatments and outcomes for recurrent CLI.

The proportion of the cohort who do not have a successful outcome from CLI surgery, require further surgery or amputation. For the proportion who do not receive amputation, tunnel states are used to increase the level of invasiveness of treatment in subsequent rounds of treatment, assuming one round of treatment per cycle. Those who have failed angioplasty are assumed to require bypass, and those who have failed bypass require a repeat surgery. All of those who have failed to achieve successful outcomes in the first 4 cycles of the tunnel state are assumed to require amputation. The risk of progressing directly to amputation post first or second treatment failure with angioplasty / bypass is obtained from CG147 as the 3-monthly transition from CLI to amputation and converted to a six-monthly probability for use in our model.

Long-term mortality risks in the arterial and mixed disease models

Transitions to the model death state for those with arterial or mixed disease are uncertain, and likely to be patient and risk-factor dependent. For example, those with diabetes and other cardiovascular risk factors are at significantly increased mortality risk.[103] Mortality risks from PAD health states include all-cause general population mortality, excess risks for PAD patients generally, excess risk for CLI, and in-hospital mortality risks for CLI related procedures (angioplasty, bypass, and amputation). Age and sex adjusted UK general population all-cause mortality risk is obtained from UK life tables.[104]

The background hazard ratio of death for asymptomatic peripheral arterial disease, assumed equivalent to Fontaine stage 1, compared to age and sex adjusted UK population all-cause mortality rates was obtained from a meta-analysis of 4 studies, reporting a pooled hazard ratio of all-cause mortality of 1.53 (1.18 to 1.99) for asymptomatic PAD (i.e., low ABPI, but no symptoms reported) compared to normal ABI.[101] Sigvant et al[100] also estimate a HR of 1.98 (1.48 to 2.65) for symptomatic PAD compared to normal ABI, based on a meta-analysis that included 5 studies. As our base case analysis assumes all patients with arterial or mixed disease have at least mild claudication, they are at least a Fontaine stage II (equivalent to Rutherford stage 1+). The hazard ratio of 1.98 is therefore applied to general population all-cause mortality rates and converted to a six-month cycle specific probability for transition to the model death state. This transition is applied as a background transition to death in all stages of the model.

Patients with critical limb ischemia (CLI) are at an even greater risk of death, with mortality rates increasing with more severe CLI disease. A systematic review identified two studies that reported mortality risks according to Rutherford disease classification stage.[105-107] For example, Luders et al. report an analysis of German health insurance data for patients with CLI over a median of 2.1 years of follow up.[106] The study found that mortality HRs, obtained from a Cox regression model controlling for co-morbidities were:

- Rutherford stage 4 (F3) vs. Rutherford stage 1-3: 2.01 (1.88 to 2.14);
- Rutherford stage 5 (F4) vs. Rutherford stage 1-3: 2.46 (2.32 to 2.61) and
- Rutherford stage 6 (F4) vs. Rutherford stage 1-3: 3.59 (3.40 to 3.78).

Assuming the HR for Fontaine 4 CLI is the midpoint of Rutherford stages 5 and 6, then a HR of (2.46+3.59)/2 = 3.025 could be applied to CLI related mortality in the model. The second

study (Reinecke, 2015) conducted a similar study, also using German insurance claims data, drawing very similar conclusions.[107] The data from Luders et al. are therefore applied in the base case model.

The additional risk of mortality for more extensive CLI disease will, by definition, include mortality in the immediate after-math of surgery such as post angioplasty and post bypass. The base case analysis therefore does not apply any further risk of 'in-hospital' mortality following surgery to avoid the risk of double counting the risk of death in the model. However, the mortality impact of a false negative test result that leads to inappropriate compression of the arterial ulcer may be better captured in our model structure by accounting for the additional mortality risk associated with more invasive / intensive procedures associated with the requirement for escalated care. National audit data (from the national vascular registry) show that patients requiring bypass surgery are at increased risk of 'in-hospital' mortality compared to those requiring angioplasty, though this additional risk is not reported according to a measurement of arterial disease severity.[98] As a scenario analysis, we therefore obtain the probability of in-hospital mortality for angioplasty, bypass, and amputation from the national audit report, and apply a treatment specific post-treatment mortality instead of applying the same mortality risk across all treatments in the CLI state. The mortality risk is obtained as a weighted average of mortality post elective and emergency procedures for angioplasty and bypass respectively.[98] Given that the model structure calculates the expected impact of FN on requirement for escalated treatment, this approach may better capture any long-term mortality impact of escalated treatment due to more invasive procedures for those who receive inappropriate compression of an arterial ulcer. However, this approach likely under-estimates overall mortality in the arterial cohort.

Table 19 Model transition probabilities (arterial / mixed pathway)

Transition from:	To:	Parameter type	Source time frame *(e.g., over 2 years)*	Parameter: n/N (%) HR / RR (CI)	6-monthy cycle prob	Alpha	Beta / Lambda	Dist.	Source / Notes
CLI	Healed post CLI	Prob	Post treatment success	Multiple	Multiple	Multiple	Multiple	Multiple	Six-monthly transition probability-based treatment specific success probabilities following angioplasty and bypass, weighed according to procedure type (elective / emergency). See table 14 for further details. Data obtained from the National vascular audit report, 2021.[98]
CLI	Death	HR	HR of F4 vs. F2 (background arterial).	3.026 (average of Rutherford 5 and 6)	Age dependent (0.044 in cycle 1 for age 70)	R5: 0.900 R6: 1.278	R5: 0.030 R6: 0.026	LN	HR of mortality for a population with a low ABPI, background excess mortality risk for a population with arterial disease (Sigvant, 2016)[101], multiplied by HR of CLI (average of Rutherford stages 5 and 6 (F4) vs.

Transition from:	To:	Parameter type	Source time frame *(e.g., over 2 years)*	Parameter: n/N (%) HR / RR (CI)	6-monthy cycle prob	Alpha	Beta / Lambda	Dist.	Source / Notes
CLI	Amp	Probability	3-month	6.9% (6.3 to 7.6%)	0.1340	372.17	4990.92	Beta	R1-3 (F2), obtained from Luders et al..[106] Obtained from CG147, based on ACC / AHA 2005 practice guidelines[23]
Healed post CLI	CLI	Rate	1 yr.	0.0466 (0.0260 to 0.0672)	0.023	18.73	383.25	Beta	Assumed equal to the transition between symptomatic PAD (e.g., IC) to CLI, in the absence of any information on long term recurrence post healing of arterial ulcers; Sigvant et al. meta-analysis.[101]
Healed post CLI	Death	HR applied to all-cause mortality rates	Median 5 year follow up	HR: 1.98 (symptomatic PAD vs. normal ABI)	Age dependent (0.015 in cycle 1 for age 70)	0.683	0.149	LN	HR obtained from Sigvant,et al. meta-analysis,[101] symptomatic PAD vs. normal ABI. Normal ABI assumed equal to UK general population ACM.

Transition from:	**To:**	**Parameter type**	**Source time frame *(e.g., over 2 years)***	**Parameter: n/N (%) HR / RR (CI)**	**6-monthy cycle prob**	**Alpha**	**Beta / Lambda**	**Dist.**	**Source / Notes**
Amputation	Death	Probability	Cycle 1 Cycle 2+	0.047 0.047/2	Tunnel 1: 0.046; Tunnel 2+: 0.023	-3.06	0.06	LN	Age adjusted risk of mortality following amputation, based on HR obtained from National vascular registry[98]

[A] Approximated from published KM curves, SE assumed = 20% of mean, capped at p=1.

ABI: Ankle brachial index; ACM: All-cause mortality; CLI: Critical limb ischemia; HR: Hazard ratio; LN: Log-Normal; PAD: Peripheral arterial disease; RR: Relative risk

Model parameters – resource use and costs

Diagnostic test costs

The costs of manual and automated doppler measurements have been calculated using a micro-costing approach. Resource usage included in the test cost calculations are:

- **Staff costs:** time to conduct the tests in clinical practice. The base case analysis assumes one band 5 community nurse is required to complete both the manual and automated tests, with test times derived from the review of diagnostic accuracy studies (See Section 3.3 for details of test times). Some studies and "how to" guides suggest that two nurses may be required to complete the manual Doppler test, and the impact of this on costs is considered in scenario analyses.[108] Further scenario analyses explore the impact of different levels of staff completing the test, including band 7 advanced nurses, for example at a leg ulcer clinic, or tests completed by a consultant at a vascular surgery clinic. A final scenario applies the resource use times as reported by the companies in their response to NICE's information request, or from the relevant product manuals. Unit costs per minute of staff time were obtained from PSSRU average cost per hour, including qualification costs.[109]

- **Equipment costs:** include the costs of measurement devices, additional purchase of a range of cuff sizes to ensure all patients can receive a measurement, software where appropriate, and replacement cuffs. Unit costs of equipment are provided by the companies or sourced from online suppliers where data are unavailable. All costs are provided exclusive of VAT. Per patient costs are allocated based on the tests useful lifetime horizon and expected throughput per year. The useful life-time horizon was obtained directly from the companies or conservatively assumed equal to two years where this information was unavailable to the EAG. Expected device throughput is uncertain and driven by the time taken to complete the respective tests and the setting in which the test may be used (e.g., at a leg ulcer clinic, at a GP practice, by a district nurse, or in a vascular surgery consultation). The base case analysis assumes that, on average, 8 tests per day might be completed. Scenario analysis explores varying this between a minimum value of 1 test per day, and a maximum value equal to the maximum number of tests that could be conducted given the time taken to conduct each test over a 7-day, 40-hour week, 52-week year. The latter analysis would allow shorter tests to have greater throughput and a lower average equipment cost allocated per patient tested.

- **Consumables:** Based on the company response to information requests, where consumable costs have been provided, these are included in the evaluation. These include the costs of printed results where these are available, and the costs of ultrasound gel for the manual doppler test. Consumables and equipment for the manual doppler test are obtained from a manual doppler technical guide available from Wounds international.[108]

- **Repeat test costs:** The proportion of tests that deliver an error message, zero reading, or other technical failure may have implications for costs. The base case analysis assumes that where a manual or an automated test fails to deliver a reading, that the patient would be re-tested once only using the same method. This assumption was validated with clinical expert opinion. The definition of a technical failure is however incompletely and inconsistently defined across the diagnostic accuracy review studies, therefore differences in rates should be interpreted cautiously. The base case assumes that all failures would be re-tested once using the same method, and implicitly that the device will then provide a correct reading. However, this may be an under-estimate of re-testing costs because some technical failures may require referral onwards to vascular services to obtain a more definitive estimate using duplex ultrasound or CT angiography. The implication is that the base case may be biased in favour of automated testing, though the magnitude of any bias is unclear because it is unknown what proportion of technical failures would provide an accurate reading upon re-test. This proportion is varied in two scenario analyses assuming that 50% and 100% of technical failures would require referral onwards to vascular services where they incur the costs of an outpatient consultation and duplex ultrasound test.

Table 20 provides a breakdown of resource use and cost for each test in the base case analysis. Table 21 details the costs of each test under a range of scenario analyses. All test costs are incorporated into the model as fixed parameters.

Table 20 Test cost calculations (base case analysis)

	Manual Doppler	**BlueDOP medical**	**Bosch and Sohn**	**Dopplex ability, Huntleigh**	**Mesi ABPI MD**	**Mesi M Tablet ABI**	**WATCH BP ABI MicroLife**	**WATCH BP Vascular MicroLife**
Staff costs								
Staff grade	Nurse (B5)	Nurse (B5)	Nurse (B5)	Nurse (B5)	Nurse (B5)	Nurse (B5)	Nurse (B5)	Nurse (B5)
Number of staff to conduct test	1	1	1	1	1	1	1	1
Staff unit cost (per minute)	£0.73	£0.73	£0.73	£0.73	£0.73	£0.73	£0.73	£0.73
Rest / preparation time (mins) [A]	10.00	3.00	5.00	2.50	2.00	5.00	10.00	10.00
Test time (mins) [A]	11.92	1.00	3.00	4.30	5.24	5.24	10.10	10.10
Interpretation time (mins) [A]	5.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total time (mins)	26.92	5.00	9.00	7.80	8.24	11.24	21.10	21.10
Staff cost	***£19.74***	***£3.67***	***£6.60***	***£5.72***	***£6.04***	***£8.24***	***£15.47***	***£15.47***
Device costs								
Device equipment fixed cost [B]	£252.81[C]	£4,995.00	£3,150.00	£2,749.00	£2,325.00	£2,700.00	£1,695.00	£1,995.00
Initial purchase of additional cuffs to complete set [B]	£87.96 [C]	£0.00	£37.10	£304.00	£174.00	£174.00	£250.00	£250.00
Software	£0.00	£0.00	£0.00	£454.00	£0.00	£0.00	£0.00	£0.00

	Manual Doppler	**BlueDOP medical**	**Bosch and Sohn**	**Dopplex ability, Huntleigh**	**Mesi ABPI MD**	**Mesi M Tablet ABI**	**WATCH BP ABI MicroLife**	**WATCH BP Vascular MicroLife**
Other fixed costs	£0.00	£0.00	£0.00	£430.00	£0.00	£0.00	£200.00	£200.00
Total fixed costs per unit	*£340.77*	*£4,995.00*	*£3,187.10*	*£3,937.00*	*£2,499.00*	*£2,874.00*	*£2,145.00*	*£2,445.00*
Number of cuffs	1	0	4	4	3	4	2	2
Replacements cuffs per year [D]	5.84	0	5.84	5.84	5.84	5.84	5.84	5.84
Unit cost per replacement cuff [B]	£21.99	£0.00	£18.50	£73.50	£46.67	£35.00	£55.00	£55.00
Useful life (years)	2[E]	3	2[E]	7	5	5	5	5
Max possible throughput per year [F]	2920	2920	2920	2920	2920	2920	2920	2920
Replacement cuff costs:	£0.04	0	£0.15	£0.59	£0.28	£0.28	£0.22	£0.22
Device cost per test	***£0.10***	***£0.57***	***£0.69***	***£0.78***	***£0.45***	***£0.48***	***£0.37***	***£0.39***
Consumable 1 (number required)	1	0	0	1	0	0	0	0
Consumable 1 (unit cost)	£0.16 [G]	£0.00	£0.00	£0.37	£0.00	£0.00	£0.00	£0.00
***Consumable 1 costs** per test*	***£0.16***	***£0.00***	***£0.00***	***£0.37***	***£0.00***	***£0.00***	***£0.00***	***£0.00***
Technical failure probability [H]	0.02	[redacted]	0.08	0.04	0.15	0.15	0.08	0.08
Additional time between tests	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00

	Manual Doppler	BlueDOP medical	Bosch and Sohn	Dopplex ability, Huntleigh	Mesi ABPI MD	Mesi M Tablet ABI	WATCH BP ABI MicroLife	WATCH BP Vascular MicroLife
proportion of technical failures referred to vascular services	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
cost per referral to vascular clinic + ultrasound [I]	£418.44	£418.44	£418.44	£418.44	£418.44	£418.44	£418.44	£418.44
Re-test costs per test	***£0.48***	[redacted]	***£0.56***	***£3.92***	***£0.96***	***£1.29***	***£1.25***	***£1.25***
Total cost per test	**£20.48**	[redacted]	**£7.86**	**£10.79**	**£7.45**	**£10.01**	**£17.09**	**£17.11**

[A] Timing estimates obtained from the included diagnostic accuracy studies where possible. Assumed equal to company provided estimates otherwise.

[B] Device and equipment costs are exclusive of VAT.

[C] According to https://www.woundsinternational.com/uploads/resources/content_9496.pdf , the following equipment is required: (1) A doppler ultrasound with an 8MHZ probe - assumed cost: £194.99 as per price on medisave.co.uk as of August 2022; (2) a sphygmomanometer (cost = AVERAGE(55.99,58.96,55.99,55.99,63.99,55.99) based on the average of all welch Allyn sphygmomanometers available on medisave.co.uk; (3) 4 x blood pressure cuffs of appropriate size, price based on Welch Allyn cuffs of various sizes, available on medisave.co.uk for £21.99 each.

[D] In a response to an EAG query to all companies, Mesi responded that a cuff would be replaced for every 500 measurements, so replacement frequency is dependent on the throughput of the test. In the absence of information from other companies, it is assumed that the replacement of once per 500 measurements can be applied across all tests, automated and manual.

[E] Assumed lifetime horizon because information was not available to the EAG, either from the companies, from literature, or from clinical expert opinion.

[F] Base case = moderate (1/hr over an 8-hour day across all settings); scenarios explore low estimate based on 1 patient per day, ad hoc usage; high estimate based on max possible throughput calculated from total test times. All calculations assume an 8-hour day, 7 day-week and 365 days per year.

[G] Consumables: ultrasound gel for contact medium (aqua sonic clear transmission gel 5 litres with dispenser): Cost £15.99 (excl VAT). Medisave.co.uk, prices checked 16.08.22; assume 50ml per patient, leads to each 5L container completing approximately 100 tests.

[H] Technical failure proportion is obtained from the published literature, or directly from companies where no literature exists. Where more than one study in the diagnostic accuracy review provided a technical failure proportion, the proportion used in the model is a weighted average of the available data (weighted according to study size). Failures for the manual doppler test are taken as a weighted average of studies that reported this data from the review.

[I] The cost of referral to vascular services includes the cost of a first attendance, face-to-face, consultant led, vascular surgery outpatient clinic (Service code: 107; Currency code: WF01B; Cost = £307.70, plus a vascular surgery outpatient ultrasound scan (currency code: RD47Z; Cost = £110.74). Costs obtained from NHS reference costs 2020/21[110]

Table 21 Intervention costing scenario analyses

Scenario description	Manual Doppler	BlueDOP medical	Bosch and Sohn	Dopplex ability	Mesi MD	Mesi M Tablet	WATCH BP ABI	WATCH BP Vascular
Base case total cost per test	£20.48	[redacted]	£7.86	£7.26	£7.45	£10.01	£17.09	£17.11
Scenario 1: Assume a grade 7 nurse conducts tests	£30.59	[redacted]	£11.41	£10.30	£10.92	£14.74	£25.44	£25.46
Scenario 2: Assume a consultant conducts tests	£56.32	[redacted]	£20.46	£18.02	£19.75	£26.78	£46.69	£46.71
Scenario 3: Test times from the companies	£20.48	[redacted]	£6.28	£5.89	£3.89	£6.44	£15.03	£15.06
Scenario 4: Assume 2 nurses required for manual doppler	£40.70	[redacted]	£7.86	£7.26	£7.45	£10.01	£17.09	£17.11
Scenario 5: Apply low test throughput	£20.90	[redacted]	£11.97	£8.66	£8.83	£11.59	£18.20	£18.38
Scenario 6: Apply high test throughput	£20.45	[redacted]	£7.36	£7.09	£7.29	£9.83	£16.99	£17.00
Scenario 7: 50% of technical failures require referral to vascular services + duplex ultrasound	£25.26	[redacted]	£23.68	£14.81	£37.94	£40.33	£32.99	£33.02
Scenario 8: 100% of technical failures require referral to vascular services + duplex ultrasound	£30.05	[redacted]	£39.51	£22.36	£68.42	£70.65	£48.90	£48.92

Model parameters – costs

Costs are evaluated from a UK NHS perspective and reported in 2020/21 GBP. Data to inform health state costs were obtained from targeted searches of the literature with preference given to studies conducted in the UK for model parameterisation. Where possible, resource use from published studies has been re-costed using the appropriate national average unit costs for 2020/21, including PSSRU for primary care and hospital staff time, NHS reference costs for procedures and the BNF for drug treatments.[109, 110, 112] Where resource use data are unavailable, source cost study estimates have been inflated from their study reported year to 2020/21 values.[109] Costs were incorporated into the model probabilistically by sampling from gamma distributions. Where a measure of spread was unavailable, we assumed a standard deviation of 20% of the mean.

Arterial and mixed pathways

All patients with a test result indicative of arterial disease are referred to vascular services for further investigation and initiation of preventative treatment for their arterial disease. The cost of referral for a first attendance at a consultant led vascular surgery outpatient clinic (£307.70) was obtained from NHS reference costs 20/21.[110] This referral cost is applied to all positive test result cases, including false positives. The base case analysis assumes that a FP result would then be recognised at the point of referral to a vascular surgery clinic and patients would then appropriately incur the venous pathway costs. Scenario analysis explores the impact of an additional duplex ultrasound investigation for all initial test positive patients who are referred to vascular services (£110.74).[110] It is assumed that no preventative treatment for arterial disease would be initiated because of a FP result.

The decision tree phase of the model also includes a nominal cost applied universally across all arterial (including mixed) pathways and is informed by resource use ascribed to the mild arterial disease state within Ezeofor, 2021 supplemented with costs sourced from CG147 and the NHS reference costs 2020/21[110, 111]. This equates to a cost of £709.06 per year, which includes: cholesterol testing, medication, 3-month supervised exercise programme and vascular nurse specialist visits (one per quarter).[111] Additional intervention costs are then applied dependent on whether the patient is modelled to undergo an angioplasty, surgical bypass, or amputation. All arterial patients will receive some intervention within the decision tree phase because clinical expert opinion indicates that arterial ulcers are unlikely to heal

with conservative management alone. Within the Markov component of the model, this cost is then applied within the healed-post CLI state, or equivalently, Fontaine stage 2.

The Markov health state cost of arterial or mixed ulcers is dependent upon the progression of their condition. All patients with an arterial ulcer would be classified as Fontaine 4 which is synonymous with CLI. Due to a lack of health care resource use data for mixed ulcer patients, it is assumed that the focus of treatment is on the arterial aetiology of their disease. However, given mixed aetiology patients have a higher ABPI (0.5-0.85) than their purely arterial counterparts, we assume a distribution of severity from Fontaine stages 2 to 4. Within the model structure, all patients of Fontaine stage 3 / 4 are assumed to undergo an invasive intervention (e.g., angioplasty / bypass) within the decision tree phase. Following successful intervention, patients would then move to the healed post-CLI state. For simplicity, we have assumed that this is synonymous with intermittent claudication (or Fontaine stage 2) where the resource use is based on the mild arterial disease state within Ezeofor et al. 2021 similar to the nominal cost applied in the decision tree phase of the model.[111] Should the ulcer not heal, or through recurrence, the patient would move to the CLI state. The CLI state consists of a consultant led appointment, angiogram, and wound management resulting in an annual cost of £1,885.07. The surgery required to treat CLI is accounted for through the tunnel state, angioplasty, and bypass, which carry respective mortality risks and resource use.

The most severe cases of CLI result in amputation. This represents a substantial burden to the health service in the short and long term as patients who were once independent often require fulltime care. Therefore, we have included an amputation pathway and health state within the decision tree and Markov components of our model. Within our analysis, we attribute costs by the first year and subsequent years post procedure. The first-year costs are substantially higher to account for recovery through rehabilitation and wound care (£35,813.44). For subsequent years, we apply the cost of any additional care related to lifestyle changes after amputation (£14,294.65). A detailed breakdown of how these costs were calculated is provided in Appendix 7.

Venous

Venous ulcer treatment costs obtained from Urwin 2021 are applied during the unhealed time in the decision tree. Urwin 2021 report a mean cost of £166.39 (95% CI: £157.78 - £175.00) for two-weeks of treatment.[113] An average daily cost of £11.89 (or £14.61 in 2020/21 prices) is applied. For ulcers which heal, a daily cost of medical management and prevention is incurred which equates to a daily cost of £0.32. This assumes 2 visits with a nurse (cost per visit of £53.33 (mean of bands 5-7)) [109] and 4 pairs of knee-high graduated compression stockings (£4.31 each) per year. [114]

Venous ulcer treatment costs, applied to the unhealed time in the decision tree and the unhealed health state within the Markov model, are also obtained from Urwin 2021. [113] The corresponding six-monthly costs for the unhealed Markov state are therefore £2,163.07 (or £2667.93 in 2020/21 prices). Patients with a healed venous ulcer are assumed to require monitoring and preventative treatment for the first 2 years post-healing and none thereafter. We accept that this may be conservative, however under limited resources within the NHS it is not reasonable that healed patients would be monitored indefinitely. We applied 2 visits with a nurse in the first year and 1 visit in the second. This results in an annual cost of £115.28 and £61.95 in years 1 and 2 respectively. It is assumed that the cost of treating a healed or unhealed venous ulcer does not depend on whether it is the primary or a recurrent ulcer.

Table 22 Summary of health state costs applied in the model

Health state	Dist.	Study year	Mean	Std. Error	Mean 2020/21 values	SE 2020 / 21 values	Alpha	Beta/ Lambda	Notes	References / sources
Healed Venous	Gamma	2013 and 2021	Yr 1. £115.28 Yr 2. £61.95 Yr 3. £0	£23.06 £12.39	Yr 1. £116.49 Yr 2. £63.16 Yr 3. £0	£23.30 £12.63	24.99 25.01	0.2416 0.3959	Includes the costs of compression stockings (2 per year at £4.31) and nurse visits (bands 5-7) for monitoring (Y1: 2 visits; Y2: 1 visit; Y3: 0 visits)	PSSRU 2021[109] Wade et al. 2015[114]
Healed post recurrence Venous	Gamma	2015	Yr 1. £115.28 Yr 2. £61.95 Yr 3. £0	£23.06 £12.39	Yr 1. £116.49 Yr 2. £63.16 Yr 3. £0	£23.30 £12.63	24.99 25.01	0.2416 0.3959	Assumed equal to the costs of a healed ulcer.	PSSRU 2021[109] Wade et al. 2015[114]
Unhealed Venous	Gamma	2019	£166.39 / 2 weeks	£104.69	£175.31 / 2 weeks	£109.98	2.84	0.0162	Converted to daily costs for DT and 6-mth costs for markov state.	Urwin et al., 2021[113]
Recurrence Venous	Gamma	2019	£166.39 / 2 weeks	£104.69	£175.31 / 2 weeks	£109.98	2.84	0.0162	Assumed equal to unhealed ulcer	Urwin et al., 2021[113]
CLI (base cost excl. surgery)	Gamma	2021	-	-	£1885.07 / year	£377.01	25.00	0.0133	Resource use assumptions sourced from severe health state of Ezeofor et al. 2021, includes: consultant led	Ezeofor et al. 2021[111]

Health state	Dist.	Study year	Mean	Std. Error	Mean 2020/21 values	SE 2020 / 21 values	Alpha	Beta/ Lambda	Notes	References / sources
									clinic appointment, weekly nurse visits and dressings, angiogram.[111]	NHS reference costs 2020/21[110] PSSRU 2021[109]
Angioplasty	Gamma	2021	-	-	£4,796.36	£959.27	25.00	0.0052	Weighted average of HRG codes YR11 & YR15	NHS reference costs 2020/21[110]
Bypass (Elective)	Gamma	2021	-	-	£15,281.37	£3,056.27	25.00	0.0016	Weighted average of elective long and short stay HRG codes YQ05, YQ12 & YQ13	NHS reference costs 2020/21[110]
Bypass (Non-elective)	Gamma	2021	-	-	£15,859.06	£3,171.81	25.00	0.0016	Weighted average of non-elective long and short stay HRG codes YQ05, YQ12 & YQ13	NHS reference costs 2020/21[110]
Healed post-CLI	Gamma	2021	-	-	£354.53 / 6 months	£70.90	25.00	0.071	Resource use assumptions sourced from Ezeofor et al. 2021. 2 visits with nurse at non-consultant led clinic. Exercise programme cost uplifted from CG147 (assumed once per year). Cholesterol tests and	NHS reference costs 2020/21[110] Ezeofor et al. 2021[111] CG147[23]

Health state	Dist.	Study year	Mean	Std. Error	Mean 2020/21 values	SE 2020 / 21 values	Alpha	Beta/ Lambda	Notes	References / sources
									medication uplifted from Ezeofor et al. 2021[111]	
Amputation (initial procedures)	Gamma	2021	-	-	£11,392.48	£2,278.50	25.00	0.002	Unit cost includes procedure only weighted by the proportion of below to above knee amputation procedures within the national vascular registry 2021 (YQ22/YQ26)	NHS reference costs 2020/21[110]
First year following amputation	Gamma	2021	-	-	£35,804.46 / year	£7,160.89	25.00	6.981	See appendix 7.	NICE Clinical Guideline. CG147[23] Davie-Smith. F, 2015[115] Taylor et al. 2005[116] NHS reference costs. 2020/2[110] PSSRU 2019/20[117]

Health state	Dist.	Study year	Mean	Std. Error	Mean 2020/21 values	SE 2020 / 21 values	Alpha	Beta/ Lambda	Notes	References / sources
										PSSRU 2020/21[109]
Second year plus, following amputation	Gamma	2021	-	-	£14,293.65 / year	£2,858.73	24.83	0.0017	See appendix 7.	NICE Clinical Guideline. CG147[23] Davie-Smith. F, 2015[115] Taylor et al. 2005[116] NHS reference costs. 2020/21[110] PSSRU 2019/20[117] PSSRU 2020/21[109]
Death	Fixed		0	--			--	--	Assumption	--

Note: Where resource use data unavailable, costs are inflated to 2020/21 values using PSSRU inflation indices; where SE not reported, SE assumed equal to mean x 20%.;

Abbreviations: CG: Clinical guideline; CLI: Critical Limb Ischaemia; PSSRU: Personal and Social Services Research Unit;

Model parameters – utilities

Venous ulcers:

Utilities for healed and unhealed venous ulcers were obtained from Iglesias et al., a large UK study, reporting an economic evaluation of the VenUS1 trial.[75] The study is preferred over alternative sources as it reports EQ-5D utility data classified by healed / unhealed status. Due to a lack of data, it is assumed that the utility of recurrent and healed post recurrence venous ulcers are equivalent to healing and recurrence of the primary venous ulcer. Similarly, for mixed venous / arterial ulcers, it is assumed that, where the ulcer is treated with compression (i.e., primarily venous), then the utility of the healed, unhealed and recurrence states is equivalent to those of venous ulcers. Mixed ulcers, where the cohort enter the arterial pathway are assigned the utilities of the arterial pathway as described below.

Arterial ulcers:

A recent review of the literature, conducted by Duff, 2019,[105] identified 2 studies that reported EQ-5D utilities for patients with CLI.[118, 119] Forbes et al. report baseline EQ-5D data from the BASIL trial prior to randomisation to angioplasty or surgery, reflecting a population of UK CLI patients (N=417; angioplasty: 214; surgery: 203) requiring active treatment.[118] UK value set utilities were mean (SD): 0.26 (0.32) and 0.28 (0.34) for those randomised to angioplasty and surgery respectively. We apply the angioplasty utility for the base case analysis. Pisa et al. was an international study of 200 CLI patients, 50 of which were from the UK.[119] UK value sets for CLI (defined as Fontaine stage three or four) were, mean (SD): 0.474 (0.303). These higher values are considered for scenario analyses, however, are not used in the base case due to the smaller uk sample and because Forbes et al., allows exploration of utilities following different procedures (angioplasty and bypass). Utility in the amputation is 0.564 based on Ernsston et al, based on EQ-5D utility (UK value set) for a below the knee amputation.[120]

Summary of utility values applied in the model:

Table 23 provides a summary of the utilities applied in the economic model. All utilities are incorporated using beta distributions. All utility input parameters are age and sex adjusted to the starting age and sex distribution of the modelled cohort. Utility inputs are then further adjusted in each subsequent model cycle by a multiplier (utility of general population at model cycle age / utility of general population at model start age) to account for reducing quality of life as the cohort ages over time. Utility of the death state is zero.

Table 23 Summary of health state utility values applied in the model

Health state	Dist.	Mean	Std. Error	Alpha	Beta	Notes	References / sources
Venous ulcers (including mixed aetiology treated as venous)							
Healed	Beta	0.75	0.03	155.50	51.83	EQ-5D, UK value set	Iglesias et al. 2005[75]
Unhealed	Beta	0.64	0.02	368.00	207.00	EQ-5D, UK value set	Iglesias et al. 2005[75]
Recurrence	Beta	0.64	0.02	368.00	207.00	Assume equal to unhealed venous ulcer	Iglesias et al. 2005[75]
Healed post recurrence	Beta	0.75	0.03	155.50	51.83	Assume equal to healed venous ulcer.	Iglesias et al. 2005[75]
Arterial ulcers (including mixed aetiology in arterial health states)							
CLI (on entry to state)	Beta	0.2967	0.0053	2203.77	5223.82	Pooled SD across randomised arms at baseline, EQ-5D, UK population	Forbes, 2010[118]
Healed post CLI	Beta	0.70	0.14	6.80	2.91	EQ-5D study with 280 respondents	Holler et al, 2006[121] Simpson et al, 2014[122]
Amputation	Beta	0.564	0.0171	473.74	366.22	Below knee amputation, EQ-5D value set.	Ernstsson 2021[120]
Death	Fixed	0	--	--	--	Assumption	--

Abbreviations: CLI: Critical limb ischemia; SD: Standard deviation

Time horizon and discounting

The decision tree phase of the model describes ulcer healing probabilities over 24 weeks, before the cohort then enter a markov cohort model, with six-monthly cycles, up until age 100, reflecting a lifetime horizon. With a starting age of 70, the entire model therefore runs for a maximum of 30.46 years. Scenario analyses explore the impact of shorter time horizons. Costs and QALYs occurring beyond year 1 are discounted at 3.5% per annum, with scenario analyses varying the discount rate between 0% and 6%.

Analyses

The model is constructed to be fully probabilistic, sampling a selected number of Monte Carlo draws from distributions applied to model input parameters as described in the parameter tables. Base case results for three alternative plausible base case assumptions are reported probabilistically. Parameter uncertainty is described using cost-effectiveness acceptability curves (CEACs). Due to computation run time challenges, it was not possible to provide probabilistic analyses for all scenario analyses considered, and these have instead been presented deterministically.

Results are reported as incremental cost per quality adjusted life year (QALY) gained from a UK NHS perspective. ICERs were first calculated for all tests compared to the standard care, manual doppler test. A fully incremental analysis was also undertaken, where all test strategies were ranked in ascending order of QALYs gained. Tests that were more costly and less effective than an alternative test were excluded based on strict dominance, with ICERs calculated relative to the next best non-dominated strategy. Tests that provided more QALYs, at a lower ICER were further excluded on the grounds of extended dominance, and ICERs again recalculated versus the next best, non-dominated alternative. The test strategy that generated the highest ICER, under the threshold value can be considered the optimal testing strategy. ICERs are also presented for pairwise comparisons of each candidate test vs. manual doppler testing.

Model validation

Several ‘black box’ error checks were undertaken, following the approach suggested by published black-box verification checklists.[123, 124] Verification checks were conducted on estimation of costs and QALYs, varying parameters between extreme value scenarios to identify any modeling errors. Distributions were examined for plausibility and expected

values of total cost, QALY, and cumulative amputation probability, at different points of the tree pathway were examined for face validity and coherence with intended modelled pathways. Several issues were identified on early model drafts and corrected for the final base case model. No remaining issues were identified following a re-check of the final base case analysis.

4.4 Modelling results

The economic model assessed the potential cost-effectiveness of six different automated ABPI tests compared to manual doppler testing for the detection of peripheral arterial disease in people with leg ulcers. There were no diagnostic accuracy studies that provided sensitivity and specificity data for people with leg ulcers and no studies in any population that assessed the impact of different tests on health outcomes such as ulcer healing or need for invasive arterial procedures, such as angioplasty or bypass.

Overview of key assumptions

Due to the lack of available data, the economic implicitly assumes that the diagnostic accuracy data from a broadly defined heterogenous population is transferrable to people with leg ulcers. It further assumes that the reference standard (manual Doppler testing) provides accurate results. Whilst it is known that manual doppler testing is not the best method for PAD diagnosis, there is insufficient information to appropriately adjust estimates for the model to account for an imperfect reference standard. These assumptions should be considered when evaluating the appropriateness of the diagnostic accuracy data to populate the model.

The model uses a linked-evidence approach, informed heavily by clinical expert opinion to describe the impact of tests on health outcomes, including the impact of inaccurate test results on delayed ulcer healing time and need for invasive surgery due to inappropriate compression of arterial (and mixed Fontaine 3 or 4) ulcers.

Importantly, it is unknown what proportion of false negative or false positive test results would be identified by healthcare professionals at the time of testing, and thus what proportion of patients would incur negative consequences of inaccurate tests. The extent to which inaccurate test results could lead to delayed ulcer healing (FP) or increased risk of invasive arterial procedures (FN) is likely to be dependent on several factors but may be higher in settings where there is a scarcity of healthcare professionals who are skilled in the assessment of leg ulcers and PAD. Conversely, these may also be the same settings in which an accurate automated test may lead to time savings or reduced unnecessary referrals to secondary care of TN venous ulcer patients.

The model base case analyses are built around the following key assumptions:

- The modelled cohort reflects a population of leg ulcer patients, rather than from the diagnostic accuracy studies that contribute sensitivity and specificity data.
- The PAD cohort are split between the proportion who have arterial vs. mixed ulcers. The arterial component of disease is described in the model according to Fontaine stage (2,3,4) to allow the application of different treatments, costs, quality of life and mortality risk according to the severity of the underlying PAD. Whilst Fontaine staging may not be used universally in clinical practice, it is a useful approach to describe the severity of disease, and in particular the implication of inappropriate compression of arterial ulcers, the consequences of which are dependent on the underlying disease severity.
- It is assumed that primary amputation is rare, and that limb salvage is attempted using bypass and / or revascularization wherever possible, though it is more likely to be required for an inappropriately compressed arterial ulcer.
- For the Markov models, it is assumed that any test errors would be identified within 24 weeks with patients being allocated to the correct disease pathway (venous, mixed, arterial) and receiving appropriate treatment for their condition within this time (i.e., compression applied to a patient with an initial FP result, and appropriate surgical management of an inappropriately compressed patients due to a FN result).
- It is assumed that the proportion of the cohort with arterial (or mixed) disease who have a recurrence after 6 months incur the same costs and utilities regardless of the number of previous cycles in the critical limb ischemia state.
- It is assumed that venous ulcers experience healing post recurrence incur the same costs and utilities as those who achieve healing of the index ulcer. It is also assumed that the risk of recurrence does not depend on the number of previous recurrences due to a lack of data to determine relative risk parameters.
- The model assumes that for the proportion of the cohort with mixed ulceration, that clinical management prioritises the arterial component of disease first.
- It is assumed that people with venous ulcer disease have similar mortality risks to the general population, and that amputation does not take place in modern clinical practice for venous disease.
- The model is run for a lifetime horizon up to death or age 100 years, whichever comes first, with costs and QALYs discounted at an annual rate of 3.5% per annum.

Base case analyses

There are no data to populate the model with regards to A) the proportion of inaccurate test results (FP or FN) that would be acted upon in clinical practice; B) the implications of inappropriately applying compression to an arterial ulcer, though this may include a requirement for more invasive surgery with more serious consequences for more advanced arterial disease (e.g. F3 or F4); C) the delay in ulcer healing associated with delayed compression of a venous ulcer due to a FP test result or D) the extent to which automated tests could generate reductions in ulcer healing time for TN cases in scenarios with limited access to manual doppler testing and compression. These are important drivers of cost-effectiveness results but are highly uncertain parameters. It has therefore not been possible for the EAG to determine a preferred "base case" set of assumptions. We have instead reported results for three possible alternative base cases, according to moderate, optimistic, and pessimistic assumptions for automated testing. The moderate set of assumptions could be considered the EAG's best guess at a set of plausible base case assumptions, but further evidence is required on several key parameters before a definitive base case analysis could be determined. The assumptions for each base case analysis are outlined in Table 24 and the corresponding results from probabilistic runs of the model (1,000 simulations) are reported in Table 25.

Table 24 Three alternative base case model configurations

Parameter / assumption	Pessimistic	Moderate	Optimistic
Time gains from early testing (TN)	None	None	16 weeks (reflecting potential to refer TN cases directly to community leg ulcer clinics for compression. Assumes that average waiting time for a non-urgent consultation at vascular outpatient clinic = 18 weeks and wait times for community leg ulcer clinics are 2 weeks.
Delayed healing time for venous ulcers with a FP test.	Healing time of at least 168 days (all venous ulcers with a FP test result remain unhealed at 24 weeks), consistent with pessimistic end of range of clinical expert opinion.	As per mean of clinical expert opinion	No delay (all FP tests correctly identified as such during holistic patient assessment, compression not delayed)
Proportion of false negative tests acted upon	Arterial: 100% Mixed: 100%	Arterial: 0% Mixed: 100%	Arterial: 0% Mixed: 0%
Proportion of false positive tests acted upon	100%	100%	0%

FP = False positive; TN = True negative

Table 25 Base case probabilistic results

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	Probability cost-effective at £20K	ICER (vs. Manual Doppler)	Prob (C/E vs. Manual Doppler)
Moderate assumptions (Table 24)								
Manual Doppler	£11,713		8.046		--	0.999	--	--
BlueDop Vascular Expert	£11,930	£217	8.043	-0.003	Dominated	0.001	Dominated	0.001
WatchBP Office ABI	£12,037	£325	8.042	-0.004	Dominated	0.000	Dominated	0.000
WatchBP Office Vascular	£12,037	£325	8.042	-0.004	Dominated	0.000	Dominated	0.000
boso ABI-system 100	£12,149	£436	8.041	-0.005	Dominated	0.000	Dominated	0.000
MESI ABPI MD	£12,189	£476	8.040	-0.005	Dominated	0.000	Dominated	0.000
MESI mTABLET ABI	£12,191	£478	8.040	-0.005	Dominated	0.000	Dominated	0.000
Dopplex Ability	£12,262	£549	8.040	-0.006	Dominated	0.000	Dominated	0.000
Pessimistic assumptions (Table 24)								
Manual Doppler	£11,680		8.042		--	1.000	--	--
BlueDop Vascular Expert	£12,136	£456	8.035	-0.007	Dominated	0.000	Dominated	0.000
WatchBP Office ABI	£12,216	£535	8.035	-0.007	Dominated	0.000	Dominated	0.000
WatchBP Office Vascular	£12,216	£535	8.035	-0.007	Dominated	0.000	Dominated	0.000
boso ABI-system 100	£12,449	£769	8.032	-0.010	Dominated	0.000	Dominated	0.000

MESI ABPI MD	£12,462	£782	8.033	-0.009	Dominated	0.000	Dominated	0.000
MESI mTABLET ABI	£12,465	£785	8.033	-0.009	Dominated	0.000	Dominated	0.000
Dopplex Ability	£12,591	£910	8.031	-0.011	Dominated	0.000	Dominated	0.000
Optimistic assumptions (Table 24)								
MESI ABPI MD	£10,977		8.072		--	0.509	Dominant	0.994
MESI mTABLET ABI	£10,980	£3	8.072	0.000	Dominated	0.000	Dominant	0.000
Dopplex Ability	£10,987	£10	8.071	0.000	Dominated	0.153	Dominant	0.981
WatchBP Office ABI	£10,988	£11	8.072	0.000	Dominated	0.270	Dominant	0.989
WatchBP Office Vascular	£10,988	£11	8.072	0.000	Dominated	0.000	Dominant	0.000
boso ABI-system 100	£11,008	£31	8.071	-0.001	Dominated	0.065	Dominant	0.956
BlueDop Vascular Expert	£11,048	£71	8.070	-0.001	Dominated	0.000	Dominant	0.000
Manual Doppler	£11,779	£802	8.053	-0.018	Dominated	0.003	--	--

Abbreviations: ICER = Incremental cost-effectiveness ratio; Prob (C/E) = Probability of cost-effectiveness; QALY = Quality adjusted life years.

Figure 13 Cost-effectiveness acceptability curves for moderate base case

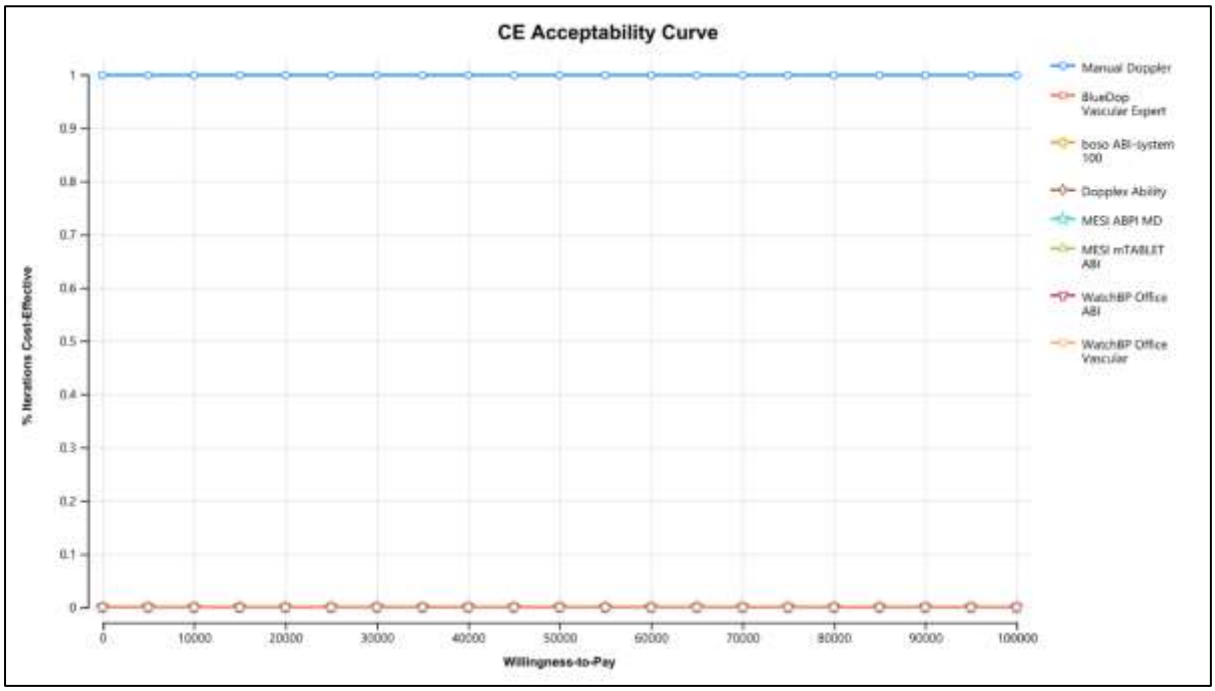


Figure 14 Cost-effectiveness acceptability curves for pessimistic base case

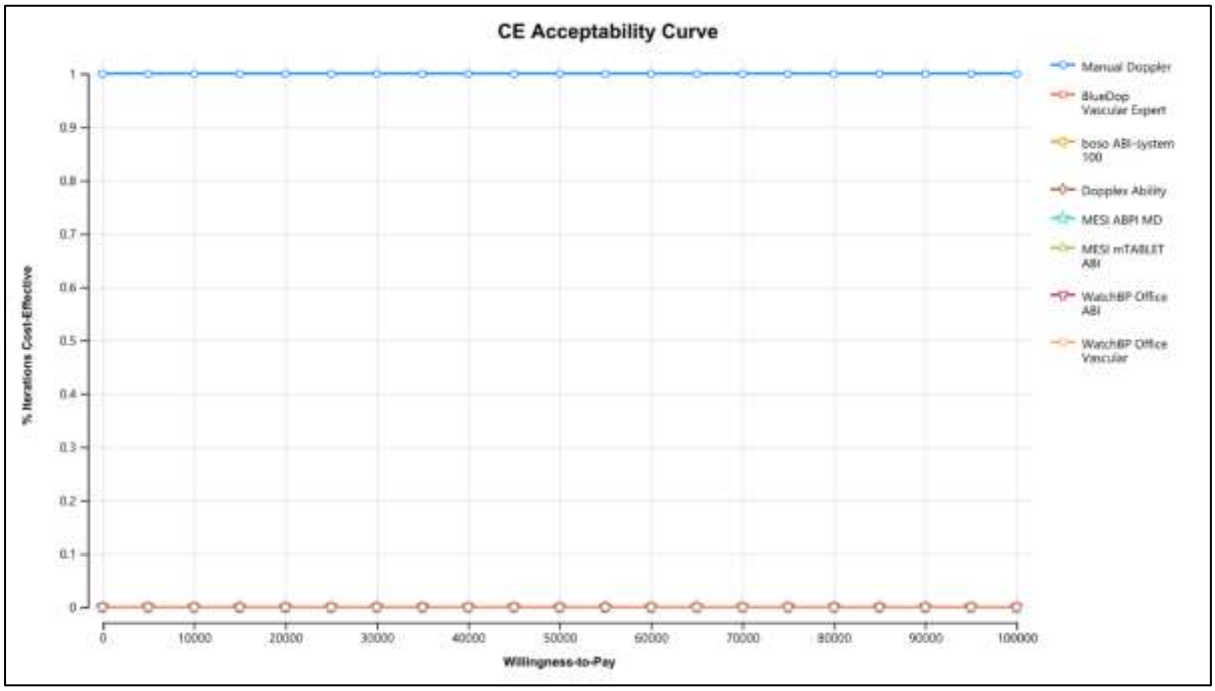
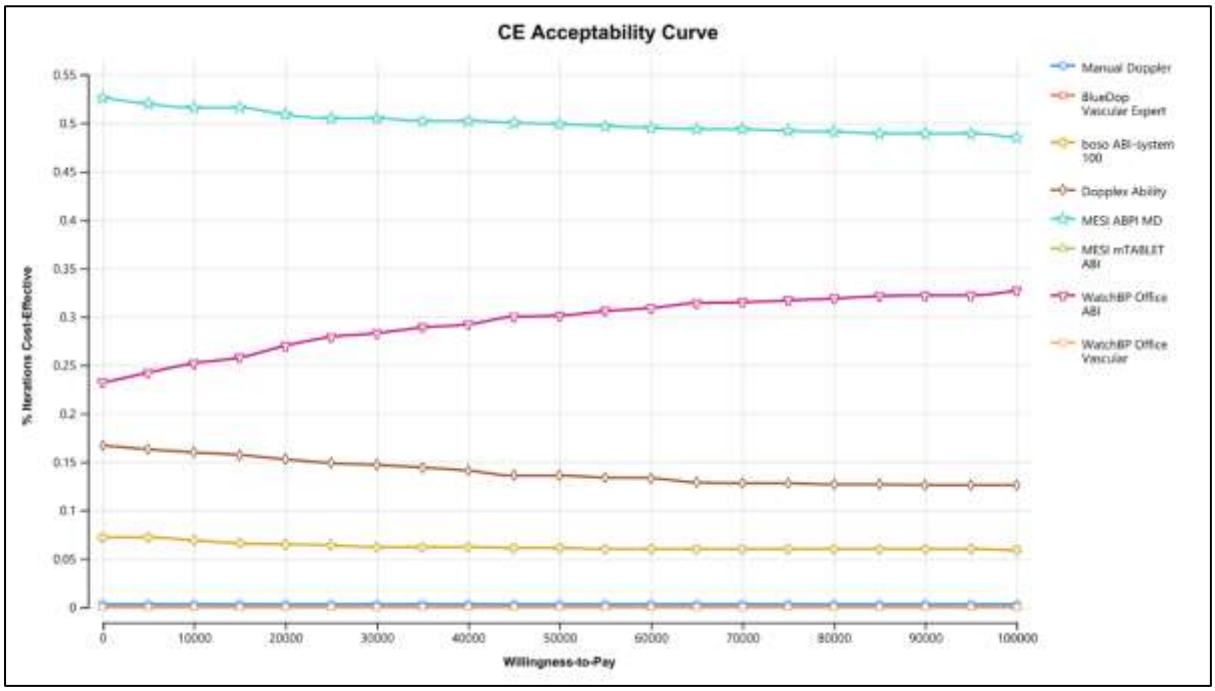


Figure 15 Cost-effectiveness acceptability curves for optimistic base case



Deterministic scenario analyses

A total of 28 deterministic scenario analyses were conducted to explore and illustrate the impact of various assumptions and alternative parameter sources on results. Scenario analyses include:

A) Scenarios 1-7 describe the impact of different assumptions about the impact of the test's diagnostic accuracy on initial patient management, varying assumptions about the proportion of inaccurate tests that are acted upon in clinical practice and exploring potential reductions in ulcer healing time if automated tests can contribute to more appropriate referrals to community leg ulcer services. Scenarios 1-7 describe the one-way changes to parameters that contribute to the pessimistic and optimistic base cases described in Table 25.

B) Scenarios 8-12 vary the diagnostic accuracy data used to populate the model for each test, using worst case studies, best case studies, pooled data from meta-analysis where available, data from studies that calculate optimal thresholds, and for studies reporting solely in a sub-group of diabetes (Scenarios 1-5 based on parameter inputs from Table 13). Scenario 13 explores the impact of applying the PAD prevalence from the

diagnostic accuracy studies (weighted average prevalence, weighted by the number of patients in each study).

C) Scenarios 14-21 varying the diagnostic test costs according to different assumptions outlined in Table 21. These scenarios explore the impact of different healthcare professionals conducting the test, the time taken to complete each test, high and low estimates of test throughput, and the cost implications of technical failures in terms of re-testing or referral. (Scenario analyses 6-13 based on test cost scenario descriptions in Table 21). Scenario 22 explores the impact of all positive test patients requiring a duplex ultrasound in addition to an outpatient consultation with vascular services to confirm the positive ABPI result.

D) Scenarios 23 and 24 vary the sources of mortality parameters used for arterial disease in the model, relying on published literature associated with health state mortality rather than applying procedure specific mortality risks.

E) Scenario 25 removes the possibility for primary amputation in the model, assuming all patients first receive an attempt at revascularisation through angioplasty or bypass surgery.

F) Scenario 26 explores the impact of assuming that all arterial procedures require non-elective intervention in the presence of a FN test result, utilising data from the national vascular registry which shows poorer outcomes post non-elective treatment.[98]

G) Scenarios 27 and 28 reduce the time horizon to 5 years and provide undiscounted ICERs respectively.

Scenario analyses are applied deterministically to the moderate base case configuration described above and are reported in Table 26.

Table 26 Deterministic scenario analysis results

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Base case (moderate) - deterministic						
Manual Doppler	£11,961		8.032			--
BlueDop Vascular Expert	£12,099	£138	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,276	£315	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,276	£315	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,392	£431	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,424	£463	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,427	£466	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,501	£540	8.027	-0.006	Dominated	Dominated
Scenario 1 – Time gains for TN tests of 16 weeks (112 days)						
BlueDop Vascular Expert	£11,255		8.051			Dominant
WatchBP Office ABI	£11,357	£102	8.053	0.002	£46,934	Dominant
WatchBP Office Vascular	£11,357	£0	8.053	0.000	Dominated	Dominant
boso ABI-system 100	£11,495	£139	8.052	-0.001	Dominated	Dominant
MESI ABPI MD	£11,498	£141	8.053	0.000	Dominated	Dominant
MESI mTABLET ABI	£11,500	£144	8.053	0.000	Dominated	Dominant
Dopplex Ability	£11,580	£224	8.053	0.000	Dominated	Dominant
Manual Doppler	£11,961	£605	8.032	-0.021	Dominated	Dominant

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 2 – Assume FP test results are not acted upon						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,058	£97	8.031	-0.001	Dominated	Dominated
WatchBP Office ABI	£12,263	£302	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,263	£302	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,367	£406	8.028	-0.004	Dominated	Dominated
MESI ABPI MD	£12,412	£451	8.028	-0.004	Dominated	Dominated
MESI mTABLET ABI	£12,414	£453	8.028	-0.004	Dominated	Dominated
Dopplex Ability	£12,484	£523	8.027	-0.005	Dominated	Dominated
Scenario 3 – Assume mixed FN test results are not acted upon.						
Manual Doppler	£11,961		8.032		--	--
MESI ABPI MD	£11,968	£7	8.032	0.000	Dominated	Dominated
MESI mTABLET ABI	£11,970	£9	8.032	0.000	Dominated	Dominated
Dopplex Ability	£11,974	£13	8.032	0.000	Dominated	Dominated
WatchBP Office ABI	£11,977	£16	8.032	0.000	Dominated	Dominated
WatchBP Office Vascular	£11,977	£16	8.032	0.000	Dominated	Dominated
boso ABI-system 100	£11,988	£27	8.032	-0.001	Dominated	Dominated
BlueDop Vascular Expert	£12,011	£50	8.031	-0.001	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 4 – Base case, optimistic combination of assumptions as described in Table 24 (Scenario 1+2+3)						
MESI ABPI MD	£11,050		8.053		--	Dominant
MESI mTABLET ABI	£11,052	£3	8.053	0.000	Dominated	Dominant
WatchBP Office ABI	£11,060	£10	8.053	0.000	Dominated	Dominant
WatchBP Office Vascular	£11,060	£10	8.053	0.000	Dominated	Dominant
Dopplex Ability	£11,061	£12	8.053	0.000	Dominated	Dominant
boso ABI-system 100	£11,086	£36	8.053	-0.001	Dominated	Dominant
BlueDop Vascular Expert	£11,130	£80	8.052	-0.002	Dominated	Dominant
Manual Doppler	£11,961	£911	8.032	-0.021	Dominated	--
Scenario 5 – Assume all FP test results remain unhealed at 24 weeks						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,248	£287	8.027	-0.005	Dominated	Dominated
WatchBP Office ABI	£12,320	£359	8.028	-0.004	Dominated	Dominated
WatchBP Office Vascular	£12,320	£359	8.028	-0.004	Dominated	Dominated
MESI ABPI MD	£12,469	£508	8.026	-0.006	Dominated	Dominated
MESI mTABLET ABI	£12,471	£510	8.026	-0.006	Dominated	Dominated
boso ABI-system 100	£12,481	£520	8.026	-0.007	Dominated	Dominated
Dopplex Ability	£12,560	£599	8.025	-0.007	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 6 – Assume all FN arterial ulcers are acted upon						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,150	£189	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,449	£488	8.027	-0.005	Dominated	Dominated
WatchBP Office Vascular	£12,449	£488	8.027	-0.005	Dominated	Dominated
boso ABI-system 100	£12,626	£665	8.025	-0.007	Dominated	Dominated
MESI ABPI MD	£12,689	£728	8.024	-0.008	Dominated	Dominated
MESI mTABLET ABI	£12,692	£731	8.024	-0.008	Dominated	Dominated
Dopplex Ability	£12,806	£845	8.023	-0.009	Dominated	Dominated
Scenario 7 – Base case pessimistic combination of assumptions as described in Table 24 (Scenario 5 + 6)						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,299	£338	8.026	-0.006	Dominated	Dominated
WatchBP Office ABI	£12,494	£533	8.026	-0.006	Dominated	Dominated
WatchBP Office Vascular	£12,494	£533	8.026	-0.006	Dominated	Dominated
boso ABI-system 100	£12,715	£754	8.023	-0.009	Dominated	Dominated
MESI ABPI MD	£12,734	£773	8.023	-0.009	Dominated	Dominated
MESI mTABLET ABI	£12,736	£775	8.023	-0.009	Dominated	Dominated
Dopplex Ability	£12,866	£905	8.022	-0.011	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 8 – Diagnostic accuracy scenario 1 (low)						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,582	£621	8.026	-0.006	Dominated	Dominated
MESI ABPI MD	£12,604	£642	8.025	-0.008	Dominated	Dominated
MESI mTABLET ABI	£12,606	£645	8.025	-0.008	Dominated	Dominated
boso ABI-system 100	£12,672	£711	8.025	-0.007	Dominated	Dominated
Dopplex Ability	£12,759	£798	8.024	-0.008	Dominated	Dominated
WatchBP Office ABI	£12,954	£993	8.022	-0.010	Dominated	Dominated
WatchBP Office Vascular	£12,954	£993	8.022	-0.010	Dominated	Dominated
Scenario 9 – Diagnostic accuracy scenario 2 (high)						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,099	£138	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,276	£315	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,276	£315	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,365	£404	8.028	-0.004	Dominated	Dominated
Dopplex Ability	£12,376	£415	8.028	-0.004	Dominated	Dominated
MESI ABPI MD	£12,424	£463	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,427	£466	8.027	-0.005	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 10 – Diagnostic accuracy scenario 3 (pooled; exclude Bluedop vascular expert, Boso ABI – system 100 and Dopplex ability)						
Manual Doppler	£11,961		8.032			
MESI ABPI MD	£12,567	£606	8.026	-0.006	Dominated	Dominated
MESI mTABLET ABI	£12,569	£608	8.026	-0.006	Dominated	Dominated
WatchBP Office ABI	£12,796	£835	8.024	-0.008	Dominated	Dominated
WatchBP Office Vascular	£12,796	£835	8.024	-0.008	Dominated	Dominated
Scenario 11 – Diagnostic accuracy scenario 4 (optimal threshold; exclude Bluedop vascular expert)						
Manual Doppler	£11,961		8.032		--	--
WatchBP Office ABI	£12,147	£186	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,151	£190	8.030	-0.002	Dominated	Dominated
MESI ABPI MD	£12,151	£190	8.030	-0.002	Dominated	Dominated
MESI mTABLET ABI	£12,172	£211	8.030	-0.003	Dominated	Dominated
Dopplex Ability	£12,174	£213	8.030	-0.003	Dominated	Dominated
boso ABI-system 100	£12,393	£432	8.027	-0.005	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 12 – Diagnostic accuracy scenario 5 (diabetes subgroup)						
Manual Doppler	£11,961		8.032		--	--
WatchBP Office ABI	£12,276	£315	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,276	£315	8.029	-0.003	Dominated	Dominated
BlueDop Vascular Expert	£12,503	£542	8.026	-0.006	Dominated	Dominated
MESI ABPI MD	£12,543	£582	8.026	-0.006	Dominated	Dominated
MESI mTABLET ABI	£12,545	£584	8.026	-0.006	Dominated	Dominated
boso ABI-system 100	£12,672	£711	8.025	-0.007	Dominated	Dominated
Dopplex Ability	£13,378	£1,417	8.018	-0.014	Dominated	Dominated
Scenario 13 - PAD prevalence obtained as weighted average of diagnostic accuracy studies						
Manual Doppler	£10,533	--	8.192	--	--	--
BlueDop Vascular Expert	£10,651	£118	8.190	-0.002	Dominated	Dominated
WatchBP Office ABI	£10,762	£230	8.190	-0.002	Dominated	Dominated
WatchBP Office Vascular	£10,762	£230	8.190	-0.002	Dominated	Dominated
boso ABI-system 100	£10,849	£316	8.189	-0.003	Dominated	Dominated
MESI ABPI MD	£10,865	£332	8.189	-0.003	Dominated	Dominated
MESI mTABLET ABI	£10,867	£335	8.189	-0.003	Dominated	Dominated
Dopplex Ability	£10,922	£389	8.188	-0.004	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 14 – Test cost scenario 1: Assume a grade 7 nurse conducts tests						
Manual Doppler	£11,971		8.032		--	--
BlueDop Vascular Expert	£12,101	£130	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,284	£313	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,284	£313	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,395	£424	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,428	£456	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,431	£460	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,504	£533	8.027	-0.006	Dominated	Dominated
Scenario 15 – Test cost scenario 2: Assume a consultant conducts tests						
Manual Doppler	£11,997		8.032		--	--
BlueDop Vascular Expert	£12,107	£110	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,305	£308	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,305	£309	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,404	£407	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,436	£440	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,443	£447	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,512	£515	8.027	-0.006	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 16 – Test cost scenario 3: Test times from the companies						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,099	£138	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,274	£313	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,274	£313	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,390	£429	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,421	£460	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,423	£462	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,499	£538	8.027	-0.006	Dominated	Dominated
Scenario 17 – Test cost scenario 4: Assume 2 nurses required for manual doppler						
Manual Doppler	£11,981		8.032		--	--
BlueDop Vascular Expert	£12,099	£118	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,276	£295	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,276	£295	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,392	£410	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,424	£443	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,427	£445	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,501	£519	8.027	-0.006	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 18 – Test cost scenario 5: Apply low test throughput						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,104	£143	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,277	£315	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,277	£316	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,396	£434	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,426	£464	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,428	£467	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,502	£541	8.027	-0.006	Dominated	Dominated
Scenario 19 – Test cost scenario 6: Apply high test throughput						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,099	£137	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,276	£315	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,276	£315	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,391	£430	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,424	£463	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,427	£465	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,501	£540	8.027	-0.006	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 20 – Test cost scenario 7: 50% of technical failures require referral to vascular services + duplex ultrasound						
Manual Doppler	£11,966		8.032		--	--
BlueDop Vascular Expert	£12,145	£179	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,292	£326	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,292	£326	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,407	£442	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,455	£489	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,457	£491	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,508	£542	8.027	-0.006	Dominated	Dominated
Scenario 21 – Test cost scenario 8: 100% of technical failures require referral to vascular services + duplex ultrasound						
Manual Doppler	£11,971		8.032		--	--
BlueDop Vascular Expert	£12,190	£220	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,308	£337	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,308	£337	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,423	£453	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,485	£514	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,487	£517	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,516	£545	8.027	-0.006	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 22 – Increased costs of referral post a positive test result (to include the costs of a duplex ultrasound in secondary care)						
Manual Doppler	£11,985		8.032		--	--
BlueDop Vascular Expert	£12,131	£147	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,302	£317	8.029	-0.003	Dominated	Dominated
WatchBP Office Vascular	£12,302	£317	8.029	-0.003	Dominated	Dominated
boso ABI-system 100	£12,420	£436	8.028	-0.005	Dominated	Dominated
MESI ABPI MD	£12,450	£466	8.027	-0.005	Dominated	Dominated
MESI mTABLET ABI	£12,453	£468	8.027	-0.005	Dominated	Dominated
Dopplex Ability	£12,528	£543	8.027	-0.006	Dominated	Dominated
Scenario 23 – Apply mortality parameters for arterial disease according to disease state rather than procedure specific						
Manual Doppler	£12,220		8.055		--	--
BlueDop Vascular Expert	£12,360	£140	8.054	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,541	£321	8.052	-0.004	Dominated	Dominated
WatchBP Office Vascular	£12,541	£321	8.052	-0.004	Dominated	Dominated
boso ABI-system 100	£12,659	£439	8.050	-0.005	Dominated	Dominated
MESI ABPI MD	£12,692	£473	8.050	-0.006	Dominated	Dominated
MESI mTABLET ABI	£12,695	£475	8.050	-0.006	Dominated	Dominated
Dopplex Ability	£12,770	£551	8.049	-0.006	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 24 - Probability of mortality post amputation sourced from external literature						
Manual Doppler	£11,497		8.014		--	--
BlueDop Vascular Expert	£11,617	£120	8.012	-0.002	Dominated	Dominated
WatchBP Office ABI	£11,752	£255	8.009	-0.005	Dominated	Dominated
WatchBP Office Vascular	£11,752	£255	8.009	-0.005	Dominated	Dominated
boso ABI-system 100	£11,846	£349	8.007	-0.008	Dominated	Dominated
MESI ABPI MD	£11,868	£371	8.006	-0.008	Dominated	Dominated
MESI mTABLET ABI	£11,871	£374	8.006	-0.008	Dominated	Dominated
Dopplex Ability	£11,931	£434	8.005	-0.010	Dominated	Dominated
Scenario 25 – Remove potential for primary amputation from the model						
Manual Doppler	£11,712		8.038		--	--
BlueDop Vascular Expert	£11,840	£128	8.036	-0.002	Dominated	Dominated
WatchBP Office ABI	£11,994	£282	8.035	-0.002	Dominated	Dominated
WatchBP Office Vascular	£11,994	£282	8.035	-0.002	Dominated	Dominated
boso ABI-system 100	£12,098	£386	8.034	-0.003	Dominated	Dominated
MESI ABPI MD	£12,125	£413	8.034	-0.004	Dominated	Dominated
MESI mTABLET ABI	£12,127	£415	8.034	-0.004	Dominated	Dominated
Dopplex Ability	£12,194	£482	8.034	-0.004	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 26 – In the presence of a FN test, assume all surgical procedures become non-elective						
Manual Doppler	£11,961		8.032		--	--
BlueDop Vascular Expert	£12,127	£166	8.030	-0.002	Dominated	Dominated
WatchBP Office ABI	£12,370	£409	8.027	-0.005	Dominated	Dominated
WatchBP Office Vascular	£12,370	£409	8.027	-0.005	Dominated	Dominated
boso ABI-system 100	£12,519	£558	8.025	-0.007	Dominated	Dominated
MESI ABPI MD	£12,568	£607	8.024	-0.008	Dominated	Dominated
MESI mTABLET ABI	£12,571	£610	8.024	-0.008	Dominated	Dominated
Dopplex Ability	£12,667	£706	8.023	-0.009	Dominated	Dominated
Scenario 27– 5-year time horizon						
Manual Doppler	£6,726		3.159		--	--
BlueDop Vascular Expert	£6,836	£110	3.158	-0.001	Dominated	Dominated
WatchBP Office ABI	£6,946	£220	3.158	-0.001	Dominated	Dominated
WatchBP Office Vascular	£6,946	£220	3.158	-0.001	Dominated	Dominated
boso ABI-system 100	£7,029	£303	3.158	-0.002	Dominated	Dominated
MESI ABPI MD	£7,045	£319	3.158	-0.001	Dominated	Dominated
MESI mTABLET ABI	£7,047	£321	3.158	-0.001	Dominated	Dominated
Dopplex Ability	£7,099	£373	3.158	-0.002	Dominated	Dominated

Test	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER (ranked)	ICER (vs. Manual)
Scenario 28 - 0% Discount rate on costs and QALYs						
Manual Doppler	£14,178		10.431		--	--
BlueDop Vascular Expert	£14,326	£147	10.428	-0.002	Dominated	Dominated
WatchBP Office ABI	£14,524	£345	10.426	-0.004	Dominated	Dominated
WatchBP Office Vascular	£14,524	£345	10.426	-0.004	Dominated	Dominated
boso ABI-system 100	£14,651	£472	10.425	-0.006	Dominated	Dominated
MESI ABPI MD	£14,689	£510	10.424	-0.006	Dominated	Dominated
MESI mTABLET ABI	£14,691	£513	10.424	-0.006	Dominated	Dominated
Dopplex Ability	£14,772	£594	10.423	-0.007	Dominated	Dominated

Abbreviations: ICER = Incremental cost-effectiveness ratio; Prob (C/E) = Probability of cost-effectiveness; QALY = Quality adjusted life years.

For most scenarios, the results remain consistent when applied to the "moderate" base case analysis, with manual doppler testing being the least costly, and also achieving small QALY gains over all automated tests. The magnitude of additional costs and QALY losses for automated tests is largely dependent on the sensitivity of the automated test. That is because low sensitivity tests lead to an increased risk of invasive and costly arterial procedures, if strong compression is applied to an arterial ulcer due to a FN test result. For a small proportion of the cohort, this could ultimately lead to an increased risk of amputation, with substantial life-long costs of health and social care. These additional risks quickly offset any cost savings due to shorter test times for automated tests. Conversely, the "optimistic" scenario shows that there may be potential for automated tests with a high specificity (TN) to generate reductions in venous ulcer healing time, reducing costs, and improving quality of life in the initial decision tree phase of the model. The extent to which these hypothetical time gains could be realised in clinical practice is unclear. However, in a scenario where healthcare professionals do not have access to the skills to conduct manual doppler tests, some efficiencies in referral pathways may be plausible if the tests are highly accurate.

Expected costs and outcomes across different branches in the model

The complexity of the model structure prevents easily categorising each test strategy within a single Markov trace, due the cloning of model arms in the structure. Hence, instead of presenting cohort traces for each test, and for the pathway at each branch of the model separately, we detail the expected outcomes at different key points in the pathway. Table 27 details the expected costs, QALYs and probability of amputation for different branches in the model for arterial, mixed and venous disease respectively, categorised depending on whether inaccurate tests are acted upon or not.

Table 27: Expected value analysis at key points in the pathway.

Model pathway			Expected value		
Disease	**Test categorisation**	**Act upon inaccurate result?**	**Cost**	**QALY**	**Proportion with amputation**
Arterial disease (F4)	TP	--	£35,792	5.82	0.16
Arterial disease (F4)	FN	Yes	£54,944	5.58	0.26
Arterial disease (F4)	FN	No	£35,792	5.82	0.16
Mixed disease (F2)	TP	--	£19,366	6.28	0.06
Mixed disease (F3)	TP	--	£34,694	6.09	0.13
Mixed disease (F4)	TP	--	£31,225	5.95	0.12
Mixed disease (all stages)	TP	--	£28,266	6.06	0.10
Mixed disease (all stages)	FN	Yes	£39,265	5.95	0.16
Mixed disease (all stages)	FN	No	£28,266	6.06	0.10
Venous disease	TN	--	£7,044	8.58	0.00
Venous disease	FP	Yes	£7,878	8.57	0.00
Venous disease	FP	No	£7,352	8.58	0.00

F2,3,4 = Fontaine stages 2, 3 and 4 respectively; FN = False negative; FP = False positive; QALY = Quality adjusted life year; TN = True negative; TP = True positive

Sub-group analyses:

There was insufficient data to explore the impact of subgroup analyses on results.

Interpretation of the results

In summary, the results are highly uncertain, and it is impossible to ascertain the most likely ICER given the available evidence. The range of variation in incremental costs across different plausible sets of assumptions is substantial and the probabilistic analyses indicate substantial uncertainties regarding the optimal test strategy, particularly in scenarios where a set of optimistic assumptions for automated tests are applied. The moderate and pessimistic base case analyses show that, whilst automated tests may be slightly less costly to use in clinical practice, due to a theoretical time saving in patient appointment duration, these cost savings are quickly offset by the potential for substantial additional costs associated with inaccurate test results, and in particular, inappropriate compression of an arterial ulcer, that could, in a small percentage of cases, lead to amputation. For this reason and given that the base case analysis is generated using information from studies showing quite a low sensitivity of the automated tests, unless a high proportion of FP and FN tests could be reliably identified in clinical practice through holistic patient assessment, it is unlikely that the automated tests would be a cost-effective use of resource.

Importantly, this conclusion assumes that automated tests cannot out-perform the imperfect reference standard (manual Doppler testing). It also assumes that there are tangible consequences of inaccurate test results, and that inaccurate test results (FP and FN) would lead to changes in patient care and outcomes. The extent to which these negative consequences would be realised in clinical practice is unclear and dependent on whether testing errors would be identified during holistic patient assessment. Similarly, the extent to which automated tests could deliver reductions in time to compression of venous ulcers without referral to secondary care is unclear, and scenarios around this parameter are speculative.

It is feasible that any of the scenarios explored might be plausible in specific settings or circumstances, and so it is important to consider the cost-effectiveness results with caution, and in light of the substantial uncertainty underlying the impact of the tests on ulcer outcomes, the potential for inaccurate results to be identified through holistic patient assessment, and whether improvements in referral of TN venous ulcer patients could offset the risk of further invasive management of arterial disease due to inappropriate compression of arterial or mixed ulcers in the presence of a FN test result.

Chapter 5. Discussion

Statement of principal findings

The primary focus of this assessment was to evaluate the performance of automatic devices to measure ABPI and detect the presence of PAD in people with leg ulcers and to assess their cost-effectiveness compared to manual doppler testing. Five different automated devices were evaluated; these include the BlueDop Vascular Expert, BOSO ABI-System 100, Dopplex Ability, MESI ABPI MD, and WatchBP Office ABI devices. Current evidence related to people with leg ulcers is limited to two studies assessing two different devices (Dopplex Ability and MESI ABPI MD); both these studies do not assess the accuracy of the automated devices for the diagnosis of PAD but report the concordance of their readings compared with those of manual Doppler as the reference device.[44-45] In general, automated devices were found to give different ABPI readings than the manual Doppler (higher readings in most cases) with only a proportion of the automated readings considered equal or similar to the manual Doppler readings (34% in one study and 17% in the other). The authors of these studies conclude that while the use of automated devices in general practice may have the potential to improve access to treatment and reduce delays for patients, the manual Doppler is still the preferable measurement tool, especially in people with symptoms of PAD, until more robust evidence on the efficacy of the automated devices becomes available.

The 22 studies assessing people without leg ulcers showed variable results. In general, automated devices demonstrated good specificity but only moderate sensitivity. The results of our meta-analysis including 12 studies with a total of 2004 participants showed a pooled sensitivity of 0.64% (95% CI 57% to 71%) and a pooled specificity of 96% (95% CI 92% to 98%) for the detection of PAD using an automated ABPI measurement. Most patients were from vascular or cardiovascular risk clinics. When we considered each specific type of device separately, we observed a pooled sensitivity of 67% and a pooled specificity of 94% for detection of PAD using the MESI ABPI MD device and a pooled sensitivity of 53% and a pooled specificity of 98% using the WatchBP Office ABI device. Not enough studies were available for conducting meta-analyses assessing the accuracy of the other devices under investigation. Our meta-analysis results are in line with the findings of recent systematic reviews and meta-analyses assessing the accuracy of automated ABPI measurement against a reference device. A meta-analysis published in 2012 by Verberk et al. showed that the average

sensitivity and specificity estimates of the automated ABPI measurement for PAD diagnosis were 69% and 96%, respectively.[125] Another meta-analysis published by Herráiz-Adillo et al. in 2017 showed an overall sensitivity of 0.65% (95% CI 57% to 74%) and specificity of 96% (95% CI 93% to 99%).[126] It is worth noting, however, that the existing published meta-analyses included various types of automated devices with only limited overlapping with those included in our meta-analysis.

The uncertainties in the diagnostic accuracy evidence base mean it is difficult to draw any firm conclusions on cost-effectiveness. A lack of evidence on the impact of the tests on important patient outcomes, the extent to which inaccurate test results would be identified in practice, and the implications of acting of inaccurate test results contributes further uncertainty to the assessment of cost-effectiveness. For most scenarios, automated tests may appear to be slightly cheaper to deliver in clinical practice but are quickly offset by any risks and costs associated with withholding compression (false positive) or inappropriately applying compression (false negative). Given the current evidence base, it is therefore unlikely that the automated tests would generate QALY gains or cost-savings, unless a high proportion of FP and FN tests could be reliably identified in clinical practice through holistic patient assessment, and automated tests could deliver improvements in patient referral over manual doppler testing.

Strength and limitations of the assessment

The methods used to conduct this assessment were detailed and thorough. The main weakness of the systematic review of clinical effectiveness evidence was the limited evidence available for each automated device, especially in people with leg ulcers. Moreover, due to the heterogeneity of the included studies in terms of the characteristics of the patient population, setting, prevalence of PAD, and testing protocols, it is hard to draw any firm conclusions on the performance of the automated devices in clinical practice and the findings of this assessment should be interpreted with caution.

Most studies used manual Doppler as the reference device. Although manual Doppler is commonly used in clinical practice, it is not the best available method to detect the presence of PAD. More reliable methods for the diagnosis of PAD include Duplex ultrasound, angiography, CT angiography and MR angiography. Therefore, the results of our included

studies should be considered with caution because the direction of bias introduced by the use of an imperfect reference standard is not straightforward.

While diabetes is known to influence the accuracy of ABPI measurement, only a few studies assessed diabetic patients. The presence of diabetics does not seem to have a significant effect on the accuracy of ABPI measurements in studies that provide subgroup analyses for diabetic and non-diabetic patients. However, it is worth pointing out that the proportion of diabetic patients in these studies was generally low. On the contrary, the study by Babaei et al., which focused exclusively on a large sample of diabetes patients, reported the lowest sensitivity estimate (20%).[54] This low diagnostic performance could be explained by the presence of calcified, incompressible arteries in diabetes patients resulting in higher, less diagnostic, ABPI levels.

Uncertainties

The moderate sensitivity of the automated ABPI measurement and consequent high false negatives rate also raises the question of whether these devices should be used as screening tools to rule out the presence of PAD in non-specialised settings (general practice, community setting). It is worth pointing out that we were not able to assess the impact that the routine use of the automated devices may have on clinical outcomes; in particular, we did not identify any study assessing the consequences of false negative results (delayed diagnosis of PAD) in clinical practice.

Most of the included studies found a relatively good correlation between the readings of the automated device and those of the reference device (manual Doppler in most cases); however, the use of correlation coefficients may be inadequate or misleading for assessing agreement between diagnostic methods because they evaluate only the linear association between sets of observations. The Bland Altman plot is considered a better method to describe the level of agreement between two measurements.[127] Across studies, the analysis of the Bland Altman plot showed a systematic trend toward higher automated ABPI readings, which according to the current threshold of 0.9, would underestimate the presence of PAD. While clinicians in specialised settings may adopt different strategies to determine whether the peripheral arterial status in patients with higher ABPI measurements is compromised, it is unclear whether less specialised professionals such as community or general practice nurses would be able to convey the same clinical judgement. It is worth noting that some of the

studies included in this assessment found that the best threshold for detection of PAD using automated ABPI was 1.0 (or close to 1.0).[48-50, 53, 54, 56, 58, 59, 61, 64] However, optimised criteria for automated ABPI measurement need to be prospectively validated in non-specialised settings.

Rates of erroneous automated measurements varied across studies but often they were not negligible indicating the need for further assessment, especially in less specialised settings. Some investigators found also that the frequency of errors with automated devices was higher in patients with PAD compared with those without PAD.[56]

In general, the automated devices required less time to measure ABPI compared with the manual Doppler device mainly because of the shorter duration of the resting period. However, considering the need for consultation time before starting ABPI measurement in primary or community care it is questionable whether this represents a real advantage.

In all included studies the automated and reference ABPI measurements were performed by experienced or trained professionals. It is unclear whether measurements performed by less skilled professionals would produce the same findings.

Conclusions and implications for future research

There is an increasing interest in the use of automated devices to measure ABPI in non-specialised settings such as primary care and community settings. These devices do not require extensive training and are less time-consuming than the current manual Doppler device. However, the current evidence base is inadequate to fully appraise the economic value of the use of the automated devices under investigation to provide cost-effective improvement in the clinical management of people with leg ulcers who require ABPI measurement. As such we have provided a large number of scenarios to illustrate the range of possible cost and QALY implications under different assumptions about how the tests may influence patient care.

Information on the performance of automated devices in people with leg ulcers was too scant to draw any meaningful conclusions. We found that automated devices for ABPI measurement have good specificity but only modest sensitivity for diagnosing PAD in people without leg ulcers; however, the current evidence base is heterogeneous in terms of patient

populations, settings, prevalence of PAD and testing procedures. In most economic modelling scenarios, the risks of providing inappropriate care on the basis of inaccurate test results offsets the cost savings of faster testing, leading to overall additional costs to the NHS and potential for QALY losses. Unless a high proportion of inaccurate test results could be identified during a holistic patient assessment, and substantial gains in efficiency could be achieved in the care pathway reducing time to compression of venous ulcers, it is unlikely, given the current evidence base that the tests could be considered cost-effective.

Additional research is required to clarify whether these devices can play a role in the management of both people with leg ulcers and people without leg ulcers who require ABPI measurement in non-specialised settings (community care, primary care). In particular, more robust evidence is needed to establish whether automated devices should be used for the general screening of clinical populations with any vascular concerns or considered an acceptable alternative or adjunct to manual Doppler in people with symptoms of PAD. In addition, the use of a different threshold, from the current recommended threshold of 0.9, should require prospective validation.

Ideally, future research should consider comparing each automated device with manual Doppler against an acceptable reference standard (i.e., Duplex ultrasound). When designing future studies, it would be useful if the experience of professionals using the devices to measure ABPI could mirror those of the professionals who are expected to use the device in clinical practice including community and general practice nurse. Studies should endeavour, where possible to also assess the impact of the tests on patient outcomes such as ulcer healing times, risk of critical limb ischemia and treatment requirements. In addition to better diagnostic test accuracy information, future economic evaluation exercises would also benefit from more robust information on the implications of inaccurate test results on patient outcomes (such as ulcer healing, and risks of requiring escalated care due to inappropriate compression), and robust evidence regarding the costs and quality of life outcomes for patients specifically with mixed aetiology disease.

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7 Appendices

Appendix 1 Literature search strategies

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 03, 2022>

1 Peripheral Arterial Disease/
2 (("Peripheral Arter*" adj3 Disease?) or PAD).tw,kw.
3 Intermittent Claudication/
4 (Intermittent adj3 Claudication).tw.
5 ("lower extremity arter* disease" or "lower limb arter* disease").tw,kw.
6 or/1-5
7 Ankle Brachial Index/
8 ((brachial or ankle or arm) adj4 (index or pressure)).tw,kw.
9 (ABPI or ABI or AAI).tw,kw.
10 7 or 8 or 9
11 Oscillometry/
12 plethysmography/ or photoplethysmography/ or plethysmography, impedance/
13 (Oscillometr* or plethysmograph* or photoplethysmograph*).tw,kw.
14 Ultrasonography, Doppler/
15 doppler.tw,kw.
16 automat*.tw,kw.
17 or/11-16
18 (BlueDop or MESI or WatchBP or Microlife or Dopplex or Huntleigh or Bosch or boso).af.
19 6 and 10 and 17 and 18

Health economics: per protocol search: automated measurement of ABPI for PAD in patients with leg ulcers

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 03, 2022>

1 Peripheral Arterial Disease/
2 (("Peripheral Arter*" adj3 Disease?) or PAD).tw,kw.
3 Intermittent Claudication/
4 (Intermittent adj3 Claudication).tw.
5 ("lower extremity arter* disease" or "lower limb arter* disease").tw,kw.
6 or/1-5
7 Ankle Brachial Index/
8 ((brachial or ankle or arm) adj4 (index or pressure)).tw,kw.
9 (ABPI or ABI or AAI).tw,kw.
10 7 or 8 or 9
11 Oscillometry/
12 plethysmography/ or photoplethysmography/ or plethysmography, impedance/

13 (Oscillometr* or plethysmograph* or photoplethysmograph*).tw,kw.
14 Ultrasonography, Doppler/
15 doppler.tw,kw.
16 automat*.tw,kw.
17 or/11-16
18 Leg Ulcer/
19 ((leg or lower) adj3 ulcer*).tw,kw.
20 18 or 19
21 (BlueDop or MESI or WatchBP or Microlife or Dopplex or Huntleigh or Bosch or boso).af.
22 *economics/
23 economics, hospital/
24 exp economics,medical/
25 economics,pharmaceutical/
26 exp models, economic/
27 exp decision theory/
28 monte carlo method/
29 markov chains/
30 exp technology assessment, biomedical/
31 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
32 economics model$.tw.
33 (economic$ or pharmacoeconomic$).tw.
34 (price or prices or pricing).tw.
35 budget$.tw.
36 (value adj1 money).tw.
37 (expenditure$ not energy).tw.
38 markov$.tw.
39 monte carlo.tw.
40 (decision$ adj2 (tree? or analy$ or model$)).tw.
41 ec.fs.
42 or/22-42
43 6 and 10 and 17 and 20 and 21 and 42

Appendix 2 Characteristics of automated devices and reference standard of included studies

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
Welsh 2016	Dopplex Ability (random order)	15 minutes	NR	1 (community vascular specialist nurse or leg ulcer clinic coordinator)	£5,700 per unit	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Manual Doppler (random order)		NR	2 (community vascular specialist nurse and leg ulcer clinic coordinator)	£470 per unit	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
Green 2020	MESI ABPI MD (order NR)	NR	NR	1 (general practice nurses, healthcare assistants or nursing students)	NR	NR
	Manual Doppler (order NR)	NR	NR	NR	NR	NR
NCT05073510 2022	BlueDop Vascular Expert (order NR)	NR	NR	[redacted]	NR	According to the Instructions for Use (IFU)
	Duplex ultrasound (order NR)	NR	NR	NR	NR	NR

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
Kordzadeh 2018	BlueDop Vascular Expert (order NR)	NR	NR	2 (physician and vascular specialist)	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Duplex sonography (order NR)	NR	NR	1 (senior vascular scientist)	NR	NR
Homza 2019	Boso ABI-system 100 (1st)	10 minutes	Supine	NR	NR	In accordance with the device manual using appropriately sized sphygnomanometric cuffs
	Manual Doppler (order NR)	NR	NR	NR	NR	In accordance with AHA guidelines for ABI measurement. A digital vascular Doppler HUNTLEIGH Dopplex DMX (Huntleigh Healthcare, United Kingdom) with an 8 MHz probe was used to measure the individual systolic pressures. An appropriately sized pneumatic cuff was applied to the right upper arm, inflated to suprasystolic pressure and deflated slowly until a Doppler flow signal was detected. The process was repeated for right leg and values for both dorsal pedal and anterior tibial arteries were measured, followed by left leg and left arm.
	Duplex ultrasound (order NR)	NR	Supine	NR	NR	Performed using Vivid S6 Ultrasound System (GE Healthcare, USA) equipped with 8L-RS (a 5-13 MHz linear transducer) and 4C-RS (1,8-6 MHz

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						curvilinear transducer). Each limb was examined in the proximal to distal direction
Jarai 2018	Boso ABI-system 100 (order NR)	NR	NR	1 (trained nurse)	NR	NR
	Manual Doppler (order NR)	NR	NR	1 (trained nurse)	NR	Performed with the validated ELITE 200 Doppler 5MHz device
Wohlfahrt 2011	Boso ABI-system 100 (order NR)	5 minutes	Recumbent	NR	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Manual Doppler (order NR)	5 minutes	Supine	2 (experienced physicians)	NR	Appropriately sized cuffs of a mercury sphygmomanometer were placed proximal to the malleolus and on the right arm. After a five-minute resting period in the supine position, systolic blood pressure was measured in the right brachial artery, right dorsal pedal and posterior tibial arteries, left dorsal pedal and tibial arteries (in this order) with a pocket Doppler device with an 8 MHz probe (Dopplex multi, Huntleigh, Cardiff, UK). Next, systolic blood pressure measurement was repeated on the right brachial artery for a second time. If the difference between the first and the second brachial systolic pressure measurements was higher than 10 mmHg, all measurements were repeated.

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
Diehm 2009	Boso ABI-system 100 (2nd)	NR	NR	1 (examiner with experience of over 30 years of ABI measurements)	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Manual Doppler (1st)	10 minutes	Supine	1 (examiner with experience of over 30 years of ABI measurements)	NR	Doppler-assisted ABI measurements were performed according to the method described by Lovelace and Moneta using a sphygmomanometer (Erka GmbH, Bad Toelz, Germany) with a cuff width ranging between 29 and 40 cm and a Doppler device with an 8.2 MHz continuous wave probe (Ultrasonic Flow Detector model 811–B, Parks Medical Electronic Inc., Aloha, Oregon, USA). In brief, the cuff was inflated to suprasystolic pressure (i.e., >30 mm Hg above expected systolic pressure) and deflated slowly until a flow signal was detected by Doppler over the dorsalis pedis artery and posterior tibial artery, respectively, thereby possibly indicating two different systolic pressures at the ankle level. These were recorded as "high" and "low" ankle systolic pressures. Brachial artery systolic pressure was determined similarly on both upper extremities, the higher systolic brachial pressure being used for ABI calculations. Hence, for each limb a "high" and a "low" Doppler-assisted ABI was registered

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
Babaei 2020	Dopplex Ability (1st)	None	Supine	1 (trained nurse with extensive experience in vascular assessment of lower limbs)	NR	In accordance with the manufacturer's guidelines and undertaken first as there is no need for resting before testing
	Doppler ultrasound (2nd)	5 minutes	Supine	1 (trained nurse with extensive experience in vascular assessment of lower limbs)	NR	After 5 minutes, measured in accordance with the American Heart Association's scientific statement for ABI measurement
	Ultrasound duplex scan (UDS) (3rd)	NR	Supine	NR	NR	From the iliac and common femoral arteries then distally assessing superficial femoral artery, popliteal and tibial arteries in the longitudinal plane. The extent and severity of any arterial disease were assessed using triplex mode by measuring the peak systolic velocity (PSV) from the Doppler waveform just proximal to and through the stenosis.
Millen 2018	Dopplex Ability (random order)	NR	NR	NR (vascular specialists)	NR	According to manufacturer's guidelines. Three repeat readings were performed on each participant and results printed out from the device. The Dopplex did not always obtain a complete set of data at the first attempt (i.e. 2 arm blood pressures, 2 ankle

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						blood pressures and 2 ABIs) and therefore the first successful set of Dopplex ABI data was used
	Doppler/air plethysmography-based Parks Flo-Lab system (random order)	NR	NR	NR (vascular specialists)	NR	ABIs were obtained using the standard Doppler method, using the supplied Parks 8 MHz Doppler probe, obtaining the brachial, posterior tibial and dorsalis pedis arteries
Davies 2016	Dopplex Ability (1st)	None	NR	1 (registered nurse with significant experience of vascular assessment of lower limb)	NR	In accordance with manufacturer's guidelines. All four limbs measured simultaneously before automatic calculation of ABI for each leg. In the event of a failed measurement, the procedure was repeated if acceptable to the participant and the clinician's time schedule permitted
	Doppler ultrasound (2nd)	NR	NR	1 (registered nurse with significant experience of vascular assessment of lower limb)	NR	In accordance with the American Heart Association's scientific statement for ABI measurement
Lewis 2016	Dopplex Ability (1st)	NR	Supine	1 (podiatrist or vascular nurse practitioner)	NR	In accordance with the manufacturer's guidelines
	Duplex ultrasound (2nd)	NR	Supine	1 (highly experienced medical physicist)	NR	Equipment utilised: Toshiba Aplio 500 with linear PLT-704SBT and curvi-linear PVT-375BT probes. The participant lay supine on the scanning couch

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						with the lower limbs exposed. The distal common femoral artery (CFA) was imaged and the Doppler waveform (DW) was assessed visually for any loss of triphasic flow due to significant iliac disease. If the DW showed indications of this, then the iliac arteries were assessed for the presence of atherosclerotic disease. The scan continued distally from the CFA assessing the superficial femoral artery and popliteal arteries in the longitudinal plane. The extent and severity of any arterial disease were assessed using triplex mode by measuring the peak systolic velocity from the DW just proximal to and through the stenosis
Lewis 2010	Dopplex Ability (random order)	10 minutes (sequence A) 5 minutes (sequence B)	NR	1 (podiatrist)	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Manual Doppler (order random)	10 minutes (sequence B)	NR	NR	NR	NR

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
		5 minutes (sequence A)				
Zebari 2022	MESI ABPI MD (2^{ND})	NR	NR	NR	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Manual Doppler (1^{st})	10 minutes	Supine	NR	NR	A non-directional vascular pen Doppler (Huntleigh Dopplex D900, Arjo Inc., Addison, IL) and a standard manual blood pressure cuff were used for the measurements, and the highest recorded pressure at ankle level was used in the ABI calculations.
Hageman 2021	MESI ABPI MD (1^{st})	3-5 minutes	Supine	1	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported). Three series of measurements were performed in each patient. For each series, the ABI was measured twice with a 1-minute pause between measurements: first, at the left brachial artery and both ankle arteries; and second, at the right brachial artery and both ankle arteries. ABIs based on the arm with the highest of the two SBPs were used in the analyses, as is standard practice. To assess the validity of the device, the average of the three series was used for

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						calculations. ABI results were blinded for the patients and the other operator.
	Manual Doppler (2nd)	15 minutes	NR	1 (trained vascular technician)	NR	In each patient, ABI measurements were repeated with vascular laboratory Doppler equipment (ELCAT vasolab 320; ELCAT Medical Systems, Wolfratshausen, Germany) some 15 minutes after the oscillometric measurements. SBPs of the brachial and ankle arteries (dorsal pedal and posterior tibial) were measured with sphygmomanometer cuffs, which were automatically inflated and deflated. SBP cutoff points of all arteries were defined as the systolic upstroke of the first arterial waveform. At the first characteristic arterial sound and at the simultaneous appearance of the first arterial waveform, the monitor screen was frozen and the SBP cutoff point was defined by precise retrospective positioning of an adjustable marker line. The ABI was calculated in each leg by dividing the highest systolic ankle pressure (either posterior tibial or dorsal pedal) by the highest systolic brachial pressure of both arms
Boilley 2020	MESI ABPI MD (1st)	10 minutes	Supine	1 (experienced vascular physician)	NR	For all patients, the ABI was measured using the MESI-ABPI-MD® immediately after lying down (MESI 1) and following a rest period of 10 min (MESI 2), after which ABI–Dop was measured. The

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						measurement was considered a diagnosis of PAD when the value was < or = 0.90 or when the device displayed a "PAD" message. Indeed, if the SBP was lower than 70 mmHg or if the ABI was lower than 0.50, the device displayed a "PAD" message since the accuracy of the measurement below 0.50 is low.
	Manual Doppler (2nd)	NR	Supine	1 (experienced vascular physician)	NR	ABI measurements using the standard manual method (continuous Doppler) were performed with a handheld Doppler (BASIC, Atys Medical, France) according to the European Society of Cardiology guidelines. The operator rounded up the values to the nearest 5 mmHg.
Catillon 2020	MESI ABPI MD (1st)	10 minutes	NR	1 (vascular specialist)	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)
	Doppler ultrasound (2nd)	NR	NR	1 (vascular specialist)	NR	Taken in line with standard procedure (i.e. right brachial artery, right posterior tibial artery, right anterior tibial artery, left posterior tibial artery, left anterior tibial artery, left brachial artery and right brachial artery). The highest brachial and ankle pressure values were used to calculate the ABI.

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
Varetto 2019	MESI ABPI MD (order NR)	NR	Supine	1	NR	According to manufacturer's instructions using 3 cuffs. ABI automatically calculated with the same ratio employed for the Doppler method
	Manual Doppler (order NR)	NR	Supine	1	NR	Performed with a calibrated sphygmomanometer and 8 MHz Doppler probes. ABI was calculated as the ratio of the highest Systolic Blood Pressure (SBP) obtained from both tibial and dorsalis pedis arteries at one ankle to the highest SBP of both brachial arteries.
Span 2016	MESI ABPI MD (2nd)	NR	NR	1	NR	According to the manufacturer's instructions using 3 cuffs
	Manual Doppler (1st)	"a few minutes"	Supine	1	NR	According to the standard protocol with a calibrated sphygmomanometer and 8 MHz Doppler probes (Dopplex SD2, Huntleigh Healthcare Ltd, Cardiff, UK). ABI was calculated as the ratio of the highest systolic blood pressure (SBP) obtained from both tibial and dorsalis pedis arteries at one ankle to the highest SBP of both brachial arteries.
Verma 2022	WatchBP Office ABI (1st)	5 minutes	NR	NR	NR	Appropriately sized cuffs were used. BP was measured simultaneously on both arms followed by both ankles. The arm and ankle with the higher SBP was selected for the ABI measurement.
	Vascular Doppler device (2nd)	NR	NR	NR	NR	The brachial and posterior tibial systolic pressures were measured using appropriately sized blood pressure cuffs linked to a mercury

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						sphygmomanometer placed successively on the upper arms and just above the ankles. Using a hand-held continuous wave Doppler probe (8 MHz, HI.dop, BT-200 Vascular Doppler, Bistos Co. Ltd. Korea), the systolic pressure in each artery was measured by inflating the cuffs 30 mmHg above the systolic blood pressure and deflated slowly until a flow signal was detected over the brachial and posterior tibial artery
Raya 2019	WatchBP Office ABI (order NR)	NR	NR	NR (nurses experienced in the technique)	NR	Three consecutive measurements separated by intervals of one minute, obtaining the mean of each arm. A cuff was then placed in the control arm and an anklet on the left leg. ABPI was calculated automatically. The same was done on the right.
	MESI ABPI MD (order NR)	NR	NR	NR (nurses experienced in the technique)	NR	One of the cuffs was placed in the control arm obtained with Doppler and an ankle brace in each of the legs The ABPI was automatically calculated for each one.
	Manual Doppler (order NR)	NR	NR	NR (nurses experienced in the technique)	NR	Huntleigh Healthcare Dopplex II model SD2 model and CORYSAN type manual sphygmomanometer. The arm with the highest SBP was determined with the Doppler probe. SBP was then obtained in the legs, first right and then left, in the pedal and tibial arteries.

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
Rodriguez-Roca 2014	WatchBP Office ABI (2nd)	NR	NR	1 (nurse specifically trained)	NR	NR
	Manual Doppler (1st)	5 minutes	Supine decubitus	1 (nurse specifically trained)	NR	Measured using a validated and calibrated sphygmomanometer and a two-way Doppler with an 8-MHz probe (BIDOP ES-100 V3). After resting for 5 min in the supine decubitus position, systolic BP was measured in both arms and the highest value was selected for calculation of the ABI (denominator). The systolic BP of the posterior tibial artery and the pedal artery was then measured in each leg, and the highest value (whether tibial or pedal) was taken as reference for calculating the individual ABI of each leg (numerator). The ABI of both the left and right legs was recorded and for the definition of PAD the lowest of the two values was considered
Sinski 2013	WatchBP Office ABI (1st)	20-30 minutes	Supine	1 (experienced technician)	NR	According to the device's manual using appropriately sized cuffs. Blood pressure was measured simultaneously on both arms and the arm with the higher systolic blood pressure selected for the ABI measurement. One of the brachial cuffs was then replaced with the ankle cuff. The ankle cuff was placed over the posterior tibial artery on the ankle. Both cuffs were inflated simultaneously, and the

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
						ABI was calculated automatically. The same measurement was performed on the other ankle.
	Ultrasound Doppler (2^{nd})	5-10 minutes	NR	1 (experienced physician)	NR	Measured within 5–10 min of the automated oscillometric measurement using a linear vascular probe with the ultrasound unit (GE Vivid 5, GE Vingmed, Horten, Norway) or Philips IE 33 (Philips Medical Systems, Andover, MA, USA) and a sphygmomanometer (Heine G5, Heine Optotechnik, Herrsching, Germany). The measurements were started by determining systolic blood pressure on the brachial arteries. A cuff was placed over the brachial artery and inflated 20 mm Hg above systolic pressure and then released until the first signal of the Doppler flow was recorded. The higher systolic blood pressure was recorded for the ABI calculation. After the brachial artery measurements, systolic blood pressure was measured in the same way on both ankles. Specifically, a Doppler probe was placed over the posterior tibial artery, which was the site used for the automatic oscillometric measurement
Kollias 2011	WatchBP Office ABI (random order)	10 minutes	Supine	1	NR	NR (but probably according to the manufacturer's instructions; description of the technical features of the device and its outputs are reported)

Study ID	Test (order administered)	Rest period	Patient position	No of operators	Cost	How was the test done
	Manual Doppler (order random)		Supine	1	NR	Manual doppler ABI was measured according to the American Heart Association guidelines using a continuous wave doppler device with an 8MHz probe.

Appendix 3 Baseline participant characteristics of included studies

Study ID	Age, years, mean (SD)	Male sex, %	Comorbidities, n (%)
Welsh 2016	NR	NR	NR
Green 2020	NR	NR	NR
[redacted]	[redacted]	[redacted]	[redacted]
Kordzadeh 2018	Median (IQR) 73 (65-81)	62.0	Hypertension, 111 (66.9) Hypercholesterolaemia, 100 (60.2) Active smoking, 71 (42.8) Ischaemic heart disease, 54 (32.5) Cardiac arrhythmias, 37 (22.3) COPD, 29 (17.5) Renal failure, 26 (15.7)
Homza 2019	67.6 (min, max 41.8, 83.2)	74.2	Diabetes, 62 (100) Coronory artery disease, 42 (67.7) Angina pectoris, 19 (30.6) MI, 15 (24.2) Stroke, 13 (21.0) Cardiostimulator, 8 (12.9) Polyneuropathy, 20 (32.3) Nephropathy, 2 (32.2) Current smoker, 13 (21.0)
Jarai 2018	63.9 (11.5)	44.6	Smoking, 96 (24.2) Peripheral vascular disease, 105 (26.4) Diabetes mellitus, 110 (27.7)
Wohlfahrt 2011	54.3 (13.8)	46.8	Coronary heart disease, 47 (5.6) Diabetes mellitus, 78(9.3) Hyperlipoproteinaemia, 383 (45.6) Stroke or TIA, 19 (2.3) Claudications, 6 (<1%)
Diehm 2009	65 (6)	62.0	Diabetes, 19 (38) Arterial hypertension, 27 (54) Hyperlipidaemia, 30 (60) Renal insufficiency, 6(12) Current smoking, 41 (82) Coronary heart disease, 17 (34)

Study ID	Age, years, mean (SD)	Male sex, %	Comorbidities, n (%)
			Cerebrovascular disease, 7 (14) Claudication, 68 legs (68) Critical limb ischaemia, 32 legs (32)
Babaei 2020	60.1 (0.3)	39.8	T2DM, 100% (mean duration 13.29±0.34 years) Known CAD, 12.5% Known stroke, 1.6% Known hypertension, 69.7% Retinopathy, 21.1% Neuropathy, 42.8% Claudication, 17.1% Rest pain, 20.1% Foot ulcer, 6.6% Vascular surgery, 17.4% Current smoker, 4.6% [n NR for above]
Millen 2018	69.5 (12)	77.3	T1DM, 4 (6.1) T2DM, 14 (21.2) Hypertension, 52 (78.8) Hyperlipidaemia, 45 (68.2) IHD, 29 (44.0) CVA/TIA, 11 (16) Current smoker, 10 (15.2) Claudication, 36 (54.5) Rest pain, 4 (6.1) Oedema, 5 (7.6) Renal failure, 1 (1.5) Amputees, 3 (4.5)
Davies 2016	64 (9)	57.0	Hypertension, 550 limbs (76.0)
Lewis 2016	67 (12)	65.1	Hypertensive, 119 (62.9) Hyperlipidaemia, 108 (57.1) Previous CVA, 25 (13.2) Family history of CVA, 45 (23.8) Known CHD, 59 (31.2) Family history of CHD, 95 (50.3) Known PAD, 49 (25.9) Family history of PAD, 28 (14.8) Diabetes, 49 (25.9) DVT history, 15 (7.9) Retinopathy, 9 (4.8) Smoker, 59 (31.2)
Lewis 2010	NR	NR	NR
Zebari 2022	72 (10)	63.4	Hypertension, 110 (71.9) Hyperlipidaemia, 68 (44.4) Diabetes, 35 (22.9) Cardiac disease, 42 (27.5)

Study ID	Age, years, mean (SD)	Male sex, %	Comorbidities, n (%)
			Pulmonary disease, 22 (14.4) Renal disease, 10 (6.5) PAD, 80 (52.3) Lower limb pain during physical activity, 77 (50.3) Rest pain, 30 (19.6) Ulceration/gangrene, 13 (8.5) Aortic aneurysm, 53 (34.6) Aortic dissection, 3 (2.0) Other vascular disease, 9 (5.9) Current smoker, 26 (17.0)
Hageman 2021	67 (11)	55.7	Current smoker, 89 (44.3) Hypertension, 118 (58.7) Hypercholesterolaemia, 85 (42.3) Obesity, 38 (18.9) Diabetes mellitus, 61 (30.3) Renal insufficiency, 17 (8.4) Atrial fibrillation, 11 (5.5) Coronary artery disease, 73 (36.3) Cerebrovascular disease, 33 (16.4)
Boilley 2020	63 (11)	84.3	Diabetes, 20/102 (19.6) Dyslipidaemia, 78/102 (76.5) Medical history: PAD, 82/102 (80.4) Atrial fibrillation, 14/102 (13.7) Vascular bypass, 15/102 (14.7) Beta blocker medication, 37/102 (37.3) Antiplatelet medication, 75/102 (73.5) ACE inhibitor medication , 28/102 (27.5)
Catillon 2020	66 (14.4)	67.4	Hypertension, 30 (69.8) Tobacco, 4 (9.3) Diabetes, 11 (25.6) Dyslipidaemia, 18 (41.9) Renal insufficiency, 16 (37.2) Cardiovascular diseases, 20 (46.5) Anticoagulants, 8 (18.6)
Varetto 2019	72.5 (13.6)	62.7	Arteriopathy, 116 (62.7) Diabetes, 46 (24.9) Hypertension, 139 (75.1) Smoker/ex-smoker, 80 (43.2) Coronary artery disease, 42 (22.7)
Span 2016	64 (7.8)	NR	Hypertension, 66 (48.5) Dyslipidaemia, 58 (42.6) Diabetes mellitus, 19 (14.0) Current smoker, 22 (16.2)

Study ID	Age, years, mean (SD)	Male sex, %	Comorbidities, n (%)
Verma 2022	27.5 (4.1)	100.0	NR
Raya 2019	63 (7)	44.1	Hypertension, 114 (56.4) Dyslipidaemia, 117 (57.9) Diabetes mellitus, 57 (28.2) Cardiovascular or cerebrovascular disease, 30 (14.9)
Rodriguez-Roca 2014	47.7	45.7	Dyslipidaemia, 227 (70.5) Hypertension 86 (26.7) Current smoker, 82 (25.5) Obesity, 80 (24.8) Diabetes mellitus, 27 (8.4) Ischaemic heart disease, 13 (4.0) Heart failure, 5 (1.6) Cerebrovascular disease, 5 (1.6)
Sinski 2013	70.1 (9.4)	66.3	Coronary artery disease, 80 (100.0) MI, 19 (23.8) Percutaneous coronary intervention, 22 (27.5) CABG, 21 (26.3) Current smoking, 27 (33.8) Previously diagnosed PAD, 10 (12.5) Hypertension, 63 (78.8) Hypercholesterolaemia, 60 (75.0) Diabetes mellitus, 26 (32.5) History of atrial fibrillation, 17 (21.3) History of lower leg pain, 34 (42.5)
Kollias 2011	62.5 (11.1)	62.4	Hypertension, 77 (82.8) Diabetes, 42 (45.2) Dyslipidaemia, 6 (68.8) Current smoking, 14 (15.1) Cardiovascular disease, 21 (22.6) Chronic renal disease, 6 (6.5) Treatment with beta blockers, 20 (21.5)

Note. NR, not reported; COPD, chronic obstructive pulmonary disease; IQR, inter quartile range; MI, myocardial infarction, TIA, transient ischaemic attack; T2DM, type 2 diabetes; T1DM, type 1 diabetes; IHD, ischaemic heart disease; CVA, cerebral vascular accident; CHD, coronary heart disease; PAD, peripheral artery disease; DVT, deep vein thrombosis, CABG, coronary artery bypass graft

Appendix 4 Risk of bias assessments

QUADAS-2

Study ID	RISK OF BIAS				APPLICABILITY CONCERNS		
	Patient selection	Index test	Reference standard	Flow & timing	Patient selection	Index text	Reference standard
[redacted]							
Kordzadeh 2018	?	☺	☺	?	☺	☺	☺
Homza 2019	☺	☺	?	☺	☺	☺	☺
Jarai 2018	☺	☺	?	?	☺	☺	☺
Wohlfahrt 2011	?	☺	?	☹	?	☺	☺
Diehm 2009	☺	☺	☺	☺	☺	☺	☺
Babaei 2020	☺	☺	☺	☹	☺	☺	☺
Millen 2018	☺	☺	?	?	☺	☺	☺
Davies 2016	☺	☺	☺	☹	☺	☺	☺
Lewis 2016	☺	☺	☺	?	☺	☺	☺
Lewis 2010	☺	☺	☺	?	☺	☺	☺
Zebari 2022	☺	☺	☺	☺	☺	☺	☺
Hageman 2021	☺	☺	?	☺	☺	☺	☺
Boilley 2020	?	☺	☹	☺	☺	☺	☺
Catillon 2020	☺	☺	☺	☺	☺	☺	☺
Varetto 2019	?	☺	?	☹	?	☺	☺
Span 2016	☺	☺	☺	☹	☺	☺	☺
Verma 2022	☺	☺	?	?	☺	☺	☺
Rodriguez-Roca 2014	?	☺	☺	☹	☺	☺	☺
Sinski 2013	☺	☺	☺	☺	☺	☺	☺
Kollias 2011	☺	☺	?	☺	☺	☺	☺

☺ Low risk ☹ High risk ? Unclear risk

QUADAS-C

	Risk of bias (QUADAS-2)				Applicability concerns (QUADAS-2)			Risk of bias (QUADAS-C)			
Study ID	**P**	**I**	**R**	**FT**	**P**	**I**	**R**	**P**	**I**	**R**	**FT**
Raya 2019	☺	☺	?	?	☺	☺	☺	☺	☺	?	?

☺ Low risk ☹ High risk ? Unclear risk

P, patient selection; I, index test, R, reference standard, FT, flow and timing

ReBIP

ReBIP item	Welsh 2016	Green 2020
Representative sample	✓	?
Inclusion/exclusion criteria clearly defined	✓	×
Participants at similar point in disease progression	✓	?
Prospective data collection	✓	✓
Intervention and comparator clearly defined	✓	✓
Intervention delivered by experienced person	?	✓
Intervention delivered in appropriate setting	✓	✓
Important outcomes considered	✓	✓
Objective outcome measures used	✓	✓
Information on dropouts	×	×
Dropouts similar to those who completed study	?	?
Important prognostic factors identified	?	?

✓ Yes, × No, ? Unclear

Appendix 5 Outcomes relating to time to use the automated device, technical failure rates and experience of using the device

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
Welsh 2016 (Dopplex Ability)	• ABPI calculations with Dopplex Ability: 3-5 minutes • ABPI calculations with manual Doppler and BP cuff: Average 15 minutes • Both above excluding additional components of assessment	NR	• Both clinicians found the device easier to use and more time efficient than the manual Doppler • Most patients found the Dopplex Ability easy to tolerate • Some found the highest point of cuff inflation uncomfortable
Green 2020 (MESI ABPI MD)	• ABPI reading with MESI ABPI MD: 10-40 minutes (including holistic patient assessment)	NR	• Challenges of using the MESI device: length of time to set up software & undertake procedure; effects of inadequate staffing; GPs not referring patients for ABPI reading • Benefits of using the device: speed; simplicity; provision of printout of results; accurate identification of PAD; improved patients' outcomes; and timely onward referral • Around half users would continue to use the device after the project • Additional staff, time and funding would be required to undertake the ABPI readings and facilitate

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
			management of patients within general practice • Most GP surgeries had not been using the device for opportunistic reviews of patients due to time and resource constraints
[redacted]	[redacted]	[redacted]	[redacted]
Kordzadeh 2018 (BlueDop)	NR	NR	NR
Homza 2019 (BOSO ABI-System 100)	NR	NR	NR
Jarai 2018 BOSO ABI-System 100)	• Mean (SD) time to take measurements, minutes: o BOSO device: 2.1 (0.4) o Manual Doppler: 5.7 (0.6)	• 61/793 (7.7%) limbs showed a zero value • 2/61 (3.3%) of Doppler values were also zero	NR
Wohlfahrt 2011 BOSO ABI-System 100)	NR	NR	NR
Diehm 2009 BOSO ABI-System 100)	• Mean (SD) time to take measurements (including patient preparation and repeated measurements): o BOSO device: 3.9 (1.3) o Manual Doppler: 11.4 (3.8)	NR	NR

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
	○ p<0.001 by paired 2-tailed t-test		
Babaei 2020 (Dopplex Ability)	NR	NR	NR
Millen 2018 (Dopplex Ability)	NR	ABI was unobtainable by Dopplex over 3 attempts in 3/129 limbs (2.3%)	NR
Davies 2016 (Dopplex Ability)	• Mean (SD) time to take measurements: ○ Dopplex Ability (including time to apply cuffs): 7 minutes 55 seconds (1.29) ○ Manual Doppler (including 10 minutes rest): 17 minutes 45 seconds (1.05) ○ p<0.01	Failed Dopplex measurements in 28/724 (3.9%) limbs, associated with presence of hypertension (p=0.015). No failed Doppler measurements	NR
Lewis 2016 (Dopplex Ability)	NR	NR	NR
Lewis 2010 (Dopplex Ability)	• Mean (range) time to take measurements: ○ Dopplex Ability (unrested): 7.1 minutes (4.4-11)		

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
	○ Dopplex Ability (rested; not including fitting of cuffs): 4.6 minutes (3-10.7) ○ Manual Doppler: 16.5 minutes (7.8-24.4) plus 15 minutes resting time		
Zebari 2022 (MESI ABPI MD)	NR	• In 306 legs (153 patients), the MESI device delivered 194 numerical ABI readings whereas 84 were classified as LEAD by a specific measurement code rather than a numeric ABI reading • 28 error codes were delivered by the device of which 14 were pathological by the manual device • 22/28 error codes indicated LEAD • 6/28 error codes were due to the automated device being unable to measure for technical reasons	NR
Hageman 2021 (MESI ABP MD)	NR	• In 63/401 (15.7%) legs, ABI was not measurable by MESI device after 2 trials (oscillometric errors); 3/63 (4.8%) had arterial calcifications, 45 (71.4%) had values consistent with PAD and	NR

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
		15/63 (23.8%) had normal values as determined by vascular laboratory equipment • The device provided an error message instead of a valid ABI reading in 28% of PAD legs (16% of all legs) • Frequency of oscillometric errors was higher in limbs with PAD than in limbs without PAD (28% and 7%, respectively; P < .001). • Incidence of oscillometric errors was similar in patients thought to have new-onset PAD compared with patients with a history of revascularisation (24% and 27%, respectively; P= 0.680)	
Boilley 2020 (MESI ABPI MD)	NR	NR	NR
Catillon 2020 (MESI ABPI MD)	• Mean time to take measurements with MESI device (not including placement of first cuff): o Students: 3.75 minutes o Vascular specialists: 2.26 minutes (p<0.01)	NR	NR

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
	○ Multiple regression model: measurement with MESI device took 3.7 times less than manual Doppler (-3.713±0.170)		
Varetto 2019 (MESI ABPI MD)	• Mean time for assessment with MESI device: 4.02 minutes • Mean time for assessment with manual Doppler: 5.28 minutes ($p<0.0001$)	• Unable to obtain assessment with MESI device in 19% of cases, compared to 11% with the manual Doppler ($p=0.02$) • Reason for failures in manual Doppler assessments was arterial incompressibility in extensive calcifications (in 2 of these cases, ABI>1.5 was found with the MESI device)	NR
Span 2016 (MESI ABPI MD)	• Mean time to take measurements with MESI device: 2 minutes • Mean (SD) time to take measurements with manual Doppler (including both left and right dorsalis pedis and tibial systolic pressures): 14 (1.5) minutes (operator 1), 14 (1.9) minutes (operator 2)	• In 14/150 (9.3%) of participants, it was not possible to assess ABPI with MESI device and/or manual Doppler due to critical limb ischaemia or incompressible arteries	NR

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device
Verma 2022 (WatchBP Office ABI)	NR	NR	NR

Raya 2019 (WatchBP Office ABI, MESI ABPI MD)	• Mean (SD) time to take measurements, minutes:
	  ○ WatchBP: 14.4 (1.6)
	  ○ MESI: 10.7 (1.3)
	  ○ Manual Doppler: 12.1 (1.8)
		• Total errors:
		  ○ WatchBP: 13%
		  ○ MESI: 14%
		  ○ Doppler: 4%
		• Type of errors: WatchBP, MESI, manual Doppler
		• Pain: 1%, 3%, 1%
		• Measurements repeated: 10%, 4%, 2%
		• No value given (arterial calcification): 0%, 0%, 1%
		• No value given (PAD): 0%, 4%, 0%
		• Could not be measured: 2%, 3%, 0%
			NR

Rodriguez-Roca 2014 (WatchBP Office ABI)	NR	NR	NR
Sinski 2013 (WatchBP Office ABI)	NR	• Unable to measure ABPI with WatchBP device on left ankle in 2/80 (2.5%) patients	NR

Study ID (automated device)	Time required for using the device	Technical failure rate	Acceptability and experience of using the device

Kollias 2011 (WatchBP Office ABI)	• Mean (SD) time to take measurements, minutes (excluding time for initial cuff placement):
	  ○ WatchBP: 5.8 (0.3)
	  ○ Manual Doppler: 9.3 (2.2)
		• WatchBP failed to measure ABI in 3/186 (1.6%) of legs
		• Frequency of errors with WatchBP was higher in limbs with PAD (35.2%) compared to those without PAD (5.7%), p<0.001
		• In limbs with Doppler ABI<0.9, there was a tendency for more errors in those with non-palpable ankle pulses (40.3%) compared with palpable ankle pulses (15.2%), p=0.07
			NR

Appendix 6 Supplementary cost-effectiveness search strategies

Search 1: Cost effectiveness of PAD diagnostic methods
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to May 06, 2022>

1 exp *Peripheral Arterial Disease/di, dg
2 exp "costs and cost analysis"/
3 *economics/
4 exp economics,medical/
5 economics,pharmaceutical/
6 exp models, economic/
7 exp decision theory/
8 monte carlo method/
9 markov chains/
10 exp technology assessment, biomedical/
11 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
12 economics model$.tw.
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Appendix 7 Cost of Amputation

The per-cycle cost of amputation used within the model was based on the methods used in CG147.[128] CG147 used a combination of clinical expert opinion (Guideline Development Group) and the external literature to determine the care needs of patients following the procedure. Within our analysis, we used the same clinical assumptions supplemented with updated literature sources where possible. Furthermore, the unit costs used within CG147 are based on the PSSRU 2010 and the NHS reference costs 2009/10 these have been updated with the 2020/21 cost year applied in our analysis. Details of the clinical assumptions, sourced from CG147, which we used in our calculations are provided below.

Clinical assumptions sourced from CG147 for post-operative care following amputation per patient

Category	Assumption	First year	Subsequent years
Prosthetics & wheelchairs	3 prosthetist appointments per patient	✓	×
	Wheelchairs replaced every 5 years	✓	✓
	50% of wheelchairs are motorised	✓	✓
Rehabilitation	All patients receive inpatient and outpatient rehabilitation services in the first year following amputation	✓	×
Inpatient rehabilitation	1 rehabilitation assessment	✓	×
	50 days of rehabilitation	✓	×
Outpatient rehabilitation	1 rehabilitation assessment	✓	×
	8.5 and 13 weeks of rehabilitation for below and above knee amputations respectively	✓	×
	2 hours of class per week	✓	×
	10 patients per class	✓	×
	2 physiotherapists and 1 physiotherapy technician per class	✓	×
Wound care	2.5 home nurse visits per week	✓	×
	90% of wounds are non-complicated with average healing time of 12 weeks	✓	×
	10% of wounds are non-complicated with average healing time of 32 weeks	✓	×
Care home	47 weeks per year	✓	✓
Community care	50% of patients who remain in the community will receive care	✓	✓
Home modifications	All patients who remain in the community will have home modifications	✓	✓

To generate the most representative subsequent care costs, we have supplemented the assumptions made in CG147 with additional screening of the literature. A study

conducted in Glasgow in 2014 of 118 patients who underwent lower extremity amputations informed the number of patients who received a prosthetic limb, where 56% of patients were referred for prosthetic rehabilitation.[115] We utilised the same study as CG147 to inform the proportion of formally independent patients who retain their independence following amputation. [116]This study reports a KM analysis of formally independent patients who lose their independence following amputation. We assumed that the number at risk at baseline represents the proportion of the total population who were independent prior to the procedure, 71.9%. This is in line with the Glasgow study, where 73% of patients had no home care pre-amputation. Therefore, we assume that 28.1% of patients were in a care home prior to the amputation. We did not include these costs as they cannot be attributed directly to amputation. At 3-months post-amputation the KM analysis finds that 77% of formally independent patients retained their independence and remain in the community, which represents 55.3% of the total population. We then utilised the assumption from CG147, that 50% of these will require care in the community (27.7%). In line with the costs of the procedure itself, we used the ratio of above to below knee amputations reported in the national vascular registry to inform the cost of wound care.[98]

Additional clinical assumptions for this analysis

Category	Assumption	Source
Prosthetics & wheelchairs	56% receive a prosthetic limb	56% of lower extremity amputation patients are referred to prosthetic rehabilitation services. Davie-Smith, 2015[115]
	44% receive a wheelchair	
	Prosthetics would be replaced every 5 years	Assumed equal to useful lifespan of wheelchairs in CG147.
Care requirements (as a result of amputation)	27.7% live independently and do not receive care within the community	KM analysis of maintenance of independent living status after major amputation. Where 383/533 (71.9%) at risk at baseline with 77% of these (55.3%) retaining their independent living status at 3 months post-amputation and 23% of these (16.5%) would then require fulltime care post-amputation. Therefore, it is assumed that 150/533 (28.1%) were not living independently prior to amputation and required fulltime care. Taylor et al. 2005[116] Following the assumption from CG147 reported in table x, 50% of those who remain in the community will receive care (50% of 55.3% = 27.65%).
	27.7% live independently but receive care within the community	
	16.5% require fulltime care as a result of amputation	
	28.1% required fulltime care (care home) prior to amputation	
Proportion of above knee and below knee amputations	49.8% above knee	3203/6429 of major unilateral lower limb amputation procedures were above the knee in 2019 and 2020. National vascular registry. 2021.
	50.1% below knee	

Costs are detailed for each category of resource use: prosthetics, wheelchairs, rehabilitation, wound care, care homes, community care and home modifications. All

costs are adjusted for the assumptions detailed above. Finally, we report the total cost by category and year. The cost of care in the first year following amputation is calculated as £35,813.44 and £14,293.65 for all subsequent years. These costs are comparable to those used within CG147 in the first year (£34,464.70 uplifted to 2020/21 prices).[109] The cost used for subsequent years is substantially less in our analysis compared to CG147, £28,651.90 in 2020/21 prices. This is primarily driven by care home costs. CG147 assumed that 36% of formally independent patients require a care home which is higher than our analysis (23%). Furthermore, unlike our analysis, CG147 bases their costing analysis upon the formally independent population only and does not account for patients who were not independent prior to the procedure.

Cost by category of resource use

Category	Assumption	Timeframe	Unit cost	Source
Prosthetics	Annuatised cost of 3 prosthetist appointments per patient	Annual	£248.08	Based on £373.36 unit cost (total cost of £1,120.08) discounted by 3.5% per annum over 5 years. Prosthetics Non-Admitted F2F attendance, Follow-up [WF01A]. NHS reference costs 2020/21
	Annuatised cost of prosthetic	Annual	£232.21	Based on £1,048.43 discounted by 3.5% per annum over 5 years. Bespoke orthopaedic prosthesis [DEV03]. NHS reference costs 2020/21
	56% of patients		**£268.96**	56% of £480.28.
Wheelchairs	Annuatised cost of non-motorised wheelchair (50% of wheelchairs)	Annual	£35.50	Based on £71 annual cost of self- or attendant-propelled chair discounted by 3.5% per annum over 5 years. PSSRU 2021/22
	Annuatised cost of motorised wheelchair	Annual	£177.50	Based on £355 annual cost of powered chair discounted by 3.5%

	(50% of wheelchairs)			per annum over 5 years. PSSRU 2021/22
	44% of patients		**£93.72**	44% of £213
Inpatient rehabilitation	1 rehabilitation assessment	-	£793.09	Complex specialised rehabilitation services level 1. Assessment for rehabilitation, unidisciplinary. [VC01Z]
	50 days of rehabilitation	-	£20,500	Based on £410 per occupied ed day of local specialist rehabilitation services. PSSRU 2020/21
	100% of patients		**£21,293.09**	
Outpatient rehabilitation	2 physiotherapists and 1 physiotherapy technician	Per hour	£139	2x Band 6 (£52). 1x Band 4 (£35). Cost per working hour of hospital-based scientific and professional staff. PSSRU 2020/21.
	2 hours of class per week	Per class	£278	2 multiplied by £139
	10 patients per class	Per patient	£27.80	£278 divided by 10
	8.5 weeks of classes (below knee)	Per course	£118.57	Multiplied by number of weeks and weighted to 50.1%. National vascular registry, 2021.

	13 weeks of classes (above knee)	Per course	£180.05	Multiplied by number of weeks and weighted to 49.8%. National vascular registry, 2021.
	100% of patients		**£1,091.72**	Based on weighted cost of classes (£298.63) plus 1 rehabilitation assessment (£793.09).
Wound care	2.5 home nurse visits	Per week	£72.50	£29 per visit. Based on data of N=644 patients, aged over 70, who were discharged from acute medical units within 72 hours of admission. PSSRU 2020/21.
	12 weeks of home nurse visits	-	£783.00	Multiplied by number of weeks and weighted to 90%. National vascular registry, 2021.
	32 weeks of home nurse visits	-	£232	Multiplied by number of weeks and weighted to 10%. National vascular registry, 2021.
	100% of patients		**£1,015**	Weighted cost of classes by severity of wound.

Care home	First year (40 weeks)	**Annual**	£54,360.00	Based on £1,359 establishment cost per permanent resident week in a local authority own-provision residential care home (PSSRU 2020/21) for 47 weeks per year minus any inpatient rehabilitation in year 1.
	16.5% require fulltime care		**£8,969.40**	
	Subsequent years (47 weeks)	**Annual**	£63,873.00	
	16.5% of patients require fulltime care		**£10,539.05**	
Community care	First year (45 weeks)	Annual	£7,425.00	Based on £165 per client week within local authority own-provision day care for older people (PSSRU 2020/21) for 52 weeks per year minus any inpatient rehabilitation in year 1.
	27.7% of patients require ongoing community care		**£2,053.01**	
	Subsequent year (52 weeks)	Annual	£8,580.00	
	27.7% of patients require ongoing community care		**£2,372.37**	
Home modifications	Fit handrail – external	Annual	£5.70	Mean annual equipment cost annuitised over 10 years by 3.5%. PSSRU 2019/20.
	Fit handrail – internal	Annual	£4.00	
	Fit handrail to bath	Annual	£2.50	
	Relocation of toilet	Annual	£1,383	
	Ramp to front/back door	Annual	£44.00	

	Widen doorway for wheelchair access	Annual	£75.00	
	Stair lift	Annual	£263.00	
	Raise electrical sockets/lower light switches	Annual	£11.40	
	55.3% of patients remain in the community		**£1,019.56**	£1,788.60 uplifted to 2020/21 prices (£1843.69). PSSRU 2020/21.

Annual costs by category and year from procedure

Item	First year	Subsequent years
Prosthetics	£268.96	£268.96
Wheelchairs	£93.72	£93.72
Inpatient rehabilitation	£21,293.09	-
Outpatient rehabilitation	£1,091.72	-
Wound care	£1,015.00	-
Care home	£8,969.40	£10,539.05
Community care	£2,053.01	£2,372.37
Home modifications	£1,019.56	£1,019.56
Total	**£35,804.46**	**£14,293.65**