Chapter II: Diagnostic Methods


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Ankle-brachial index; Doppler ultrasound; Computed tomography; Magnetic resonance; Angiography

Abstract
Non-invasive vascular studies can provide crucial information on the presence, location, and severity of critical limb ischaemia (CLI), as well as the initial assessment or treatment planning.

Ankle-brachial index with Doppler ultrasound, despite limitations in diabetic and end-stage renal failure patients, is the first-line evaluation of CLI. In this group of patients, toe-brachial index measurement may better establish the diagnosis. Other non-invasive measurements, such as segmental limb pressure, continuous-wave Doppler analysis and pulse volume recording, are of limited accuracy. Transcutaneous oxygen pressure (TcPO2) measurement may be of value when rest pain and ulcerations of the foot are present. Duplex ultrasound is the most important non-invasive tool in CLI patients combining haemodynamic evaluation with imaging modality.

Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are the next imaging studies in the algorithm for CLI. Both CTA and MRA have been proven effective in aiding the decision-making of clinicians and accurate planning of intervention. The data acquired with CTA and MRA can be manipulated in a multiplanar and 3D fashion and can offer exquisite detail. CTA results are generally equivalent to MRA, and both compare favourably with contrast angiography. The individual use of different imaging modalities

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1. Non-invasive vascular laboratory tests

In patients with critical limb ischaemia (CLI) an accurate diagnosis can be established with modern non-invasive vascular diagnostic techniques to provide adequate information for creation of a therapeutic plan. When required, non-invasive physiological and anatomical data will be supplemented by the use of more accurate imaging techniques, such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA), and selective use of lower extremity angiographic techniques.

The objectives of modern non-invasive testing of patients with peripheral arterial disease are:

- to confirm the presence of the disease
- to provide reproducible physiological data concerning disease severity
- to document the location and haemodynamic importance of vascular lesions
- to make a detailed plan in case intervention is needed.

These tests can be repeated over time to follow disease progression and results of treatment.

Non-invasive assessment of patients with CLI can be broadly grouped into three general categories of techniques:

- physiologic or haemodynamic measurements
- measurements of tissue perfusion
- anatomic imaging.

Each modality has advantages, disadvantages and limitations.

Non-invasive techniques assessing physiological parameters of pressure and flow can provide an initial assessment of the location and severity of arterial disease. Doppler ultrasonography and plethysmography, each with various forms and techniques, are the two most commonly used haemodynamic methods to evaluate patients with CLI.

Measurements of tissue perfusion include microcirculation techniques; the most commonly employed is transcutaneous partial pressure of oxygen (TCPo2) measurements.

Non-invasive anatomic imaging is usually based on a combination of Doppler haemodynamic and B-mode ultrasonography imaging and will be detailed in the second part of this chapter ("Imaging techniques. Duplex ultrasound").

2. Physiological and haemodynamic measurements (Table 1)

2.1. Doppler ultrasonography

Doppler ultrasonography is the single most important modality in non-invasive evaluation of vascular disease extent. Ultrasound techniques are based on the principle that sound waves emitted from a probe are reflected at the interface of two surfaces; the observation that an ultrasound wave undergoes a frequency shift proportional to the velocity of any moving object encountered (e.g. red blood cells) is known as Doppler principle. Both quantitative and qualitative measurements of flow are allowed by Doppler ultrasonography. Quantitative analyses are based on pressure measurements and include ankle-brachial and toe-brachial indices and segmental pressure; qualitative measurements are based on the analysis of the shape and morphology of Doppler waveforms.

2.1.1. Ankle-brachial index (ABI)

The single most valuable and commonly used diagnostic test in the evaluation of peripheral arterial occlusive disease is measurement of the ankle-to-brachial systolic blood pressure ratio, termed ankle-brachial index (ABI). The ABI is a simple, inexpensive, non-invasive test that can be performed easily in most clinical settings; it is measured with a handheld continuous-wave Doppler ultrasound probe and a blood pressure cuff: the highest systolic pressure measured from either the posterior tibial or dorsalis pedis artery (in each leg) is divided by the highest brachial artery pressure taken from either arm. Optimal recordings are obtained with blood pressure cuffs that are appropriately sized to the patient’s lower calf, immediately above the ankle. Systolic pressures are recorded with a Doppler probe after the patient has been at rest in supine position for 5 minutes. Pulse wave reflection in healthy individuals causes the ankle pressure to be 10–15 mmHg higher than the brachial artery systolic pressure.2–4 If the arm blood pressures are not equal, a subclavian/axillary stenosis or occlusion might be present, and the arm with the highest blood pressure is used for subsequent blood pressure ratio calculations. In patients with ischaemic ulcers, the ankle pressure is typically 50–70 mmHg, and in patients with ischaemic rest pain it is typically 30–50 mmHg. However, falsely high values can be recorded in CLI patients, in whom the ABI test is not reliable due to incompressible calcified vessels as in patients with long-standing diabetes, advanced age or end-stage renal disease.

The ABI provides objective data that serve as the first-line assessment for the diagnosis of lower limb vascular disease and has been used either as a baseline diagnostic tool for patients with CLI (foot ulcer or rest pain) or to monitor the efficacy of therapeutic interventions. The normal range of ABI is quoted as 0.91–1.31.4,5 The cut-off point for diagnosis of vascular disease is typically set at <0.90 at rest.1 ABI values between 0.41 and 0.90 are considered "mildly to moderately" diminished and an ABI of 0.40 or less as "severely" decreased. Although it has been suggested that patients with an ABI <0.40 are more likely to develop ischaemic rest pain, ischaemic ulceration, or gangrene, compared to patients with an ABI ≥0.5, there is no general consensus regarding the prognostic value of these ABI categories for peripheral disease.1,2,5–11 In diabetic patients, Clairiotte et al. reported that the cut-off values for the highest sensitivity and specificity for vascular disease screening were between 1.0 and 1.1.11

ABI measurement is claimed to be a simple and reproducible test. Reporting standards require a change of 0.15 to be considered clinically relevant, or >0.10 if associated
with a change in clinical status. Well-controlled, repeated measurements are accurate enough to be used as a clinical indicator in decision-making. However, the reproducibility may vary among experienced physicians.\textsuperscript{5,7,8,12,13} It has been shown that the reproducibility of ABI assessment by pocket Doppler may depend on the level of experience of the operator.\textsuperscript{6,14–17} Inter-observer variability among experienced physicians has a reported $k$-statistic of 0.77 to 1.0.\textsuperscript{5} Intra-observer variability ranges from 7.3\% to 12\%.\textsuperscript{5,7,8,12,13} Klein and Hage found 39 different ways to calculate the index.\textsuperscript{1} Holland-Letz and Endres and colleagues\textsuperscript{18,19} found small intra- (8\%) and inter-observer errors (0–9\%) among different practitioner groups in large unselected populations.

Different modes of determination and calculation of the ABI can be applied especially in primary care practices.\textsuperscript{6} Klein and Hage found 39 different ways to calculate the ABI.\textsuperscript{20} Nicolai et al., investigating the use of ABI in non-specialist settings, showed that eight different methods were commonly used for calculation of the ABI in primary care practices.\textsuperscript{6} A recently published literature analysis that evaluated the methodology of ABI determination in 100 random publications demonstrated great variability with respect to the methods of ankle and brachial blood pressure measurements as well as calculation of the index.\textsuperscript{21} Major international societies\textsuperscript{2,4} recommend calculating the ABI by dividing the highest pressure in the leg by the highest pressure in the arm to guarantee good reproducibility. Use of a standardised step-by-step technique for measuring ABI is required for reproducibility of measurements.

ABI has been largely validated against contrast-enhanced angiography to determine obstructions greater than 50\%. The ABI has been reported to be 95\% sensitive and 99\% specific for peripheral disease detection when a 0.9 cut-off level from measurements is used.\textsuperscript{22–25} In general, the sensitivity of ABI ranges from 80\% to 95\% and the specificity from 95\% to 100\%, with positive and negative predictive values in excess of 90\%.\textsuperscript{1,5,6,22} However, as pointed out by Al-Qaisi et al. in a recent update on ankle-brachial index (2009 review), the majority of authors quoting detection accuracy for ABI normal/abnormal ranges refer back to original data from pioneering works performed in the 1970s and 1980s.\textsuperscript{5,26–31}

The diagnostic accuracy of ABI as a screening test may be limited in diabetic patients, especially those with nephropathy, foot lesions and old age, probably due to the high prevalence of medial arterial calcifications causing a high prevalence of false negative values. Sensitivity ranging from 63\% to 100\% and specificity values of 85–97\% have been reported in these patients.\textsuperscript{5,22–31} In a recent study analysing patients undergoing both ABI and angiography measurements, Chung et al. showed that the most significant factor affecting the validity of ABI was diabetes (OR 4.36 for false-negative results).\textsuperscript{32} Although CLI is very common in

<p>| Table 1 Non-invasive physiologic vascular diagnostic techniques: advantages and limitations\textsuperscript{a} |
|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td>Ankle-brachial index (ABI)</td>
<td>Simple, inexpensive, quick, widely applicable,</td>
<td>May be falsely elevated in patients with diabetes,</td>
</tr>
<tr>
<td></td>
<td>cost-effective.</td>
<td>renal insufficiency and advanced age.</td>
</tr>
<tr>
<td></td>
<td>Sensitive in establish or refute CLI diagnosis.</td>
<td>Indirect measure.</td>
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<tr>
<td></td>
<td>Useful to monitor efficacy of therapeutic interventions in CLI.</td>
<td>Does not provide localisation of the disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not allow visualisation of artery lesion.</td>
</tr>
<tr>
<td>Toe-brachial index (TBI)</td>
<td>Simple, inexpensive and quick.</td>
<td>Limited accuracy.</td>
</tr>
<tr>
<td></td>
<td>Useful in the presence of small vessel artery disease.</td>
<td>Requires careful techniques and small cuffs (not widely applicable).</td>
</tr>
<tr>
<td></td>
<td>Useful in non-compressible pedal arteries.</td>
<td>Indirect measure.</td>
</tr>
<tr>
<td>Segmental pressure</td>
<td>Useful in initial anatomical localisation of CLI disease.</td>
<td>Not accurate in non-compressible pedal arteries as in very old patients, in diabetics and in those with end-stage renal disease.</td>
</tr>
<tr>
<td></td>
<td>Useful in creating therapeutic plan based on disease localisation.</td>
<td>Does not provide direct visualisation of the disease.</td>
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<tr>
<td></td>
<td>Provides data to predict wound healing and limb survival.</td>
<td>Old-fashioned measure of perfusion.</td>
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<tr>
<td></td>
<td>Useful to monitor efficacy of therapeutic intervention.</td>
<td></td>
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<tr>
<td>Continuous-wave Doppler ultrasound</td>
<td>Useful in initial evaluation of CLI anatomy, severity and progression.</td>
<td>Limited sensitivity.</td>
</tr>
<tr>
<td></td>
<td>Can provide adjunctive information in incompressible arteries.</td>
<td>Limited specificity especially for aorto-iliac occlusive disease.</td>
</tr>
<tr>
<td></td>
<td>Can provide localising information.</td>
<td>Old-fashioned measure of perfusion.</td>
</tr>
<tr>
<td></td>
<td>Can provide qualitative data to monitor after successful revascularisation.</td>
<td>Does not provide visualisation of the disease.</td>
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<tr>
<td></td>
<td></td>
<td>Limited overall accuracy.</td>
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<tr>
<td>Pulse volume recording (PVR)</td>
<td>Initial evaluation of CLI in vascular laboratories.</td>
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<tr>
<td></td>
<td>Useful in non-compressible pedal arteries especially in diabetic patients (photoplethysmography).</td>
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<tr>
<td></td>
<td>Useful to monitor limb perfusion after revascularisation.</td>
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<tr>
<td>CLI, critical limb ischaemia.</td>
<td>Adapted from Hirsch et al.\textsuperscript{1}</td>
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</table>
diabetic patients (prevalence of vascular disease estimated around 13.6% vs. 4% in the general population), it often remains under-recognised in this population. Diagnosis is often difficult because the co-existence of peripheral neuropathy could mask the ischaemic pain. In these settings, sensitivity in detecting vascular disease of ABI ranges from 50% to 71% and specificity from 30% to 96.8%. The ABI is relatively insensitive for determining progression of lower limb occlusive disease when compared to arteriography or duplex ultrasonography. McLafferty et al. found an ABI sensitivity of 41%, specificity of 84%, positive predictive value of 59% and overall accuracy of 68% in detecting disease progression.

In addition to its use in evaluating symptomatic patients affected by peripheral vascular disease, decreased ABI is a strong predictor of cardiovascular events and premature mortality. An ABI <0.90 is associated with a 3- to 6-fold increased risk of cardiovascular mortality. A meta-analysis in 2008 by Fowkes et al. found an ABI sensitivity of 41%, specificity of 84%, positive predictive value of 59% and overall accuracy of 68% in detecting disease progression.

Summary messages (advantages and limitations of ABI):
- ABI can be useful as a routine measurement in primary care practices providing objective and reproducible first-line assessment of CLI. It is sensitive and specific in the differential diagnosis of leg symptoms to identify or rule out a vascular aetiology.
- ABI measurement is a widely applicable, simple, quick, cost-effective and non-invasive tool to establish or disprove the baseline for CLI and to follow revascularisation results.
- ABI can provide objective data that serve as the standard in office practice, vascular laboratories and epidemiological surveys.
- ABI provides indirect information on arterial disease but cannot localise the anatomical level of a pressure-reducing obstruction.
- The reproducibility of ABI measurements is dependent on the level of experience of the operator and may vary among experienced physicians, university hospitals and in community settings.
- ABI may not be accurate in the presence of incompressible lower extremity arteries as occurs in very elderly individuals, diabetics, or patients with long-standing renal disease.
- Use of a standardised step-by-step technique for measuring ABI is required to ensure reproducibility of measurements.

Recommendations

The resting ABI is useful in the initial evaluation for CLI and can be easily and quickly measured on both legs to confirm diagnosis and establish the severity of disease in patients with rest leg/foot symptoms as well as individuals with foot non-healing ulcer and lower limb rest pain.

(Level 2b; Grade B)

The resting ABI in all new patients with CLI can be used to establish the baseline to evaluate the effect after revascularisation procedures.

(Level 2b; Grade B)

ABI is less reliable in CLI diagnosis in patients with incompressible arteries (long-standing diabetes, end-stage renal disease, advanced age) and should be supported by more reliable techniques in these settings.

(Level 2b; Grade B)

2.1.2. Toe-brachial index

Since the presence of CLI is higher in patients with diabetes and end-stage renal disease, this may preclude accurate assessment of ABI in most subsets of these patients.

Incompressible arteries are suggested when the ABI is greater than 1.3. The digital vessels are usually spared from calcification; therefore, toe systolic blood pressures are often more accurate in quantifying vascular disease in diabetic, dialysis-dependent or very old patients. Toe pressures are obtained by placing small occlusive cuffs around each toe (usually at the proximal portion of digit I and II) with a digital flow sensor beyond the cuff. Toe systolic pressure can be expressed as a ratio of the toe pressure to the highest pressure recorded in either arm to obtain the toe-brachial index (TBI).

Normally the toe pressure is approximately 30 mmHg less than the ankle pressure and TBI should be >0.75. Values <0.7 are considered abnormal and TBI <0.25 is consistent with severe CLI. Absolute toe pressures <30 mmHg are required to diagnose CLI in patients with rest pain. For patients with ulcers or gangrene, the presence of CLI is diagnosed by toe systolic pressure <50 mmHg. Absolute toe pressure of 55 mmHg or greater has been correlated to be predictive for foot ulcer healing in diabetic patients, and TASC requires toe pressure <50 mmHg (critical level) to confirm CLI diagnosis in diabetic patients.

Toe pressure measurements were shown to be more reliable than ABI measurements in patients with diabetes associated with falsely high ABI values and peripheral neuropathy. Brooks et al. compared TBI and ABI in 174 diabetics and 53 controls and found comparable indices when ABI was low or normal (84% and 78% agreement, respectively), but not when ABI was elevated. In the presence of clinical peripheral neuropathy, toe pressure sensitivity has been evaluated to be 100% and ABI sensitivity 53%.

However, TBI measurement requires appropriate technique and tools (small cuffs), therefore it is not widely applicable and the overall accuracy may be limited. Furthermore, it may be impossible to measure toe pressures in patients with inflammatory lesions, ulceration or loss of tissue.
Summary messages (advantages and limitations of toe-brachial index):

- Toe-brachial index is a quick way to non-invasively establish or disprove the CLI diagnosis in patients with lower limb rest pain or non-healing ulcers.
- Toe-brachial measurements are particularly useful in individuals with incompressible crural and pedal arteries.
- The test requires small cuffs and a careful technique to preserve accuracy.

**Recommendation**

Toe-brachial index is useful to establish CLI diagnosis in patients in whom CLI is clinically suspected (non-healing ulcer, rest pain) but the ABI test is not reliable due to incompressible vessels as in patients with diabetes, advanced age or long-standing renal failure. *(Level 2b; Grade B)*

2.1.3. **Segmental limb pressure**

The location and extent of CLI can be indirectly defined in a non-invasive laboratory by segmental limb systolic pressure measurements, recorded with a Doppler instrument and blood pressure cuffs placed over the brachial arteries and sequentially at various points on the lower limbs, including the upper and lower thigh, the upper calf, the ankle, and metatarsal. Theoretically, the cuff width should be 20% greater than the diameter of the limb at the point where it is applied. Narrow cuffs may be associated with the appearance of falsely high pressures and do not permit accurate disease localisation.\(^1\)\(^2\) The examination is performed by placing a Doppler probe over the most prominent arterial signal at the ankle with the patient in supine position. In most laboratories a 20 mmHg gradient between adjacent segment cuffs is regarded as indicative of a significant occlusive lesion. Thus, by comparing the pressures obtained at different levels, segmental pressure measurement can detect the location of arterial occlusive lesions with reasonable accuracy. Segmental pressure measurements can provide information in patients with multi-level disease and predict ulcer healing, limb survival or the need for further additional revascularisation.\(^54\)\(^6\) However, as already stated by the TASC II and AHA Guidelines,\(^1\)\(^2\) there are a number of limitations and potential problems in the analysis of segmental limb pressure that render it an old-fashioned diagnostic technique for CLI evaluation.

- Isolated moderate stenosis (usually iliac) that produces little pressure gradient may be missed.
- Calcified arteries may lead to falsely elevated ankle pressures.
- In patients with multi-level disease, decreased proximal pressures may mask more distal gradients.
- Segmental pressure gradients are not suitable to differentiate between short- and long-segment lesions or between highly stenotic arteries and occlusions.
- Reduced thigh pressures is usually indicative of a pressure-reducing obstruction along the aorto-iliac axis; however, similar findings may be produced by an obstruction of the common femoral or proximal superficial femoral and deep femoral arteries.
- Artefacts on measurements due to inappropriate cuff size/position are common.

Summary messages (advantages and limitations of segmental limb pressure):

- Segmental pressure can provide first-line information on anatomical localisation of lower limb vascular disease in patients with CLI.
- Segmental pressure measurement can be helpful to establish more sophisticated imaging techniques to determine a detailed localisation of the disease.
- The test may not be accurate in the presence of incompressible arteries.
- Measurements of segmental pressure can provide only indirect information on vascular disease and results can be biased by a number of artefacts and drawbacks. The test should not be used as the sole diagnostic technique but should be associated with ultrasound imaging.

**Recommendation**

Lower limb segmental pressure measurements can provide a first-line localisation of arterial lesion along lower limb in patients with CLI. Segmental pressure should not be used as the sole diagnostic technique. *(Level 2b; Grade B)*

2.1.4. **Continuous-wave Doppler ultrasound**

Quantitative and qualitative analysis performed by continuous-wave Doppler ultrasound remains an old-fashioned technique which is no longer routinely used in many modern diagnostic vascular laboratories. The AHA guidelines recognise that Doppler waveforms analysis needs to be combined with ultrasound visualisation of arterial vessel (“duplex imaging”) to maximise the benefits of this technique.\(^1\)

- **Analysis of morphology of the continuous-wave Doppler waveform**

  Quantitative and qualitative analysis performed by continuous-wave Doppler ultrasound was suggested to provide useful information in localising and quantifying vascular disease in patients with poorly compressible arteries. Many patients with diabetes or end-stage renal disease, without palpable pulses and monophasic Doppler signals, may have an ABI greater than 1.0, which is a deceptive and misleading quantitative assessment of the severity of vascular disease.\(^5\)

  The most commonly used “pulsatility index” is defined as the peak systolic velocity (or “frequency shift”) divided by the mean blood flow velocity. Normally, the pulsatility index increases from the most proximal to the most distal segments of the lower extremities; a decrease between adjacent segments implies the presence of occlusive disease between these two locations.\(^5\)\(^7\)

  However, reversion to a normal waveform below a proximal stenosis may often occur. This phenomenon of “pulse normalisation” distal to some arterial stenosis is a recognised major diagnostic limitation of the technique that may occur especially in the presence of multi-level disease with high-resistance flow.

  Furthermore, quantitative assessment of the pulsatility index is weakened in the presence of arterial calcifications.

  Currently, the benefits of continuous Doppler waveform analysis are limited, and it should always be combined with ultrasound greyscale or colour visualisation of the arterial wall. Such “duplex imaging” represents one of the most widely used non-invasive vascular laboratory techniques replacing the traditional continuous-wave Doppler velocity analysis.
Summary messages (advantages and limitations of continuous-wave Doppler ultrasound):
- Continuous-wave Doppler ultrasound can be used as an initial step to indirectly assess lower limb vascular disease. The test enables indirect qualitative evaluation of blood flow, vessel localisation and flow detection in nonpalpable arteries, and quantitative systolic blood pressure measurements along lower limb vessels.
- Continuous-wave Doppler ultrasound does not provide visualisation of vessel anatomy.
- Continuous-wave Doppler ultrasound is limited in accuracy and is relatively insensitive especially for iliac arterial disease detection. “Pulse normalisation” downstream from stenosis can diminish test sensitivity.
- Continuous Doppler waveform should be combined with other imaging (ultrasound greyscale or colour visualisation of the arterial wall: “duplex ultrasound imaging”).
- Continuous-wave Doppler ultrasound remains an old-fashioned technique no longer routinely used in many modern laboratories.

Recommendations
Continuous-wave Doppler ultrasound is of limited use in providing initial qualitative and quantitative assessment of lower limb vascular disease location and severity, and in following outcomes of vascular disease with or without revascularisation. (Level 3b; Grade C)

Since continuous Doppler ultrasound does not allow direct arterial visualisation, this test should always be combined with real imaging through ultrasound greyscale or colour visualisation of the arterial wall (“duplex ultrasound imaging”). (Level 2c; Grade B)

2.2. Plethysmography

Plethysmography in CLI evaluation has been introduced in the past to detect changes in limb volume by “pulse volume recording” (PVR) which produces recordings that are similar to continuous Doppler waveforms.\(^59,60\)

However, the lack of reliable, reproducible quantitative data limits the utility of plethysmography for diagnosis or arterial disease and CLI in most modern vascular laboratories today. With more widespread utilisation of ultrasound methods, the use of plethysmography has declined substantially.

The main value of PVR waveform analysis may be that it is not affected by medial calcification and therefore it is relatively useful in the diabetic population.\(^61\)

Accuracy of PVR and photoplethysmography has been tested against Doppler ultrasound in several studies,\(^56,62,63\) indicating that the techniques might be useful in diabetic patients with CLI, including those with oedema, but the method may have poor accuracy in vascular diseases located in distal limb segments.\(^64\)

PVR tracings at the foot level have been used as an indicator of healing potential for foot wound or amputation procedures.\(^8,45,56,65,66\)

Limitations of PVR include that it may be a rather subjective tool for evaluation of CLI since measurements are based on subjective waveform analysis. PVR may be abnormal in patients with low cardiac stroke volume and overall accuracy is limited. Although quantitative criteria have been proposed in PVR, they are not widely used clinically owing to limited accuracy.\(^1\)

Summary messages (advantages and limitations of pulse volume recording):
- PVR remains an old-fashioned technique no longer routinely used in many modern laboratories.
- PVR may be useful as an initial diagnostic test for patients with foot pain or ulcers and suspected CLI, to assess limb perfusion and predict risk of amputation in CLI patients.
- PVR can provide a tool to evaluate individuals with incompressible vessels in whom ABI and segmental pressures are spuriously elevated.
- PVR does not allow reliable quantitative measure of perfusion and may not be accurate.
- PVR may be abnormal in patients with low cardiac stroke volume.
- PVR in evaluation of limb perfusion is affected by “subjective influence” and is less accurate than other non-invasive tests in providing arterial anatomical localisation of disease.
- Although PVR may be useful and cost-effective as a baseline tool in office practice or vascular laboratories, other non-invasive techniques can today provide more quantitative and accurate information on perfusion and anatomical localisation of lower limb disease in CLI.

Recommendations
Pulse volume recording may be used as an initial step in the evaluation of patients with foot pain and ulcer and suspected CLI and can be applied to establish diagnosis, assess localisation or severity of the disease and follow status of revascularisation procedures, but accuracy is limited. (Level 3b; Grade C)

Pulse volume recording may be applied to establish the initial lower limb CLI diagnosis in diabetic patients and patients with incompressible arteries, but it should be combined with additional tests (e.g., “duplex ultrasound imaging”). (Level 2a; Grade B)

Advantages and limitations of each non-invasive physiological and haemodynamic diagnostic test are summarised in Table 1.

3. Measurements of tissue perfusion

Different non-invasive measurements of tissue perfusion have been used to assess the severity of lower limb ischaemia. The applicability and reliability are generally limited with respect to Doppler ultrasonography.

Measurements of transcutaneous oxygen pressure (TcPO\(_2\)) reflect the metabolic state of lower limbs with CLI and diabetic feet. Small electrodes consisting of a circular silver–silver chloride anode surrounding a central platinum cathode are placed on the skin; oxygen diffusing to the surface of the skin is reduced at the cathode to produce a current proportional to the partial pressure of oxygen (PO\(_2\)) within the sensor. In patients with foot ulcers, tissue loss or rest pain, TcPO\(_2\) values can be used to assess the presence and severity of vascular disease, the need for revascularisation, and to predict the success of healing with or without revascularisation. This test is performed by placing probes with electrodes on the foot...
and the leg, using the chest as a reference site. Common locations for assessment are the dorsum of the foot, the anteromedial aspect of the calf 10 cm below the knee, and the thigh 10 cm above the knee. Normal TcPO2 values depend on age (higher for younger) and position (higher for proximal). Normal TcPO2 levels are approximately 60 mmHg, while levels of 20 mmHg or less strongly suggest that revascularisation will be required to achieve healing. TASC II requires a critical level of TcPO2 <30 mmHg to confirm diagnosis of CLI in patients with non-healing foot ulcers or diabetic foot.2

Measurement of TcPO2 is most helpful for evaluating cases of severe limb ischaemia, while it is relatively insensitive to mild or moderate degrees of peripheral vascular disease because the oxygen supply to the skin is far greater than the demand. TcPO2 measurements combined with clinical determination may be of value to predict healing at various levels of amputation, especially in diabetic patients, because it is not affected by arterial calcification.67–49

Nevertheless, measurements of TcPO2 must be interpreted cautiously, since the test is often unreliable because it is affected by many factors that are difficult to control, including skin temperature, sympathetic tone, cellulitis, hyperkeratosis, obesity, oedema, metabolic activity, oxygen diffusion through tissue, age, vertical position of the site of measurements. In addition, when values are low, TcPO2 is not linearly related to flow: a value of zero does not mean that there is no flow to the area of interest; rather it indicates that all the available oxygen has been consumed. Therefore, TcPO2 is not routinely used in most vascular laboratories.

Measurement of skin perfusion pressure (SPP) is another microcirculatory assessment tool that can be utilised to assess foot healing potential.70 SPP is measured with laser Doppler and represents the blood pressure required to restore microcirculatory or capillary flow after inducing controlled occlusion and return of flow. The ability of this test to predict amputation healing is not as good as that of TcPO2 measurements. Normal pressures of 50–70 mmHg are decreased to 10–20 mmHg in limbs with severe limb ischaemia. Pressures below 30 mmHg are predictive of CLI.

Laser Doppler is not widely used in vascular laboratories, mainly because of an inability to calibrate the instrument to actual levels of blood flow and the availability of more accurate, direct methods for assessing CLI.

Hyperspectral tissue oxygenation measurements have also been used to predict healing of diabetic foot ulcers. The test should identify microvascular abnormalities in the diabetic foot, but this technology is currently being utilised mainly as a research tool.71

Summary messages (advantages and limitations of tissue perfusion measurements):

• Tissue perfusion measurement can be useful to assess the severity of lower limb ischaemia.
• These techniques can be used in monitoring and/or re-evaluating patients following endovascular or surgical revascularisation.
• Microcirculatory assessment of perfusion can be utilised to assess wound healing potential.
• Transcutaneous oxygen pressure (TcPO2) is valuable to examine the metabolic state of the target tissue.
• Measurements of TcPO2 are time-consuming and may be unreliable because influenced by many physiological, methodological and technical factors (skin temperature, sympathetic tone, cellulitis, hyperkeratosis, obesity, oedema, metabolic activity, oxygen diffusion through tissue, age, etc.).
• TcPO2 could not be measured in advanced CLI because of intolerable pain during the examination in the supine position.

Recommendations

Patients with ischaemic rest pain or foot ulcers can be investigated with objective tests of tissue perfusion to confirm diagnosis of CLI. (Level 2a; Grade B)

These may include TcPO2, laser Doppler and hyperspectral measurements to assess metabolic state of tissue perfusion. (Level 3b; Grade C)

Tissue perfusion tests (TcPO2, laser Doppler, spectral imaging) can be used to assess healing potential of ulcers/amputation in patients with CLI (Level 3b; Grade C – Level 4; Grade D)

4. Imaging techniques

The purpose of vascular imaging for patients with CLI is to assess the anatomical location, morphology and extent of disease to determine suitability for open or endovascular revascularisation. Major technical advances have been accomplished in recent years in the development of non-invasive imaging modalities. Today, the following options for imaging are available:

- duplex ultrasound (DUS)
- magnetic resonance angiography (MRA)
- computed tomography angiography (CTA)
- digital subtraction angiography (DSA).

The main characteristics of these imaging modalities, including their principal advantages and disadvantages, are summarised in Table 2.

4.1. Duplex ultrasound

Duplex ultrasound (DUS) enables identification of the anatomical location and the degree of stenosis in lower extremity peripheral arterial disease (PAD) by combining both B-mode ultrasound and colour Doppler ultrasound. Haemodynamic assessment is performed by measuring peak systolic velocity (PSV) and PSV ratios within or beyond an obstruction compared with the adjacent upstream segment, the presence or absence of turbulence, and preservation of pulsatility. A PSV ratio of greater than 2:1 is considered to indicate a >50% stenosis, a PSV ratio greater than 4:1 a >75% stenosis and a PSV ratio of greater than 7:1 a >90% stenosis.74

Accuracy of DUS: Several studies have reported a high accuracy of DUS in comparison with DSA. A recent meta-analysis of studies published between 1996 and 2005 produced a pooled sensitivity of 88% (84–91%) and a pooled specificity of 94% (93–96%) for DUS, confirming data from a former meta-analysis75–77 (Table 3). When used by experienced operators and in suitable patients, DUS can produce a map of significant obstructive disease from the abdominal aorta to the feet.78
Table 2 Comparison of different imaging modalities for patients with PAD\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>DUS</th>
<th>CTA</th>
<th>MRA</th>
<th>Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Availability</strong></td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Appointment time (minutes)</strong></td>
<td>40+ (both legs)</td>
<td>15</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Equipment cost</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Operator expertise</strong></td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Arteriographic map</strong></td>
<td>Yes, by experienced operators</td>
<td>Yes (requires post-processing)</td>
<td>Yes (immediately available)</td>
<td>Yes (immediately available)</td>
</tr>
<tr>
<td><strong>Diagnostic accuracy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorto-iliac</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Femoro-popliteal</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>tibial</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Stent assessment</strong></td>
<td>++</td>
<td>+</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td><strong>Limitations by vascular calcification</strong></td>
<td>++</td>
<td>+</td>
<td>None</td>
<td>Almost none</td>
</tr>
<tr>
<td><strong>Complications and risks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access site</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Rare</td>
</tr>
<tr>
<td>Ionising radiation exposure</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Higher than CTA</td>
</tr>
<tr>
<td>Contrast-enhanced nephropathy</td>
<td>None</td>
<td>++</td>
<td>Extremely rare</td>
<td>+</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>None</td>
<td>None</td>
<td>Very rare</td>
<td>None</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>None</td>
<td>Rare</td>
<td>Very rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Contraindications</td>
<td>None</td>
<td>Severe renal impairment, known allergy to contrast agents</td>
<td>Cerebrovascular clips, electronic implants (infusion or monitoring devices, neurostimulation devices), pacemakers, cardioverter-defibrillators, claustrophobia</td>
<td>Severe renal impairment, known allergy to contrast agents</td>
</tr>
</tbody>
</table>

CTA, computed tomography angiography; DUS, duplex ultrasound; MRA, magnetic resonance angiography; mSv, millisievert; PAD, peripheral arterial disease.

\(^a\) Modified from Norgren et al.,2 Owen and Roditi\(^72\) and Kramer et al.\(^73\)

DUS can be used for pre-intervention decision-making by predicting whether a patient has anatomy suitable for femoro-popliteal angioplasty with an accuracy of 84–94%.\(^61\),\(^82\) It has also been used as a substitute for DSA for infrainguinal bypass grafting to select the most appropriate tibial vessel for distal anastomosis, although some studies have suggested that DUS alone is inferior to DSA for evaluation of tibial arteries for distal bypass surgery.\(^83\)–\(^90\)

Another study has demonstrated no difference in patency of infrapopliteal bypass grafts in non-randomised cohorts of patients evaluated by pre-operative DUS vs. angiographic methods.\(^85\)

DUS can also be used for post-revascularisation surveillance of venous and prosthetic grafts. Venous grafts may fail due to de novo obstructions either within the body of the graft or at the anastomoses (intimal hyperplasia), or due to progression of atherosclerotic obstructions upstream or downstream from the graft. DUS surveillance studies can detect these obstructions during impeding graft thrombosis with greater sensitivity than evaluation by clinical history, physical examination, or use of the resting ABI.\(^1\),\(^91\)–\(^96\) In general, low velocities indicate poor arterial inflow, proximal stenosis, or large graft diameter. One study showed that presence of a PSV less than 45 cm/s within a graft indicates that subsequent graft failure is likely to occur.\(^97\),\(^98\) Another study found that vein grafts that were revised on the basis of positive DUS findings had a 90% 1-year patency rate, similar to grafts with initially normal duplex examinations. Grafts that were not revised despite the presence of a DUS-detected stenosis had a patency rate of only 66% at 1 year.\(^92\) Unfortunately, three RCTs offered conflicting results, with a 3-year primary assisted patency rate of vein grafts monitored with DUS of 78% vs. 53% for those followed up clinically and with the ABI in one study and no improved patency in the others.\(^99\),\(^100\) The Vein Graft Surveillance Randomised Trial (VGST)\(^101\) assessed the benefits of DUS compared with clinical vein graft surveillance in terms of amputation rates, quality of life and healthcare costs in patients after femoro-popliteal and femorocrural vein bypass grafts. A total of 594 patients with a patent vein graft at 30 days after surgery were randomised to either a clinical or a duplex follow-up programme at 6 weeks, then 3, 6, 9, 12, and 18 months post-operatively. Both groups had similar amputation rates (7% for each group) and vascular mortality rates (3% vs. 4%) over 18 months. More patients in the clinical group had vein graft stenoses at 18 months (19% vs. 12%, \(p = 0.04\)), but primary patency, primary assisted patency and secondary patency rates, respectively, were similar in the clinical group (69%, 76% and 80%) and the duplex group (67%, 76% and 79%). There were no apparent differences in health-related quality
of life, but the average health service costs incurred by the DUS surveillance programme were greater by £495 (95% CI £83–807) per patient. The authors concluded that intensive surveillance with DUS did not show any additional benefit in terms of limb salvage rates for patients undergoing vein bypass graft operations, but it did incur additional costs. In a further prospective study, a normal DUS scan 6 weeks subsequent to infragenual vein bypass grafting was associated with a 40-month cumulative patency rate of 82%, indicating that further DUS surveillance in these patients is not beneficial. There is an ongoing transatlantic discussion whether or not DUS surveillance is beneficial in patients with infragenual venous bypass grafting, with a tendency for routine DUS in these patients in North America, while the situation in Europe remains equivocal.

DUS surveillance of synthetic grafts is of questionable value. Several studies have found no improvement in patency of grafts, whereas other studies have successfully detected stenoses and found some improvement in patency. This lack of evidence may be due to DUS-associated technical challenges (inability to visualise the stenosis, vascular anatomic challenges) or procedural challenges, such that the subsequent graft revision does not help to improve long-term graft patency.

DUS surveillance after angioplasty (PTA) procedures is also of questionable value. Immediately after PTA, several studies suggested that velocities in the treated segment may be abnormally elevated and do not predict decreased subsequent patency rates. This may be due to angioplasty-induced vessel dissections that successfully remodel over time. DUS is useful in evaluations for recurrent obstructions, although it is reasonable to assume that revisions of post-PTA restenoses that are detected by DUS studies might improve patency, there are no published studies confirming this approach on a high evidence level.

Summary messages: Advantages and disadvantages of duplex ultrasound:
- DUS is non-invasive, relatively inexpensive and as an outpatient procedure well tolerated by patients.
- DUS can also be performed in emergency situations on the ward or in the operating theatre.
- There are limitations to the visualisation of iliac vessels in the pelvis (due to body habitus and bowel gas), very distal arteries and collaterals. In addition, extensive calcification may produce incomplete examinations and in patients in whom multi-level PAD downstream stenoses are detected the sensitivity is decreased, perhaps owing to slow flow.
- The technique is highly operator-dependent and proper training is mandatory.
- Since the vast majority of DUS studies were performed in mixed populations, the validity of DUS imaging for CLI patients alone is still uncertain.
- No side effects or adverse events have been reported.

### Table 3 Systematic reviews and meta-analyses to assess the diagnostic accuracy of duplex ultrasound (DUS), magnetic resonance angiography (MRA) and computed tomography angiography (CTA) in the detection of >50% stenosis or occlusion in patients with peripheral arterial disease (PAD)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Modality</th>
<th>Characteristics</th>
<th>Anatomical region</th>
<th>Pooled sensitivity</th>
<th>Pooled specificity</th>
</tr>
</thead>
</table>
| Visser, 2000\(^78\)        | Contrast-enhanced MRA | • 9 studies (1990–1998) with a total of 216 pts (11–30)  
• CLI in only 3 studies, in 2 studies no clinical data | Whole leg         | 98% (96–99%)       | 96% (94–98%)       |
|                            | DUS               | • 18 studies (1984–1998) with a total of 1059 pts (12–167)  
• CLI in 9 studies (10–84% of the study population), in 7 studies no clinical data | Whole leg         | 88% (84–91%)       | 95% (93–96%)       |
| Collins et al., 2007\(^76,77\) | DUS               | • 7 studies (1996–2005) with a total of 369 pts (20–76)  
• 134–3108 segments per study (median 404 segments)  
• CLI in about 10% (range 0–19%) of pts | Whole leg         | 88% (80–98%)       | 96% (89–99%)       |
|                            | 2D time-of-flight MRA | • 5 studies (1996–2005) with a total of 287 pts (20–155)  
• 206–1188 segments/study (median 378 segments)  
• CLI in 82–100% of pts (no clinical data in 3 studies) | Whole leg         | 92% (79–94%)       | 88% (74–92%)       |
|                            | Contrast-enhanced MRA | • 7 studies (1996–2005) with a total of 279 pts (20–76)  
• 418–1780 segments/study (median 520 segments)  
• CLI in 0–92% of pts (no data in 3 studies) | Whole leg         | 95% (92–100%)      | 97% (64–99%)       |
| Menke et al., 2010\(^79\)  | Contrast-enhanced MRA | • 32 studies (2004–2009) with a total of 1022 pts (10–76)  
• 120–1780 segments per study (median 384 segments)  
• 24% of all investigated arterial segments had stenoses or occlusions  
• CLI in 26% (range 0–100%) of pts | Aorto-iliac       | 94% (91–96%)       | 96% (94–97%)       |
|                            | Femoro-popliteal   | Tbial 92% (90–94%)                                                                                   |                   |                    |                    |
|                            | Tibial             | 92% (90–94%)                                                                                       |                   |                    |                    |
| Met et al., 2009\(^80\)    | CTA               | • 20 studies (1966–2008) with a total of 957 pts (16–279)  
• 167–4743 segments per study (median 730 segments)  
• 29% of all investigated arterial segments had stenoses or occlusions  
• CLI in >20% (range 0–100%) of all pts (68% IC, 10–20% no data) | Aorto-iliac       | 96% (91–99%)       | 98% (95–99%)       |
|                            | Femoro-popliteal   | Tbial 97% (95–99%)                                                                                   |                   |                    |                    |
|                            | Tibial             | 95% (85–99%)                                                                                       |                   |                    |                    |
Table 4  Recommendations in current guidelines for duplex ultrasound imaging in patients with CLI

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex ultrasound of the extremities is useful to diagnose anatomical location and degree of obstruction in PAD patients.(^a)</td>
<td>A</td>
<td>1a</td>
</tr>
<tr>
<td>Duplex ultrasound may be considered for routine surveillance after femoropopliteal or femorotibial-pedal venous bypass grafts.(^a)</td>
<td>B</td>
<td>2b</td>
</tr>
<tr>
<td>Duplex ultrasound of the extremities can be useful to select patients as candidates for endovascular intervention.(^a)</td>
<td>B</td>
<td>2b</td>
</tr>
<tr>
<td>Duplex ultrasound may be useful to select patients as candidates for surgical bypass and to select the sites of surgical anastomosis.(^a)</td>
<td>B</td>
<td>2b</td>
</tr>
<tr>
<td>Duplex ultrasound may be considered for routine surveillance after femoropopliteal bypass with a synthetic conduit.(^a)</td>
<td>B</td>
<td>3b</td>
</tr>
<tr>
<td>The use of duplex ultrasound is not well established to assess long-term patency of percutaneous transluminal angioplasty.(^a)</td>
<td>B</td>
<td>3b</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from Hirsch et al.\(^1\)

Critical issues

- The majority of DUS studies are more than 10 years old. New studies should consider following the STARD guidelines for reporting of diagnostic accuracy studies and should also consider reporting results by patient or by limb, as well as by segment.\(^122\)–\(^124\)
- Future reviews should make use of the QUADAS as a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies.\(^125\)
- Further research should consider comparing DUS directly with MRA and/or CTA as the reference standard.
- The value of the operative or endovascular correction of DUS-detected post-PTA lesions has to be evaluated in further studies.
- Future studies should identify patients with infragenual vein or prosthetic bypasses, who benefit from a standardised DUS surveillance programme.
- The validity of DUS imaging for patients with CLI needs to be evaluated in patient cohorts suffering from rest pain or non-healing ischaemic lesions in the foot.

4.2. Computed tomography angiography

Computed tomography angiography (CTA) is increasingly attractive due to rapid technical developments. Shorter acquisition times, thinner slices, higher spatial resolution, and improvement of multidetector computed tomographic (CT) scanners enable scanning of the entire vascular tree in a limited period with a decreasing amount of contrast medium and radiation burden.

Accuracy of CTA: In a recent meta-analysis, 20 studies published between 1966 and 2008 (957 patients) were reviewed systematically by use of the QUADAS checklist.\(^126\) Between 167 and 4743 arterial segments were analysed in each study (median 730 segments) and 29% of all segments had stenoses or occlusions. Slice thickness varied between 0.75 and 5.0 mm (median 2.0 mm). Various contrast media were used for the CTA (iomeprol in 6 studies, iopromide in 4 studies, and the remaining studies used other iodine-based contrast media). The iodine concentration varied between 300 and 400 mg/mL. The amount of contrast volume administered per scan varied between 88 and 170 mL (median 130 mL). Interpretation of CTA was always based on the axial images. Other image reconstructions used were maximum-intensity projections (n = 17), volume-rendering technique (n = 15), multiplanar reformation (n = 6), curved-planar reformation (n = 4), and virtual endoscopy (n = 1). The pooled sensitivity to detect a >50% stenosis or occlusion was 95% (92–97%) and the pooled specificity 96% (93–97%). CTA correctly identified occlusions in 94% of segments, the presence of >50% stenosis in 87% of segments, and absence of significant stenosis in 96% of segments. Overstaging occurred in 8% of segments and understaging in 15%. The data included trials of CTA vs. DSA across three different generations of CT technology (i.e., scanners with 4, 16, and 64 detector rows) and with technological advancement there has been a corresponding improvement in diagnostic accuracy (sensitivity and specificity has increased from 75–99% and 83–99% with 4 detector rows to 98–99% and 96–99% for 64 detector rows). Diagnostic accuracy was lower for smaller arteries compared with proximal lesions, but the diagnostic performance below the knee remains good (sensitivity 85–99%, specificity 79–97%) (Table 3). Inter-observer agreement is good to excellent (k values >0.8) in most studies.\(^126\)

The great majority of patients in trials of peripheral arterial
Table 5  Recommendations in current guidelines for CT angiography imaging in patients with CLI

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA of the extremities may be considered to diagnose anatomic location and presence of significant stenosis in patients with lower extremity PAD.</td>
<td>B</td>
<td>3a</td>
</tr>
<tr>
<td>CTA of the extremities may be considered as a substitute for MRA for those patients with contraindications to MRA.</td>
<td>B</td>
<td>3a</td>
</tr>
<tr>
<td>Patients with baseline renal insufficiency should receive hydration before undergoing CTA.</td>
<td>A</td>
<td>2b</td>
</tr>
</tbody>
</table>

CLI, critical limb ischaemia; CTA, computed tomography angiography; MRA, magnetic resonance angiography; PAD, peripheral arterial disease.

Adapted from Hirsch et al.¹

Imaging are claudicans and there are limited data in patients with CLI. In a recent study of 28 patients with CLI who were evaluated with 16-detector-row CTA, 23 had treatment plans confidently formulated on the basis of the CTA alone.

**Side effects/adverse events:** The average radiation dose reported in the CTA literature is 7.47 mSv,¹²⁷ although average doses as high as 13.7 mSv have been reported in some series.¹²⁸ In a trial of 16-detector-row CTA vs. DSA, Willmann et al. reported a four-fold higher radiation dose for DSA compared with CTA.¹²⁹ To place these doses in context, the average annual background radiation exposure is between 2 and 3 mSv.⁸⁰ It has been suggested that patient radiation dose issues are of limited concern in patients with advanced PAD, as their life expectancy is significantly less than the latent period of a radiation-induced malignancy.¹³⁰ The late effects of radiation exposure are more important in younger patients, however; physicians should be aware of this issue and strive to keep dosing as low as reasonably possible.

Iodinated contrast agents are associated with an increased risk for contrast-induced nephropathy (CIN), defined as an increase in serum creatinine level >25% or >0.5 mg/dL above baseline within 3 days of contrast administration in the absence of other causes.⁷³,¹³¹ Patients who are considered at highest risk are those with baseline renal insufficiency, especially those with concomitant diabetes mellitus. Other risk factors for CIN include multiple myeloma, proteinuria, concomitant nephrotoxic drug use, hypertension, congestive heart failure, hyperuricaemia, and dehydration. The risk of CIN is dose-dependent and is higher when contrast is administered intra-arterially than when given intravenously.¹³² A systematic review revealed an overall risk of CIN in high-risk patients of 16.8%,¹³² although the clinical implications for the development of CIN are not fully understood. Only a minority go on to require renal replacement therapy (<1%), but in a retrospective review of over 16,000 inpatients exposed to contrast media, inhospital mortality rates were five-fold higher (34% vs. 7%) among patients who developed CIN, even after adjustment for comorbidity.¹³³ High-osmolar contrast puts patients with pre-existing renal impairment at twice as high a risk of developing CIN as low-osmolar contrast.¹²⁷ However, in a review from 2004 it was concluded that all patients with pre-existing renal insufficiency were at higher risk for CIN, no matter what type of contrast was used.¹³⁴ To prevent CIN pre-emptive hydration is recommended, especially for those patients with renal insufficiency. The optimal type, route, volume, and timing of hydration are not well defined.¹ Likewise, given the ability of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists to induce efferent arteriole vasodilatation, these medications should be withheld the morning of contrast exposure and restarted after monitoring of normal renal function. Administration of antioxidants, such as mannitol, advocated as renoprotective agents, is not supported by evidence.

Further information is provided by the European Society of Urogenital Radiology (http://www.esur.org).

**Summary messages: Advantages and disadvantages of computed tomography angiography:**

- CTA in comparison to MRA offers better patient acceptance, a higher speed of examination, a better spatial resolution, and the ability to evaluate previously stented arteries. It is mostly applicable in patients with contraindications for MRA (Table 5).
- Disadvantages of CTA include image interference from calcified arteries and the need for potentially nephrotoxic contrast agents and radiation exposure.⁸⁰

Criteria for other guidelines (Table 5):

The current ACC/AHA Practice Guidelines give a moderate recommendation for CTA of the extremities to diagnose anatomic location and presence of significant stenosis in patients with lower extremity PAD. (Level 2B; Grade B)

In addition, CTA of the extremities may be considered as a substitute for MRA for those patients with contraindications to MRA.² (Level 2B; Grade B)

TASC II stated that DUS, MRA and CTA are suitable for decision-making. The individual use may depend on local availability, experience, and costs.¹ (Level 2B; Grade B)

**Critical issues:**

- Patients with CLI who require a complete assessment of their lower extremity arteries for planning an open or endovascular intervention are under-represented in the current studies. More research is needed to determine the clinical value of CTA in the CLI target population.⁸⁰
- CTA assessment of aorto-iliac and femoral lesions seems to be sufficient for decision planning, whereas this may not be the case for smaller calcified arteries.
- Specificity is probably overestimated due to the fact that all studies divided the vascular tree into segments with a relatively high proportion of segments without a significant stenosis (segments that are likely to be correctly identified by CTA). From a clinical standpoint, it is more useful to divide the vascular tree into clinically relevant segments (eg, aorto-iliac, femoropopliteal, and distal runoff).
The claim that MRA is more sensitive than DSA for distal revascularisation MRA surveillance.

There have been major technical advances in recent years including 3D contrast enhanced magnetic resonance angiography (ce-MRA) and the development of moving tabletops which enable whole limb examinations with a single contrast injection.

**Accuracy of MRA**: A number of meta-analyses and systematic reviews support the diagnostic accuracy of MRA when compared to DSA. Two meta-analyses determined that 3D ce-MRA is superior to 2D time-of-flight MRA. The meta-analysis by Collins et al. detected a pooled sensitivity of 95% (92–100%) and a pooled specificity of 97% (64–99%) for MRA which was superior to CTA and DUS when compared separately to DSA. There was no direct comparison between MRA and DUS in any of the studies. A well-conducted systematic review concluded that MRA is also cost-effective in comparison to DSA when both are available locally. The most recent meta-analysis included 32 studies published between 1998 and 2009 (120–1780 segments per study, median 384 segments, altogether 1022 patients, 26% with CLI). The pooled sensitivity of MRA was 95% (92–96%) and the specificity was 96% (94–97%) for diagnosing segmental stenosis >50% or occlusions. The accuracy for tibial lesions was slightly worse compared to aorto-iliac and femoropopliteal lesions (Table 3). MRA correctly classified 95.3%, overstaged 3.1%, and understaged 1.6% of arterial segments. Some studies claim that MRA is superior to DSA in the detection of outflow vessels suitable for distal bypass in patients with CLI. Kreitner et al. found that in 24 diabetic patients with CLI, 38% had pedal vessels detected by MRA that were not detected by catheter angiography. Such vessels treated with surgical bypass may enjoy satisfactory patency.

The claim that MRA is more sensitive than DSA for distal vessels is controversial and is affected by the quality of the comparative catheter angiography. Such vessels treated with surgical bypass may enjoy satisfactory patency. The claim that MRA is more sensitive than DSA for distal vessels is controversial and is affected by the quality of the comparative catheter angiography. Such vessels treated with surgical bypass may enjoy satisfactory patency.

**Side effects/adverse events**: Gadolinium-enhanced MRA avoids radiation and gadolinium chelates cause anaphylactic reactions less often than iodinated contrast medium (<1% of all patients). The US Food and Drug Administration has recommended that patients not receive gadolinium-based contrast agents if they have acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min per 1.73 m²) or renal dysfunction due to the hepatorenal syndrome, or are in the peri-operative liver transplantation period, because of the risk for nephrogenic systemic fibrosis (NSF). Apart from other factors, this risk seems to depend on the stability and the dose of the applied gadolinium chelates. However, most patients with PAD do not belong to these risk groups and do not have a specific risk for NSF according to current knowledge.

Summary messages: Advantages and disadvantages of magnetic resonance angiography

- **MRA**, in comparison with DSA and CTA, eliminates exposure to ionising radiation and there is no risk of CIN when gadolinium is used in recommended doses.
- Unlike DUS and CTA, MRA is unaffected by arterial calcification.
- MRA is performed as a fast non-invasive outpatient procedure (<15 minutes).
- Three-dimensional images of the entire arterial tree are presented in a maximum intensity projection format produced on a workstation.
- Relative disadvantages include a tendency to overestimate stenosis. Venous contamination can obscure arteries below the knee. Claustrophobia and the presence of metallic implants (such as pacemakers) or foreign bodies may preclude the examination or produce artefacts.
- MRA tends to overestimate the degree of stenosis because of turbulence and metal clips can cause artefacts that mimic vessel occlusions. Similarly, some metal stents will obscure vascular flow.
- Patients with pacemakers and defibrillators and some cerebral aneurysm clips cannot be scanned safely.

**Recommendations from other guidelines (Table 6)**:

The current ACC/AHA Practice Guidelines give a strong recommendation for MRA to diagnose anatomical location and presence of significant stenosis in patients with lower extremity PAD. (Level 1a; Grade A) In addition, strong recommendations are given to perform MRA with gadolinium enhancement (Level 1a; Grade A) and to use MRA in selecting patients with lower extremity PAD as candidates for endovascular intervention. (Level 1a; Grade A)

The ACC/AHA gives moderate recommendations for MRA as a suitable tool to select the sites of surgical anastomosis for surgical bypass and to consider MRA for postrevascularisation (endovascular and surgical bypass) surveillance in patients with lower extremity PAD. (Level 2b; Grade B)

The Scottish Guideline also gives a strong recommendation that non-invasive imaging modalities should be employed in the first instance for patients with intermittent claudication in whom intervention is being considered. No recommendation is given for patients with CLI.
Critical issues

- Patients with CLI who require a complete assessment of their lower extremity arteries for planning an open or endovascular intervention are under-investigated in the current studies. More research is needed to determine the clinical value of ce-MRA in the CLI target population.
- Specificity is probably overestimated due to the fact that all studies divided the vascular tree into segments with a relatively high proportion of segments without a significant stenosis (segments that are likely to be correctly identified by MRA). From a clinical standpoint, it is more useful to divide the vascular tree into clinically relevant segments (e.g. aorto-iliac, femoropopliteal, and distal runoff).
- The statistical power of the available meta-analyses is limited by the relatively small sample size of most included studies. Larger studies are needed.
- New MRA studies should consider to follow the STARD guidelines for reporting of diagnostic accuracy studies and should also consider reporting results by patient or by limb, as well as by segment.
- Future MRA reviews should make use of the QUADAS as a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies.

4.4. Intra-arterial angiography

Digital subtraction angiography (DSA) has been the traditional first-line imaging investigation for patients with PAD for many years and, although it is a two-dimensional technique, is still considered the gold standard against which other techniques are compared.

Accuracy of DSA: Angiography served as reference tool for new non-invasive diagnostic tools, such as DUS, MRA and CTA. Even though non-invasive modalities are used as first-line diagnostic methods for patients with PAD by many physicians, DSA is still the only universally accepted method for guiding percutaneous peripheral interventional procedures.

Even though DSA is still considered to be the gold standard, there are a number of flaws:
- It may not be possible to determine haemodynamic significance even with multiple projections.
- It may overestimate the length of occlusions.
- It may not always demonstrate patent crural vessels.
- Eccentric lesions are sometimes difficult to quantify; axial imaging techniques (e.g., MRA and CTA) may offer an advantage for visualising these pathologies, because these techniques offer a 3D view.

Side effects/adverse events: Although it has been estimated that 1.7% of complications may be severe, improvements in catheter and guidewire technology have reduced their incidence significantly. According to the TASC II Consensus, angiography carries an approximately 0.1% risk of severe reaction to contrast medium, a 0.7% risk of complications severe enough to alter patient management, and 0.16% mortality risk and significant expense. Contrast agents are also associated with a small but important incidence of nephrotoxicity. Patients who are at increased risk of contrast nephropathy include those with severe baseline renal dysfunction, diabetes, low cardiac output state, or dehydration. Recent studies have suggested that use of low-osmolar contrast agents (e.g. iodixanol) may reduce the incidence of renal compromise. In patients who are high risk for nephrotoxicity, data suggest that vigorous hydration before administration of contrast may serve as the most important strategy to prevent post-procedural deterioration in renal function. Because the occurrence of nephrotoxicity appears to be dose-dependent, it is also important to minimise contrast usage. This dose minimisation can be accomplished by using DSA techniques and placing catheters close to the site to be imaged (selective angiography). The dose–nephrotoxicity relationship is complex and cannot be calculated precisely. Preliminary data suggest that nephrotoxicity might be further minimised by use of preprocedural haemofiltration in individuals with chronic renal failure (defined as a creatinine level >2.0 mg/dL). The procedure involves exposure to ionising radiation and short-stay recovery facilities. Other complications include arterial dissection, atheroemboli and access site complications (e.g. pseudoaneurysm, arteriovenous fistula and haematoma). These problems have been greatly mitigated by technological improvements in the procedure, including the use of non-ionic contrast agents, DSA, intra-arterial pressure measurements across a stenosis with and without vasodilator (significance peak systolic difference 5–10 mmHg pre-vasodilatation and 10–15 mmHg post-vasodilatation), and more sophisticated image projection and retention. Alternatively, carbon dioxide and magnetic resonance contrast agents (e.g. gadolinium) can be used instead of conventional contrast media. In high-risk (e.g. renal impairment) patients, restriction to a partial study with selected views rather than visualising the entire infrarenal vascular tree is recommended.

Table 6 Recommendations in current guidelines for MR angiography imaging in patients with CLI

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of evidence</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>MRA of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD and to select patients for endovascular or open surgical intervention</td>
<td>A</td>
<td>1a</td>
</tr>
<tr>
<td>MRA of the extremities should be performed with gadolinium enhancement</td>
<td>A</td>
<td>2a</td>
</tr>
<tr>
<td>MRA of the extremities is useful in selecting patients with lower extremity PAD as candidates for endovascular intervention</td>
<td>A</td>
<td>2a</td>
</tr>
<tr>
<td>MRA of the extremities may be considered for post-revascularisation (endovascular and surgical bypass) surveillance in patients with lower extremity PAD</td>
<td>B</td>
<td>3b</td>
</tr>
</tbody>
</table>

CLI, critical limb ischaemia; MRA, magnetic resonance angiography; PAD, peripheral arterial disease.

Adapted from Hirsch et al.
<table>
<thead>
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**Recommendations from other guidelines (Table 7):**

The current ACC/AHA Practice Guidelines give the following **Grade A** recommendations:

1. DSA provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularisation is contemplated. *(Level 2b; Grade B)*

2. A history of contrast reaction should be documented before the performance of contrast angiography and appropriate pretreatment administered before contrast is given. *(Level 2b; Grade B)*

3. Decisions regarding the potential utility of invasive therapeutic interventions (percutaneous or surgical) in patients with lower extremity PAD should be made with a complete anatomic assessment of the affected arterial territory, including imaging of the occlusive lesion, as well as arterial inflow and outflow with angiography or a combination of angiography and non-invasive vascular techniques. *(Level 2b; Grade B)*

4. DSA is recommended for contrast angiographic studies because this technique allows for enhanced imaging capabilities compared with conventional unsubtracted contrast angiography. *(Level 2a)*

5. Before performance of contrast angiography, a full history and complete vascular examination should be performed to optimise decisions regarding the access site, as well as to minimise contrast dose and catheter manipulation. *(Level 2b)*

6. Selective or superselective catheter placement during lower extremity angiography is indicated because this can enhance imaging, reduce contrast dose, and improve sensitivity and specificity of the procedure. *(Level 2b)*

7. The diagnostic lower extremity arteriogram should image the iliac, femoral, and tibial bifurcations in profile without vessel overlap. *(Level 2b)*

8. When conducting a diagnostic lower extremity arteriogram in which the significance of an obstructive lesion is ambiguous, transstenotic pressure gradients and supplementary angulated views should be obtained. *(Level 2b)*

9. Patients with baseline renal insufficiency should receive hydration before undergoing contrast angiography. *(Level 2b)*

10. Follow-up clinical evaluation, including a physical examination and measurement of renal function, is recommended within 2 weeks after contrast angiography to detect the presence of delayed adverse effects, such as atheroembolism, deterioration in renal function, or access site injury (e.g., pseudoaneurysm or arteriovenous fistula). *(Level 2b)*

11. Non-invasive imaging modalities, including MRA, CTA, and colour flow duplex imaging may be used in advance of invasive imaging to develop an individualised diagnostic strategic plan, including assistance in selection of access sites, identification of significant lesions, and determination of the need for invasive evaluation. *(Level 2b)*

**CLI, critical limb ischaemia; CTA, computed tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; PAD, peripheral arterial disease.**

\( ^a \) Adapted from Hessel et al.\(^ {154} \)

\( ^b \) Adapted from Hirsch et al.\(^ 1 \)

arterial tree has decreased the contrast load, length of study and associated risks. Despite this, full angiography, with visualisation from the level of the renal arteries to the pedal arteries using DSA techniques, remains the choice in most cases.

**Summary messages: Advantages and disadvantages of digital subtraction angiography**

- **Advantages:**
  - DSA provides a complete arterial map of the lower limb circulation that is easily interpretable. Images are easily displayed and interpreted by the vast majority of physicians caring for patients with PAD.
  - Pressure gradients can be measured to determine haemodynamic significance and it can be used to guide endovascular intervention.
  - Disadvantages include complications of catheterisation which may occur both within the vessel and at the puncture site.

- **Disadvantages:**
  - DSA is not recommended as the primary imaging modality for patients with PAD.\(^ a \)
  - Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularisation is contemplated.
  - A history of contrast reaction should be documented before the performance of contrast angiography and appropriate pretreatment administered before contrast is given.\(^ b \). The opportunity to replace DSA with MRA could be considered.
  - Decisions regarding the potential utility of invasive therapeutic interventions (percutaneous or surgical) in patients with lower extremity PAD should be made with a complete anatomic assessment of the affected arterial territory, including imaging of the occlusive lesion, as well as arterial inflow and outflow with angiography or a combination of angiography and non-invasive vascular techniques.\(^ b \).
  - DSA is recommended for contrast angiographic studies because this technique allows for enhanced imaging capabilities compared with conventional unsubtracted contrast angiography.\(^ b \).
  - Before performance of contrast angiography, a full history and complete vascular examination should be performed to optimise decisions regarding the access site, as well as to minimise contrast dose and catheter manipulation.\(^ b \).
  - Selective or superselective catheter placement during lower extremity angiography is indicated because this can enhance imaging, reduce contrast dose, and improve sensitivity and specificity of the procedure.\(^ b \).
  - The diagnostic lower extremity arteriogram should image the iliac, femoral, and tibial bifurcations in profile without vessel overlap.\(^ b \).
  - When conducting a diagnostic lower extremity arteriogram in which the significance of an obstructive lesion is ambiguous, transstenotic pressure gradients and supplementary angulated views should be obtained.\(^ b \).
  - Patients with baseline renal insufficiency should receive hydration before undergoing contrast angiography.\(^ b \).
  - Follow-up clinical evaluation, including a physical examination and measurement of renal function, is recommended within 2 weeks after contrast angiography to detect the presence of delayed adverse effects, such as atheroembolism, deterioration in renal function, or access site injury (e.g., pseudoaneurysm or arteriovenous fistula).\(^ b \).
  - Non-invasive imaging modalities, including MRA, CTA, and colour flow duplex imaging may be used in advance of invasive imaging to develop an individualised diagnostic strategic plan, including assistance in selection of access sites, identification of significant lesions, and determination of the need for invasive evaluation.\(^ b \).
Recommendations from other guidelines (cont’d):

(4) DSA is recommended for contrast angiographic studies because this technique allows for enhanced imaging capabilities compared with conventional unsubtracted contrast angiography. (Level 1a; Grade A)

(5) Before performance of contrast angiography, a full history and complete vascular examination should be performed to optimise decisions regarding the access site, as well as to minimise contrast dose and catheter manipulation. (Level 3b; Grade C)

(6) Selective or superselective catheter placement during lower extremity angiography is indicated since this can enhance imaging, reduce contrast dose, and improve sensitivity and specificity of the procedure. (Level 3b; Grade C)

(7) The diagnostic lower extremity arteriogram should image the iliac, femoral, and tibial bifurcations in profile without vessel overlap. (Level 2b; Grade B)

(8) When conducting a diagnostic lower extremity arteriogram in which the significance of an obstructive lesion is ambiguous, trans-stenotic pressure gradients and supplementary angulated views should be obtained. (Level 2b; Grade B)

(9) Patients with baseline renal insufficiency should receive hydration before undergoing contrast angiography. (Level 2b; Grade B)

(10) Follow-up clinical evaluation, including a physical examination and measurement of renal function, is recommended within 2 weeks after contrast angiography to detect the presence of delayed adverse effects, such as atheroembolism, deterioration in renal function, or access site injury (e.g., pseudoaneurysm or arteriovenous fistula). (Level 3b; Grade C)

The ACC/AHA also suggests that non-invasive imaging modalities, including MRA, CTA, and colour flow duplex imaging, may be used in advance of invasive imaging to develop an individualised diagnostic strategic plan, including assistance in selection of access sites, identification of significant lesions, and determination of the need for invasive evaluation. (Level 2b; Grade B)

Funding/Conflicts of Interest
None

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Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, ProHance) on 15 July 2010.


