



Guidelines for Critical Limb Ischaemia and Diabetic Foot – Introduction

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1. Purpose of these guidelines

The European Society for Vascular Surgery appoints Guidelines Committees to write clinical practice guidelines for vascular surgery. Guidelines for the care of patients with critical limb ischaemia accompany this commentary. Guideline development was recommended in 1990 by the Institute of Medicine, to improve decision-making for specific patient circumstances, and to decrease the variability between healthcare providers.^{1,2} Appropriate decision-making is critical to achieving excellent outcomes.

Guidelines have become more popular in surgery and medicine. This probably results from increased attention to evidence-based medicine, the desire for reproducibility in the choice of treatment for a specific patient, increasing government legislation, the need to satisfy insurance regulations, and legal pressures.

Critical limb ischaemia (CLI) is a complex condition and there is significant variability in clinical practice, although a valid evidence base is available to guide recommendations. The significant increase in the volume of scientific literature concerning critical limb ischaemia published in recent years along with the number of technical and medical advances supports guideline recommendations with more certainty than before. Potential increases in healthcare costs and risks due to industry and the public-driven use of novel treatments, makes the current guidelines increasingly important.³⁻⁶

Many clinical situations of patients with critical limb ischaemia have not been the subject of randomised clinical trials. Patient care, however, needs to be delivered and decisions have to be made in these situations. Therefore, this document should also provide guidance for decisions where extensive Level 1 evidence is not available, and recommendations are determined on the basis of the currently available best evidence.

By providing information about the relevance and quality of evidence, this document will enable the reader to locate the most important and evidence-based information relevant to the individual patient.⁷

To optimise the implementation of the current guideline document, its length has been kept as short as possible

to enable easy access to its information. This document is supposed to be a guide, not a set of rules, and allows flexibility for specific patient circumstances.

2. Methodology

The Critical Limb Ischaemia Guidelines Committee performed a systematic literature search in the MEDLINE, EMBASE and COCHRANE Library databases for each of the different topics that are discussed in this guidelines document. The Guidelines Committee used a grading system based on levels of evidence and grades of recommendation from the Oxford Centre for Evidence-Based Medicine.⁸ The level of evidence classification provides information about the study characteristics supporting the recommendation, according to the categories detailed in Table 1.

The recommendation grade indicates the strength of a recommendation. Definitions of the grades of recommendation are given in Table 2.

The Critical Limb Ischaemia Guidelines Committee aims to report the calculated estimates of effects, with their 95% confidence intervals. Every part of the document has been prepared by at least two members of the Committee and has been reviewed by the entire Committee. The initial document has been subsequently reviewed by the CLI Guidelines Review Committee. After incorporation of all comments and recommendations, these guidelines have been submitted to the *European Journal of Vascular & Endovascular Surgery* and peer reviewed.

3. Limitations

The guidelines should not be regarded as the only path to follow, since every individual patient's disease is unique. This is particularly true in case of CLI, bearing in mind that specific evidence for this selected population is still limited, and patient characteristics, including geographic location, can influence the suitability of a certain treatment for a certain patient, and can limit the value of a single recommendation.

Table 1 Levels of evidence

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) of inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with >80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre
1c	All or none	All or none case-series	Absolute SpPins and SnNouts
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; derivation of CDR or validated on split-sample only	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or databases
2c	"Outcomes" research; ecological studies	"Outcomes" research	
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies
3b	Individual case-control study		Non-consecutive study; or without consistently applied reference standards
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

SR, systematic review; RCT, randomised controlled trial; CDR, clinical decision rule; SpPin, Specificity is so high that a positive result rules-in the diagnosis; SnNout, Sensitivity is so high that a negative result rules-out the diagnosis.

Table 2 Grades of recommendation

Grade	Strength
A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies <i>or</i> extrapolations from Level 1 studies
C	Level 4 studies <i>or</i> extrapolations from Level 2 or 3 studies
D	Level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level

3.1. Appraisal of the level of evidence for critical limb ischaemia

Since there are almost no RCTs dealing exclusively with CLI patients, most of the lesser recommendations are based on prospective evidence from subgroup analysis of "PAOD" trials, or from prospective cohorts.

Where data originate from a RCT, the level of evidence is given by that study design. Where results of subgroup analysis are applied to a particular recommendation, it has been downgraded according to the definitions above.

The concept of downgrading recommendations based on extrapolation from higher-level studies may be considered a limitation of these guidelines. In addition, in the absence of the original data, downgrading published evidence carries a risk of individual and arbitrary judgements unlikely to be standardised and or standardisable. However, we accept that there is an obvious risk of artificially inflating the available evidence, which could lead to a false impression

of certainty, since evidence for the subset of CLI tends to be extremely poor.

For example, since there are few RCTs directly comparing surgical vs. endovascular treatment of CLI patients, there is still a lack of objective grounds on which the choice between the two approaches can be made.

In such cases the validation of a new technique (such as an endovascular approach) does not depend only on a comparison with the traditional technique (open surgery) but also on the results that can be obtained by this treatment with regard to the objectives for the treatment of CLI. These objectives (limb salvage etc.) can clearly be reached with the new technique and therefore there is evidence for its use, but with a downgraded recommendation. To require that the evidence depend on the presence of direct comparisons with the traditional technique could also be reversed: there is no absolute evidence for the traditional technique as there are no RCTs comparing this to the new technique.

3.2. Geography-related factors

The importance of geographic factors in the choice of treatment and eventual prognosis in vascular disease has been addressed only infrequently. However, these differences can be partly responsible for the contradictory results of different studies, with an apparently similar design.

Previous studies have reported on the importance of geographic influences on the outcome of treatment of vascular disease. Singh et al. reported that the incidence of angiographic restenosis and ischaemia-driven revascularisations after percutaneous coronary interventions differed substantially between patients treated in the USA compared with other countries mainly located in Western Europe.⁹ Moreover, large differences in amputation rates due to gangrene in patients with diabetes originating from different geographic regions, were reported by Chaturvedi and co-workers.¹⁰ Differences in mortality due to cardiovascular disease and cerebrovascular disease are also striking even within the same continent as has been reported by Levi et al.¹¹ Similar differences in the incidence of cardiovascular disease within quite closely related geographic areas have been reported by others, for example between Northern and Southern European countries.^{12,13} The differences in clinical outcomes are also reflected in the composition of atherosclerotic plaques reported by Tanganelli et al.¹⁴ Literature addressing the mechanical underpinnings of these geographic variances in cardiovascular disease incidence and outcome is scarce, but genetics, dietary factors and other environmental and life style-related factors are likely to play a role.

It is likely that the geographic influence on cardiovascular disease incidence and outcome is reflected by plaque composition, and has at least some influence on the durability and efficacy of vascular reconstructions. Therefore, the results of studies originating from countries different from where the vascular surgeon works should be interpreted cautiously.

Since we aim for an European Society for Vascular Surgery-wide distribution of this guideline we did not specifically address the geographic origin of the studies, but it should be stressed that these factors should be borne in mind when reading it. Moreover, the ethnic and geographic mechanisms underlying the observed differences should receive more attention in future studies.

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Chapter I: Definitions, Epidemiology, Clinical Presentation and Prognosis

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Abstract The concept of chronic critical limb ischaemia (CLI) emerged late in the history of peripheral arterial occlusive disease (PAOD). The historical background and changing definitions of CLI over the last decades are important to know in order to understand why epidemiologic data are so difficult to compare between articles and over time. The prevalence of CLI is probably very high and largely underestimated, and significant differences exist between population studies and clinical series. The extremely high costs associated with management of these patients make CLI a real public health issue for the future. In the era of emerging vascular surgery in the 1950s, the initial classification of PAOD by Fontaine, with stages III and IV corresponding to CLI, was based only on clinical symptoms. Later, with increasing access to non-invasive haemodynamic measurements (ankle pressure, toe pressure), the need to prove a causal relationship between PAOD and clinical findings suggestive of CLI became a real concern, and the Rutherford classification published in 1986 included objective haemodynamic criteria. The first consensus document on CLI was published in 1991 and included clinical criteria associated with ankle and toe pressure and transcutaneous oxygen pressure (TcPO₂) cut-off levels (≤ 50 mmHg, ≤ 30 mmHg).

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and ≤ 10 mmHg respectively). This rigorous definition reflects an arterial insufficiency that is so severe as to cause microcirculatory changes and compromise tissue integrity, with a high rate of major amputation and mortality. The TASC I consensus document published in 2000 used less severe pressure cut-offs (<50 – 70 mmHg, <30 – 50 mmHg and <30 – 50 mmHg respectively). The thresholds for toe pressure and especially TcPO₂ (which will be also included in TASC II consensus document) are however just below the lower limit of normality. It is therefore easy to infer that patients qualifying as CLI based on TASC criteria can suffer from far less severe disease than those qualifying as CLI in the initial 1991 consensus document. Furthermore, inclusion criteria of many recent interventional studies have even shifted further from the efforts of definition standardisation with objective criteria, by including patients as CLI based merely on Fontaine classification (stage III and IV) without haemodynamic criteria. The differences in the natural history of patients with CLI, including prognosis of the limb and the patient, are thus difficult to compare between studies in this context. Overall, CLI as defined by clinical *and* haemodynamic criteria remains a severe condition with poor prognosis, high medical costs and a major impact in terms of public health and patients' loss of functional capacity. The major progresses in best medical therapy of arterial disease and revascularisation procedures will certainly improve the outcome of CLI patients. In the future, an effort to apply a standardised definition with clinical and objective haemodynamic criteria will be needed to better demonstrate and compare the advances in management of these patients.

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1. Introduction

The concept of chronic critical limb ischaemia (hereafter referred to as CLI) emerged late in the history of peripheral arterial occlusive disease (PAOD). It refers to a state of arterial insufficiency that reduces distal perfusion pressure to such an extent that microcirculation and nutrient blood flow to tissues are severely disturbed. Much of the interest in CLI originally focused on defining an accurate and objective description of patients that could allow a thorough comparison between various treatment modalities. Indeed, early in the history of CLI, a true need for greater objectivity in characterising patients undergoing surgical procedures was felt, with the aim of getting rid of subjective terms such as "limb-threatening ischaemia" and "limb salvage operations". Later, such standardisation was also judged necessary to define patients in non-surgical management trials.

This review first presents the historical background of CLI and its evolving definitions over time, as well as the available epidemiologic data. Then, the hallmarks of CLI clinical presentation are described, with an emphasis on the need for objective haemodynamic confirmation of the causal link between PAOD and clinical findings. Finally, the prognosis of CLI is discussed as well as some risk stratification tools.

2. Historical background

In 1952, during the first meeting of the European Society for Cardiovascular Surgery dedicated to aorto-iliac lesions, Fontaine et al. introduced a simple clinical classification of patients with chronic arterial disease of lower limbs (LL) in four stages.¹ At that time, vascular surgery was emerging and patients used to present with advanced disease often associated with obvious symptoms and signs of chronic severe ischaemia. Moreover, haemodynamic measurements were almost non-existent (the first demonstration of a fall in ankle pressure in PAOD was made by Windsor in 1950), so

that Fontaine's classification implied a causal link between the symptoms and signs and PAOD. Unfortunately, Fontaine's classification is nowadays too often used as "(any) rest pain + PAOD = PAOD stage III" or "(any) ulceration or gangrene + PAOD = PAOD stage IV", regardless of the actual severity of PAOD.

In 1969, Yao introduced measurement of the ankle-brachial pressure index (ABI) with a 10 MHz Doppler probe, and demonstrated a pressure drop proportional to the severity of occlusive lesions.² Yao also showed significant differences in ABI ranges across Fontaine stages, despite some overlap between stages II and III, and stages III and IV.³ However, only patients with proximal (iliac or femoro-popliteal) lesions were included, thus excluding a significant number of patients with leg artery calcification. At the same period, the accuracy of toe pressure for quantification of arterial insufficiency in PAOD was demonstrated by Carter et al.⁴

The expression "critical ischaemia" appeared in 1982 in the literature to describe LL ischaemia of such severity that major amputation became necessary in the absence of successful revascularisation.⁵ This definition included an absolute ankle systolic pressure <40 mmHg in case of rest pain and <60 mmHg in case of ulcer or gangrene. Nevertheless, it soon appeared that ankle pressure was inadequate in case of ulcer or gangrene, toe pressure being a better predictor of foot viability particularly in diabetic patients, and that an evaluation of skin perfusion could be useful.^{6,7}

In 1986, the First Society for Vascular Surgery/International Society for CardioVascular Surgery (SVS/ISCVS) Standards for reports dealing with lower extremity ischaemia were published,⁸ including a recommendation for staging chronic limb ischaemia that would become known as the Rutherford classification. This classification is similar to Fontaine's classification, but its originality lies in adding an objective criterion to each clinical category: resting ankle pressure <40 mmHg/flat or barely pulsatile forefoot pulse volume recording/toe pressure <30 mmHg for ischaemic

rest pain (Grade II, Category 4); resting ankle pressure <60 mmHg/flat or barely pulsatile forefoot pulse volume recording/toe pressure <30 mmHg for minor (Grade III, Category 5) or major (Grade III, Category 6) tissue loss. All these criteria remained unchanged in the 1997 revised version of SVS/ISCVS Standards for reports dealing with lower extremity ischaemia.⁹ Unfortunately, in the Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease¹⁰ and thereafter, only the clinical description of Rutherford categories are maintained, and Rutherford classification as often used nowadays has lost what made its strength compared to Fontaine's classification.

Of note, Fontaine and Rutherford classifications were suggested by individual physicians. The first experts' consensus document on CLI was published in April 1991 after the Second European Meeting on Chronic Critical Leg Ischemia,^{11,12} followed by TASC I and II consensus documents.^{10,13}

These different suggested definitions of CLI are discussed in detail in the following section, but this historical reminder seemed important to us. Indeed, when reading many recent articles, one can wonder if the original purpose of creating the term CLI with a rigorous and objective definition has not been somewhat forgotten.

3. Definitions of chronic critical limb ischaemia

CLI represents the end stage of PAOD, in which macrovascular lesions induce such a reduction of distal perfusion pressure that microcirculation and nutrient blood flow to the tissues are severely disturbed. It is important to emphasise that the definition of CLI has evolved over time, from the initial document of 1991 to TASC I and II consensus documents published more recently. These three definitions are presented and commented on below. The concept of chronic subcritical limb ischaemia is also briefly discussed at the end of this section.

3.1. Second European Meeting Consensus document on CLI (1991)¹¹

This document includes two levels of CLI definition reproduced below as they appear in the original version: one for clinical use in daily practice, and the second for clinical research and publications.

Recommendation 1

CLI, in both diabetic and non-diabetic patients, is defined by either of the following two criteria:

- *persistently recurring ischemic rest pain requiring regular adequate analgesia for more than two weeks with an ankle systolic pressure ≤ 50 mmHg and/or toe systolic pressure ≤ 30 mmHg;*
- *ulceration or gangrene of the foot or toes, with an ankle systolic pressure ≤ 50 mmHg or toe systolic pressure ≤ 30 mmHg.*

Of note, the terms rest pain, ulceration or gangrene should be applied according to the classical description of *ischaemic* rest pain and trophic changes (see section 5 on clinical presentation of CLI).

Recommendation 2

A more precise description of the type and severity of CLI is also necessary for the design and reporting of clinical trials. In addition to the above definition (Recommendation 1), the following information is also desirable:

- *arteriography to delineate the anatomy of the large vessel disease throughout the leg and foot;*
- *toe arterial pressure in all patients, including those who are not diabetic;*
- *a technique for quantifying the local microcirculation in the ischemic area [e.g. capillary microscopy, transcutaneous oxygen pressure (TcPO₂), or laser Doppler].*

Of note, TcPO₂ is usually ≤ 10 mmHg in supine position in CLI patients and is not increased with inhalation of oxygen; further sensitivity may be obtained by performing the measurements in sitting position.

Soon after its publication, this definition was criticised, mainly because an ankle pressure threshold of 50 mmHg was judged too low. Furthermore, the true interest of ankle pressure was questioned, particularly in diabetic patients.^{12,14} Nevertheless, these criteria seemed well accepted by vascular surgeons, as demonstrated by a computer-interactive voting session during the European Society for Vascular Surgery (ESVS) meeting in Barcelona in 1993. Among 158 participants, of whom 82% were vascular surgeons, 83% agreed on either ankle pressure ≤ 50 mmHg (55%) or toe pressure ≤ 30 mmHg (28%), and 12% preferred to add a microcirculatory parameter to define CLI.¹⁵

3.2. Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease (2000)¹⁰

This document includes the following recommendations concerning CLI.

Recommendation 73 Clinical definition of critical limb ischemia (CLI)

The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The CLI implies chronicity and is to be distinguished from acute limb ischemia.

Recommendation 74 Trials and reporting standards definition of CLI

A relatively inclusive entry criterion is favoured, the aim being to ensure that the ulceration, gangrene, or rest pain is indeed caused by peripheral arterial disease and that most would be expected to require a major amputation within the next 6 months to a year in the absence of a significant haemodynamic improvement. To achieve this, it is suggested to use absolute pressures of either ankle pressure <50–70 mmHg or toe pressure <30–50 mmHg or reduced supine forefoot TcPO₂ <30–50 mmHg.

Some points need to be discussed. First, the expression "attributable to objectively proven PAOD" used in Recommendation 73 is very important. Indeed, the association of rest pain or trophic changes on the distal part of a leg with PAOD does not mean *ipso facto* that PAOD is in CLI stage, i.e. severe enough to explain the clinical symptoms and/or signs presented by the patient. Second,

raising the threshold of ankle pressure to 70 mmHg does not seem a good compromise in response to the criticisms on ankle pressure mentioned above. It might have been a better choice to favour toe pressure measurement instead for the objective confirmation of CLI in a given patient (see the recommendations in section 7). Third, the new threshold values used in this document for toe pressure are just below the ranges found in patients with intermittent claudication. For forefoot TcPO₂, the suggested cut-off is even at the lower limit of values found in patients without PAOD.

3.3. *Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease II (2007)*¹³

In this document, the recommendations are presented in a summarised version.

Recommendation 16 *Clinical definition of critical limb ischemia (CLI)*

The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity and is to be distinguished from acute limb ischemia.

Recommendation 19 *Diagnosis of critical limb ischemia (CLI)* *CLI is a clinical diagnosis but should be supported by objective tests.*

Details and objective criteria can only be found in the full text as follows: "Ischemic rest pain most commonly occurs below an ankle pressure of 50 mmHg or a toe pressure less than 30 mmHg. [...] For patients with ulcers or gangrene, the presence of CLI is suggested by an ankle pressure less than 70 mmHg or a toe systolic pressure less than 50 mmHg. (It is important to understand that there is not complete consensus regarding the vascular haemodynamic parameters required to make the diagnosis of CLI.)"

As summary recommendations are more often read than the full text, only the items rest pain and ulcer or gangrene remain highlighted over time, and the objective criteria have lost their importance, being perceived as accessory. This trend has unfortunately led to a major backward step in the development of the concept of CLI, with a return to initial definitions of 1950s based merely on clinical findings, as in Fontaine stages III and IV. This is highly regrettable, considering all the efforts undertaken over the last two decades to standardise an objective and reproducible definition of CLI.

3.4. *General comments on the haemodynamic parameters used to define CLI*

After presenting the different definitions suggested for CLI, it seems important to discuss some points concerning the haemodynamic assessment methods used in these definitions.

First, it should be emphasised that ankle systolic pressure (expressed as an absolute value or as ABI) is not a highly reliable parameter in patients with suspected CLI. Although an ABI ≤ 0.40 or an ankle pressure ≤ 50 mmHg (measured in supine position or using the "pole test" method)^{16,17} is consistent with a diagnosis of CLI, toe pressure measurement should clearly be recommended for all patients with

suspected CLI.^{18,19} Indeed, ankle pressure measurement is subject to erroneous results in patients with leg artery calcification, mainly represented by patients with diabetes or end-stage renal failure and in the very old, the measured value reflecting arterial wall rigidity rather than the actual perfusion pressure.^{19,20} If the arteries are still partially compressible, falsely elevated (and reassuring) pressure values are measured. In case of incompressibility, no pressure result can be obtained. Lack of compressibility is exceptionally an issue when measuring toe pressure.

Then, methods providing functional information on tissue perfusion and skin viability, such as forefoot TcPO₂, are still too seldom used mainly because of their limited availability.²¹ When performed properly, forefoot TcPO₂ has a high prognostic value (see section 6.2 on risk stratification). Its use on a larger scale should therefore be strongly encouraged in vascular clinics.

3.5. *Chronic "subcritical" limb ischaemia*

The expression "chronic subcritical limb ischaemia" was first introduced by Wolfe et al. to name a state of lower limb ischaemia borderline to CLI as defined in the 1991 European consensus.²² It represents a subgroup of patients who do not meet the 1991 CLI criteria or in whom severely reduced flow to the foot does not present as rest pain, ischaemic ulceration, or ischaemic gangrene. Patients in this stage of "transition" between exercise-induced ischaemia and permanent critical ischaemia are nevertheless a subgroup at risk that is important to identify.^{22,23} Although distal blood flow might be just sufficient to maintain skin integrity in these patients, it will probably not meet the needs of the wound healing process, which requires a higher and pulsatile flow.

4. Epidemiology

4.1. *Estimated incidence and prevalence of CLI*

The precise assessment and comparison of epidemiologic data on CLI is extremely difficult – almost impossible – for several reasons.

First, whereas identification of PAOD based on an ABI < 0.90 is fairly easy, identification of CLI (rest pain and trophic changes attributable to PAOD) needs an expertise not readily available when evaluating large numbers of patients in the setting of epidemiological studies.

Second, data are subject to major differences between studies due to differences between definitions of CLI used in these studies. Indeed, as already mentioned above, CLI definition has evolved over time, but more importantly, a strict definition including objective haemodynamic parameters is not always used, and all patients with rest pain or trophic lesions are sometimes included without confirming the severity and causative effect of arterial insufficiency, therefore leading to higher rates of "CLI".

Third, the actual statistical data on incidence and prevalence of CLI are often inferred from two indirect markers: the overall incidence of major amputations (assuming that about 25% of CLI patients will undergo amputation) and the natural history of PAOD.²⁴ Both are debatable. Indeed, depending on the country, 70–90% of

amputations are considered to have a vascular cause, even though many amputations are still performed without any vascular workup.²⁵ Then, the natural history of PAOD does not follow a standardised progression through different clinical stages. It is estimated that 5–10% of patients with asymptomatic PAOD or claudication will progress to CLI at 5 years and that 1–3% of patients with PAOD are in CLI stage at initial presentation.¹³ This latter group is often represented by older and sedentary patients who have limited mobility (and therefore do not claudicate), patients with sensory neuropathy who have impaired pain sensation, and patients with additional medical conditions reducing peripheral perfusion (such as cardiac failure), who present directly with advanced disease. Studies suggest that half of CLI patients do not present any PAOD symptoms 6 months prior to the onset of CLI.²⁶

Nevertheless, the **incidence** of CLI derived from natural history of PAOD and major amputation rates has been estimated to be approximately 500–1000 per million per year in a European or North American population (150,000 cases per year for the USA).¹³

In contrast, the incidence of CLI based on large prospective population studies is 220 new cases per million per year in the general population.²⁷ The **prevalence** of CLI in the population aged 60–90 years is estimated at 1% (0.5–1.2%), but figures vary widely between population-based studies and vascular registries. For instance, in 2004 in Sweden, the prevalence of CLI was estimated to be at least 15,000 patients, but the number of vascular interventions for CLI was only 1700 for the same period.²⁸ The reported gender differences in CLI prevalence vary between studies. In series of patients with CLI, the men to women ratio is around 3:1.¹³ However, in population-based epidemiological studies, age-adjusted prevalence of CLI is equal in men and women after 50 years, a finding that correlates with epidemiological studies on prevalence of PAOD based on ABI measurement.^{28–30}

4.2. Risk factors for CLI

In the vast majority of cases, CLI is caused by multi-level occlusive atherosclerotic disease. Consequently, CLI patients share the same traditional risk factors as patients with atherosclerosis in other territories. Moreover, as CLI is an advanced stage of PAOD occurring late in the course of patients' atherosclerotic disease, concomitant severe cerebrovascular (CVD) and coronary artery diseases (CAD) are more frequent than in patients with claudication. Indeed, 50–75% of CLI patients have associated CVD and about 20% have associated CAD.

Among cardiovascular risk factors, some are more strongly associated with progression to CLI: threefold increase in the risk of developing CLI in the case of a long history of chronic heavy smoking and fourfold in the case of diabetes.^{10,13} The risk of developing CLI rises proportionally to the number of cigarettes smoked.³¹ The duration of smoking cessation needed to return to baseline risk is however not known, but is usually considered to be around 2 years in patients at risk of cardiovascular diseases. Diabetes may be known and treated or unknown and revealed by the CLI episode. In some countries in which

the care of diabetic patients is less well established and generalised, CLI incidence may be 10 to 20 times higher in diabetic compared to non-diabetic patients. The true impact of diabetes is, however, difficult to assess, and the proportion of diabetic patients varies dramatically between published series of CLI, ranging from 35% to 80%. As already discussed in the preceding section, diagnosing CLI in diabetic patients is particularly challenging due to the presence of numerous confounding factors, such as sensory neuropathy and frequent infectious complications that can possibly lead to ulceration and gangrene even in the absence of any PAOD. In contrast, calcification of leg arteries (Monckeberg disease) may cause an overestimation of ankle pressure, leading to falsely reassuring results.

Increasing age is another risk factor for CLI. The mean age of CLI patients is higher than that of non-CLI patients (about 75 years) but the range is wide (35–100 years). In the elderly, the CLI event often occurs in the setting of arterial and non-arterial poly-morbid conditions. Chronic renal failure is also associated with increased risk of PAOD and CLI, as well as increased cardiovascular mortality.³² As in diabetics, diagnosis of CLI can be difficult in the very old and in patients with chronic renal failure due to frequent calcification of leg arteries and sensory neuropathy.^{33,34} African-American ethnicity may also represent a risk factor independent from other traditional atherosclerotic risk factors, based on data concerning PAOD, but there are no data specific to CLI.³⁵

Some other factors can cause or lead to progression of CLI without being actual risk factors. Atheroembolic (ulcerated plaques, popliteal aneurysms) or thromboembolic (mainly cardioembolic) disease, *in situ* arterial thrombosis due to congenital or acquired hypercoagulable states, vasculitis, thromboangiitis obliterans, popliteal entrapment, or trauma can all lead to compromised distal perfusion of the extremity with the potential progression to a clinical picture of CLI. Generally, arterial insufficiency and CLI secondary to these diseases present as a more rapidly progressive disease than atherosclerotic PAOD. Although rare, some anatomical variations of leg arteries can also lead more readily to CLI in case of occlusive disease, due to altered blood-flow distribution to foot arteries. Finally, some associated conditions can represent aggravating and/or confounding factors, particularly peripheral neuropathy.

In summary, in spite of the limitations of epidemiological data, partly related to varying definitions of CLI, one thing is beyond doubt: the total cost of CLI is considerable! And as for venous ulcers and chronic venous disorders, a small percentage of cases cost more than all others due to high rates of re-interventions, amputations, comorbidities and disability. In the presence of an ageing population and increasing worldwide prevalence of diabetes, an increase in CLI incidence and prevalence is to be expected over the future decades, making it a major public health issue.

5. Clinical presentation of CLI

As mentioned above, CLI refers to the extreme stage of chronic arterial insufficiency of a lower extremity in which distal blood flow and microcirculatory function (vasomotor adaptation, capillary recruitment) are severely

compromised,³⁶ resulting in a clinical picture including ischaemic rest pain, ischaemic ulcer and/or gangrene as well as other clinical signs related to forefoot haemodynamic and trophic changes described in this section.

5.1. Ischaemic rest pain

According to the main guidelines and the 1991 European consensus,¹¹ ischaemic rest pain must be named as such if it corresponds to the description by Cranley: "ischemic rest pain is pain that occurs in the toes or in the area of the metatarsal heads. Occasionally, it occurs in the foot proximal to the metatarsal heads. Elevation of the limb above or at the horizontal position aggravates the pain and pendency, to some degree at least, brings relief".³⁷ In more than 90% of cases, the toes are involved. Three degrees can be described. First, the pain starts at primo-decubitus and declines quickly – the patient can thus stay supine; of note, the patient can experience numbness or tingling instead of pain. Second, the patient needs to dangle his leg to relieve the pain. Third, the patient has to remain seated to relieve the pain. In second and third degrees, dependent foot oedema develops, worsening the ischaemia because increased tissue pressure exceeds capillary pressure. It is important to bear in mind that rest pain depends on pain perception, which can be reduced or abolished in the case of sensory neuropathy (secondary to diabetes, ageing, or to ischaemia itself).

5.2. Ischaemic ulcer and gangrene

Ulcerations occurring in the context of severe ischaemia related to PAOD are located at the limb extremity, involving the toes and foot (especially on pressure areas like the heel or the first and fifth metatarsal heads). Clinically, they have an inactive edge, pale necrotic base or are covered with fibrinous material. Whereas ischaemic rest pain has a typical and standardised presentation (in the absence of sensory neuropathy), ischaemic ulcer and toe gangrene are much more difficult to identify as lesions clearly attributable to end-stage PAOD.^{11,26–28} Schematically, three situations can be encountered. First, arterial insufficiency is severe, and the ischaemic skin lesion occurs spontaneously or after a minor trauma. Second, arterial insufficiency is moderate but severe enough to impair the healing process of any skin lesion (skin flow needed for wound healing is much higher than skin flow necessary for baseline nutritional requirements of an intact skin). Third, PAOD is present, but only as an associated condition, with no causal relationship with skin lesions. Even in the presence of toe gangrene, the potential morphological lesions of lower limb arteries identified by imaging techniques may be innocent if perfusion pressure remains well above threshold values for critical ischaemia. This issue is particularly important in diabetic foot lesions because of numerous potential confounding factors, and the causative link between PAOD and trophic changes should be documented with particular attention in these patients.

As a general rule, all patients with ulcers or gangrene of the extremity should first be thoroughly examined for other associated clinical signs suggestive of chronic compromised blood flow to the foot (see below). Then, an

objective quantification and confirmation of the severity of foot ischaemia by distal pressure measurement and microcirculatory assessment (mainly forefoot TcPO₂) should be performed. This indeed seems the only way to avoid the simplifying equation "gangrene/ulcer = critical limb ischaemia".

5.3. Other clinical signs of CLI-related forefoot haemodynamic changes

Other less well known signs of CLI can easily and rapidly be assessed by simple inspection and palpation of the foot and are highly informative.

Some of these signs are related to low residual perfusion pressure and consequent vasomotor paralysis. Refilling of the foot's superficial veins after emptying with the physician's thumb and capillary refilling time at forefoot level are normally nearly instantaneous, but become more and more prolonged as arterial insufficiency becomes more severe. Also, hydrostatic pressure changes when elevating or letting the foot in a dependent position induce the following colour changes: rapid (<30 seconds) appearance of foot sole pallor by elevating the limb at 60° above bed level (Buerger's test), and foot erythrocyanosis in dangling position (also called dependent rubor).

Other signs already reflect trophic changes secondary to chronic severe ischaemia: shrinking and atrophy of the toe pulp or heel pad, with bone contact felt on palpation.^{38,39}

When present, these clinical signs are predictive of severe arterial insufficiency (ABI <0.50, toe pressure <30 mmHg, forefoot TcPO₂ <30 mmHg in supine position; $p < 0.01$ [personal unpublished data]). On the contrary, absence of these signs makes the diagnosis of CLI unlikely. Looking for these clinical changes is thus an important part of the initial assessment of clinical probability of CLI.^{40,41}

The pole test, a variant of Buerger's test, is yet another useful clinical tool to evaluate ankle or toe pressure.^{16,17} It allows estimating a toe pressure <55–70 mmHg and ankle pressure <45 mmHg, and is particularly useful when calcification of leg arteries impairs accurate ankle pressure measurement and a device for toe pressure measurement is not available.

6. Natural history and prognosis

6.1. Natural history of CLI patients

CLI is a very severe medical condition with a high risk of major amputation, disability and death. In a way, it behaves like a malignant disease. In the consensus documents discussed above, as well as in review articles, the natural history of CLI patients is summarised as follows:

- At presentation: 20–25% of patients undergo primary amputation, 50–60% have vascular reconstruction (surgical and/or endovascular), and 25% are treated medically.
- One year later: 20–25% of patients will have died, 25–30% will have had major amputation, 20% will still be in CLI state, and 25% will be alive without major amputation and free from signs and symptoms of CLI.^{10,13}

Although these figures are always cited in the introduction of articles published on CLI, they often do not correlate with more recent publications on CLI patients' outcome, for at least two main reasons. First, the overall management of cardiovascular patients has dramatically changed in recent years, and an increasing proportion of patients are offered "best medical treatment" and risk-factor modification counselling, which could of course partly account for a better global prognosis of CLI patients. However, there seems to be a second important reason for the discordance between prognosis data derived from original series compared to more recent series. As discussed in previous sections, inclusion criteria of many recent studies have been described as "Fontaine stage III or IV" as if it was an equivalent of CLI, without any haemodynamic criteria. Therefore, less severe patients (in terms of systemic atherosclerotic disease) might have been included in recent series, contributing to a better overall prognosis.

The TAMARIS trial probably offers the most reliable recent data on the natural history and prognosis of CLI.²¹ It included patients with CLI defined according to the TASC I document, who were unsuitable for revascularisation as assessed by a vascular surgeon. Patients were randomised to an angiogenic treatment (NV1FGF) or placebo. From December 2007 to July 2009, 525 patients were included in 171 hospitals in 30 countries. No patient was lost to follow-up. The primary combined endpoint was time to major amputation of the treated leg or death from any cause during the study period of 12 months. Primary outcome was encountered in 33% (95%CI: 27–39%) of patients in the placebo group (major amputation or death 33%, major amputation 21%, death 15%). Death was from a cardiovascular cause in 49%, a non-cardiovascular cause in 41%, and unknown origin in 10%.²¹

6.2. Risk stratification

After establishing a precise diagnosis of CLI based on clinical and haemodynamic criteria, which clearly helps evaluating and comparing different treatment modalities (surgical and/or endovascular strategies, angiogenic treatments, conservative medical management, etc.) in terms of outcome and cost-effectiveness, the next step is to stratify local and general risk in order to better identify which patients benefit most from each management strategy. A prediction model derived from the BASIL study has been proposed to facilitate clinical decision-making in patients with severe ischaemia.⁴² It mainly illustrates the fact that this stage of advanced PAOD is associated with high cardiovascular risk due to major comorbidities.

There is a need for risk stratification tools taking into account quantitative assessment of the degree of ischaemia. As with venous thromboembolism (VTE), we may apply the following decision process: (1) clinical probability assessment, (2) diagnostic validation, (3) risk stratification. A thorough assessment of the symptoms and signs described above establishes the clinical probability of CLI. Then, objective measurement of distal perfusion pressure (toe pressure, pole test) is needed to confirm the diagnosis of CLI,⁴³ with the role of additional vascular imaging being mainly to define the actual treatment

strategy. Finally, the same haemodynamic measurements used for diagnosis confirmation can be used for risk stratification.

Nevertheless, the capability of distal pressure (ankle pressure and even toe pressure) to predict amputation risk is limited.^{7,44–46} Forefoot TcPO₂, if measured according to methodological rules (particularly avoiding areas of thick or oedematous skin) is probably the best non-invasive method for quantification of ischaemia severity and prognostic assessment.⁴¹ Forefoot TcPO₂ may be considered a marker of total distal run-off (arterial and arteriolar run-off) and perfusion reserve. In the setting of risk stratification, different values have been suggested, but almost all series are in agreement with the following criteria: in case of supine forefoot TcPO₂ >35–40 mmHg, local prognosis is fairly good even with conservative management, and these patients can therefore not be truly considered to have CLI; in case of supine forefoot TcPO₂ 10–35 mmHg, local prognosis is intermediate; in case of supine forefoot TcPO₂ ≤10 mmHg (which corresponds to the 1991 European consensus document's recommendation for the diagnosis of CLI¹¹), local prognosis is very poor. Of note, further prognostic stratification of patients with low supine forefoot TcPO₂ (<20 mmHg) can be performed by testing perfusion reserve in sitting position or under oxygen inhalation (oxygen inhalation being more efficient when performed in sitting position).^{46,47}

In a personal prospective series of 205 patients with CLI defined according to the 1991 European consensus with supine forefoot TcPO₂ ≤10 mmHg, all operated on (bypass surgery and/or PTA) with a follow-up >1 year, the overall rate of major amputation-free survival at 1 year was 50%. It was 75% in case of TcPO₂ improvement in sitting position (to ≥40 mmHg) and only 35% if TcPO₂ remained <40 mmHg in sitting position.⁴⁶

Data are insufficient to give a grade A recommendation, but seem enough to give a grade B recommendation for a baseline risk stratification scale (major amputation or death) in four degrees, based on forefoot TcPO₂ in addition to initial careful clinical examination.

- Degree 1: 10 mmHg < forefoot TcPO₂ ≤35 mmHg in supine position.
- Degree 2: forefoot TcPO₂ ≤10 mmHg in supine position but clear improvement (≥40 mmHg) in sitting position or under oxygen inhalation.
- Degree 3: forefoot TcPO₂ ≤10 mmHg in supine position and inadequate or no improvement (<30–40 mmHg) in sitting position or under oxygen inhalation.
- Degree 4: forefoot TcPO₂ ≤10 mmHg in supine and in sitting position and/or under oxygen inhalation (very poor prognosis).

7. Conclusion and recommendations

As CLI prevalence is expected to increase over the future decades and become a major public health issue, it is of utmost importance to bear in mind some major key points that help to characterise patients with precision in order to assess and compare current or future treatment modalities. These can be summarised as follows:

Recommendations

- (1) The expression chronic critical limb ischaemia (CLI) defines the extreme stage of chronic arterial insufficiency of a lower limb in which stenosis and/or occlusion of the arterial tree lower the downstream perfusion pressure to such an extent that nutritional flow to tissues is severely compromised and does not allow maintaining skin integrity or wound healing without revascularisation. **(Level 1a; Grade A)**
- (2) The presence of rest pain or a wound, ulcer or toe gangrene on a lower limb with arterial disease (PAOD) is not sufficient to qualify as CLI. They must be recognised as **attributable to** the PAOD by combining specific clinical characteristics of pain and/or skin lesions, as well as other signs of severe chronic forefoot ischaemia, with objective haemodynamic measurements. **(Level 2b; Grade B)**
- (3) Ankle systolic pressure (absolute value or ABI) is not a reliable parameter for CLI diagnosis. **(Level 2b; Grade B)**
- (4) Toe pressure measurement is more accurate and is recommended in all patients with suspected CLI. **(Level 2b; Grade B)**
- (5) Assessment of distal tissue perfusion pressure by forefoot TcPO₂ measurement should be recommended for diagnostic validation and prognostic stratification, at least in the setting of clinical trials. **(Level 2b; Grade B)**

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None

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Chapter II: Diagnostic Methods

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KEYWORDS

Ankle-brachial index;
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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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depends on local availability, experience, and costs. Contrast angiography represents the gold standard, provides detailed information about arterial anatomy, and is recommended when revascularisation is needed.

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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.^{1,2,6–11} In diabetic patients, Clairotte 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

Table 1 Non-invasive physiologic vascular diagnostic techniques: advantages and limitations^a

Technique	Advantages	Limitations
Ankle-brachial index (ABI)	Simple, inexpensive, quick, widely applicable, cost-effective. Sensitive in establish or refute CLI diagnosis. Useful to monitor efficacy of therapeutic interventions in CLI.	May be falsely elevated in patients with diabetes, renal insufficiency and advanced age. Indirect measure. Does not provide localisation of the disease. Does not allow visualisation of artery lesion.
Toe-brachial index (TBI)	Simple, inexpensive and quick. Useful in the presence of small vessel artery disease. Useful in non-compressible pedal arteries.	Limited accuracy. Requires careful techniques and small cuffs (not widely applicable). Indirect measure. Does not provide localisation of the disease.
Segmental pressure	Useful in initial anatomical localisation of CLI disease. Useful in creating therapeutic plan based on disease localisation. Provides data to predict wound healing and limb survival. Useful to monitor efficacy of therapeutic intervention.	Not accurate in non-compressible pedal arteries as in very old patients, in diabetics and in those with end-stage renal disease. Does not provide direct visualisation of the disease. Old-fashioned measure of perfusion.
Continuous-wave Doppler ultrasound	Useful in initial evaluation of CLI anatomy, severity and progression. Can provide adjunctive information in incompressible arteries. Can provide localising information. Can provide qualitative data to monitor after successful revascularisation.	Limited sensitivity. Limited specificity especially for aorto-iliac occlusive disease. Old-fashioned measure of perfusion. Does not provide visualisation of the disease. Limited overall accuracy.
Pulse volume recording (PVR)	Initial evaluation of CLI in vascular laboratories. Useful in non-compressible pedal arteries especially in diabetic patients (photoplethysmography). Useful to monitor limb perfusion after revascularisation.	Old-fashioned technique affected by subjectivity (waveforms interpretation). Qualitative and not quantitative measure of perfusion. Limited accuracy. May be abnormal in low cardiac stroke volume. Does not provide localisation or visualisation of the disease.

CLI, critical limb ischaemia.

^a Adapted from Hirsch et al.¹

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.^{5,7,8,12,13} It has been shown that the reproducibility of ABI assessment by pocket Doppler may be dependent on the level of experience of the operator.^{6,14–17} Inter-observer variability among experienced physicians has a reported *k*-statistic of 0.77 to 1.0.⁵ Intra-observer variability ranges from 7.3% to 12%.^{5,7,8,12,13} Holland-Letz and Endres and colleagues^{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.⁶ Klein and Hage found 39 different ways to calculate the ABI.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.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.²¹ Major international societies^{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.^{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%.^{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.^{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.^{7,32–36} 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).³⁷ Although CLI is very common in

diabetic patients (prevalence of vascular disease estimated around 13.6% vs. 4% in the general population),^{7,38} it often remains under-recognised in this population.^{7,39} 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%.^{7,11,34,40–42}

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.⁴³

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.^{44–47} An ABI <0.90 is associated with a 3- to 6-fold increased risk of cardiovascular mortality.^{45–48} A meta-analysis in 2008 by Fowkes et al.⁴⁹ found that abnormal ABI was associated with approximately twice the 10-year total mortality, cardiovascular mortality, and major coronary event rate compared with the overall rate in each Framingham risk score category. The American Diabetes Association recommends screening for ABI in all diabetic patients aged >50 years, as well as in younger insulin-dependent patients with other vascular risk factors.^{35,45,47,50,51} ABI measurement can be used as a prognostic index to facilitate initiation of treatment (hypertension, dyslipidaemia, diabetes, etc.) to reduce cardiovascular events and should be routinely performed in patients aged ≥70 years, with rest pain or ulcers, and those with a history of diabetes or smoking.⁴⁷

Although the ABI has gained widespread acceptance as a single, accurate and reproducible first-line method to evaluate arterial occlusive disease and a valid cardiovascular prognostic instrument, the test has definite limitations and it should be associated with duplex ultrasound imaging.

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.^{7,38} 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.^{52,53} Absolute toe pressures <30 mmHg are required to diagnose CLI in patients with rest pain.² 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.²

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.^{34,54,55} 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.⁵⁴ In the presence of clinical peripheral neuropathy, toe pressure sensitivity has been evaluated to be 100% and ABI sensitivity 53%.³⁴

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 20mmHg 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.⁵⁴⁻⁵⁶

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 pressure 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 waveform 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 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.⁵⁷

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.^{57,58}

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 (TcPO₂) 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 (PO₂) within the sensor. In patients with foot ulcers, tissue loss or rest pain, TcPO₂ 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.^{67–69}

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-analysis^{75–77} (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

	DUS	CTA	MRA	Angiography
Availability	+++	++	++	+++
Appointment time (minutes)	40+ (both legs)	15	30	30
Equipment cost	+	++	+++	+++
Operator expertise	+++	+	++	++
Arteriographic map	Yes, by experienced operators	Yes (requires post-processing)	Yes (immediately available)	Yes (immediately available)
Diagnostic accuracy				
Aorto-iliac	++	+++	+++	+++
Femoro-popliteal	+++	+++	+++	+++
tibial	+	+	++	+++
Stent assessment	++	+	Steel: poor Nitinol: fair	+++
Limitations by vascular calcification	++	++	None	Almost none
Complications and risks				
Access site	None	None	None	Rare
Ionising radiation exposure	None	7.5–13.7 mSv	None	Higher than CTA
Contrast-enhanced nephropathy	None	++	Extremely rare	++
Nephrogenic systemic fibrosis	None	None	Very rare	None
Allergic reaction	None	Rare	Very rare	Rare
Contraindications	None	Severe renal impairment, known allergy to contrast agents	Cerebrovascular clips, electronic implants (infusion or monitoring devices, neurostimulation devices), pace-makers, cardioverter-defibrillators, claustrophobia	Severe renal impairment, known allergy to contrast agents

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 Roditi⁷² 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%.^{81,82} 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 impending 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

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)

Reference	Modality	Characteristics	Anatomical region	Pooled sensitivity	Pooled specificity
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	95% (91–98%)	96% (95–98%)
			Tibial	92% (90–94%)	93% (90–96%)
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	97% (95–99%)	94% (85–99%)
			Tibial	95% (85–99%)	91% (79–97%)

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.¹⁰¹ In a further prospective study, a normal DUS scan 6 weeks subsequent to infrainguinal 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.¹⁰² There is an ongoing transatlantic discussion whether or not DUS surveillance is beneficial in patients with infrainguinal venous bypass grafting, with a tendency for routine DUS in these patients in North America,^{103–105} while the situation in Europe remains equivocal.^{102,106,107}

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.^{1,100,101,108–111}

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.^{1,112–119} 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.¹

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.^{120,121}
- The technique is highly operator-dependent and proper training is mandatory.⁹⁸
- 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 4 Recommendations in current guidelines for duplex ultrasound imaging in patients with CLI

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

CLI, critical limb ischaemia; PAD, peripheral arterial disease.

^a Adapted from Hirsch et al.¹

Recommendations in current guidelines (Table 4)

The current ACC/AHA Practice guidelines for PAD patients give a strong recommendation that DUS is useful to diagnose the anatomical location and degree of obstruction of PAD. **(Level 1a; Grade A)**

Despite the discrepancies mentioned above, DUS surveillance of venous grafts is also recommended with regular follow-up intervals (3, 6, 12 months, and then yearly after graft placement).¹ **(Level 2b; Grade B)**

The guidelines for non-invasive vascular laboratory testing from the American Society of Echocardiography and the Society for Vascular Medicine and Biology recommend DUS evaluation of the graft twice during the first post-operative year, and annually thereafter.⁹⁸ The ACC/AHA guidelines consider DUS also as useful to select patients as candidates for endovascular intervention or surgical bypass **(Grade B)** and state that DUS may also be considered for routine surveillance after femoropopliteal bypass with a synthetic graft **(Level 2b; Grade B)**.

Finally, DUS is not well established to assess long-term patency of PTA.¹ **(Level 2b; Grade B)**

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 infrainguinal 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

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

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

^a Adapted from Hirsch et al.¹

imaging are claudicants 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, in-hospital 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

Recommendations from 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 statistical power of the available meta-analyses is limited by the relatively small sample size of most included studies. Larger studies are needed.
- New CTA 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.^{123–125}
- Future reviews should make use of the QUADAS as a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies.¹²⁶

4.3. Magnetic resonance angiography

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.^{78,135,136} Two meta-analyses determined that 3D ce-MRA is superior to 2D time-of-flight MRA.^{123,137} The meta-analysis by Collins et al.¹²³ 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.^{78,123} A well-conducted systematic review concluded that MRA is also cost-effective in comparison to DSA when both are available locally.¹³⁷ 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.¹³⁸ Some studies claim that MRA is superior to DSA in the detection of outflow vessels suitable for distal bypass in patients with CLI.^{79,139} 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.¹³⁹ Such vessels treated with surgical bypass may enjoy satisfactory patency.¹⁴⁰ The claim that MRA is more sensitive than DSA for distal vessels is controversial and is affected by the quality of the comparative catheter angiogram.¹⁴¹ At least one study has shown MRA to be inferior to catheter angiography, particularly for patients with CLI.¹⁴² However, other studies have demonstrated agreement between pre-operative plans based on MRA vs. DSA of at least 90%, and many centres no longer perform DSA before revascularisation.

MRA has been used anecdotally for the assessment of surgical and endovascular revascularisation. Several series of small numbers of patients have shown that the sensitivity and specificity of MRA compared with catheter angiography for detection of stenoses in vein or synthetic bypass grafts is 90–100%.^{143–146} For immediate post-procedural evaluation of angioplasty sites, agreement with catheter angiography is 80–95%.^{147,148} There have been no published studies that validate improved patient outcomes from post-revascularisation MRA surveillance.

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).¹⁴⁹ 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).¹⁵⁰ 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.¹⁵¹
- Patients with pacemakers and defibrillators and some cerebral aneurysm clips cannot be scanned safely.^{147,152}

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.¹ (**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.¹⁵³

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

	Grade of recommendation	Level of evidence
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 ^a .	A	1a
MRA of the extremities should be performed with gadolinium enhancement ^a .	A	2a
MRA of the extremities is useful in selecting patients with lower extremity PAD as candidates for endovascular intervention ^a .	A	2a
MRA of the extremities may be considered for post-revascularisation (endovascular and surgical bypass) surveillance in patients with lower extremity PAD ^a .	B	3b

CLI, critical limb ischaemia; MRA, magnetic resonance angiography; PAD, peripheral arterial disease.
^a Adapted from Hirsch et al.¹

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.⁷⁹
- 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.^{123–125}
- Future MRA reviews should make use of the QUADAS as a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies.¹²⁶

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:^{1,154}

- 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.^{154,155} 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.² 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.^{156–159} 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).¹⁶⁰

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

Table 7 Recommendations in current guidelines for catheter angiography in patients with CLI

	Grade of recommendation	Level of evidence
DSA is not recommended as the primary imaging modality for patients with PAD ^a .	A	1a
Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularisation is contemplated.	A	2a
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.	A	2a
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 .	A	2a
DSA is recommended for contrast angiographic studies because this technique allows for enhanced imaging capabilities compared with conventional unsubtracted contrast angiography ^b .	A	2a
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 .	A	3b
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 .	A	2b
The diagnostic lower extremity arteriogram should image the iliac, femoral, and tibial bifurcations in profile without vessel overlap ^b .	A	2b
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 .	A	2b
Patients with baseline renal insufficiency should receive hydration before undergoing contrast angiography ^b .	A	2b
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 .	A	3a
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 .	A	2a

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

- 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.

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**)

continued on next page

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)**

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None

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Chapter III: Management of Cardiovascular Risk Factors and Medical Therapy

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KEYWORDS

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Abstract Critical limb ischaemia (CLI) is a particularly severe manifestation of lower limb atherosclerosis posing a major threat to both limb and life of affected patients. Besides arterial revascularisation, risk-factor modification and administration of antiplatelet therapy is a major goal in the treatment of CLI patients.

Key elements of cardiovascular risk management are smoking cessation and treatment of hyperlipidaemia with dietary modification or statins. Moreover, arterial hypertension and diabetes mellitus should be adequately treated.

In CLI patients not suitable for arterial revascularisation or subsequent to unsuccessful revascularisation, parenteral prostanoids may be considered. CLI patients undergoing surgical revascularisation should be treated with beta blockers. At present, neither gene nor stem-cell therapy can be recommended outside clinical trials. Of note, walking exercise is contraindicated in CLI patients due to the risk of worsening pre-existing or causing new ischaemic wounds.

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CLI patients are oftentimes medically frail and exhibit significant comorbidities. Co-existing coronary heart and carotid as well as renal artery disease should be managed according to current guidelines.

Considering the above-mentioned treatment goals, interdisciplinary treatment approaches for CLI patients are warranted.

Aim of the present manuscript is to discuss currently existing evidence for both the management of cardiovascular risk factors and treatment of co-existing disease and to deduct specific treatment recommendations.

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Critical issue

Most of the outlined recommendations apply to peripheral arterial disease (PAD) patients in general. Thus, it has to be kept in mind that recommendations are frequently extrapolated to the subgroup of PAD with critical limb ischaemia (CLI).

1. Smoking

Smoking is the most important risk factor in PAD patients. The extent of smoking exposure correlates with PAD disease severity, rates of lower limb amputation, bypass re-occlusion as well as with mortality.^{1–3} Thus, CLI patients should be advised to quit smoking with the aim to reduce the risk of adverse cardiovascular events and amputation.

Physician smoking cessation advice coupled with a formal smoking cessation programme and nicotine replacement was shown to be associated with a 22% cigarette smoking cessation rate out to 5 years.¹ In this randomised controlled trial (RCT), cessation rate was only 5% in the group of patients not undergoing this programme. Fourteen years post randomisation, the group of patients on this programme still exhibited a significant survival benefit as compared to the control group.

The clinical utility of nicotine replacement therapy was assessed in a Cochrane review⁴ for which a total of 132 RCTs were summarised. All of the commercially available forms of nicotine replacement therapy (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) were shown to increase the odds of successfully stopping cigarette smoking by 50–70%.

A number of RCTs supported the use of bupropion, an antidepressant agent, in cigarette smokers with cardiovascular disease. Abstinence rates were reported to be 34%, 27% and 22% at 3-, 6- and 12-month follow-up as compared with 15%, 11% and 9%, respectively, with placebo treatment.⁵

Finally, the efficacy of nicotine receptor partial agonists was assessed in a recently published systematic Cochrane review summarising 11 RCTs with more than 10,300 patients.⁶ In this analysis, the pooled risk ratio for continuous smoking abstinence at 6 months or longer for varenicline vs. placebo was 2.31 (95%CI 2.01–2.66). Moreover, varenicline was shown to be superior to bupropion [pooled RR for varenicline vs. bupropion at 1 year: 1.52 (95%CI 1.22–1.88)].

Of note, smoking cessation may be associated with important benefits such as improvement of respiratory symptoms⁷ and vascular tone already during short-term follow-up.⁸

Recommendations

CLI patients should be strongly and repeatedly advised to stop smoking. **(Level 2a; Grade B)**

Smoking cessation rates can be improved by offering medical advice, group counseling session, nicotine replacement, nicotine receptor partial agonists (varenicline) or antidepressant drug therapy (bupropion). **(Level 1a; Grade A)**

2. Hyperlipidaemia

Increased cholesterol, low-density lipoprotein (LDL), triglyceride and lipoprotein (a) concentrations are independent major PAD risk factors. Moreover, PAD is considered a coronary heart disease risk equivalent.⁹

The Heart Protection Study assessed the impact of statin intake on mortality and fatal and non-fatal vascular events.¹⁰ For that purpose, a total of 20,536 patients with coronary artery disease (CAD), other arterial occlusive disease or diabetes mellitus were randomly assigned to 40mg simvastatin daily vs. placebo. In that study, all-cause mortality and cardiac death were significantly reduced by statins irrespective of the patients' cholesterol concentration. Importantly, simvastatin reduced major vascular events by 22% in the subgroup of PAD patients. Remarkably, there was no threshold cholesterol value below which statin therapy was not associated with clinical benefits.

In the 4S study (Scandinavian Simvastatin Survival Study), a total of 4444 coronary heart disease patients were randomised to simvastatin vs. placebo.¹¹ In the statin group, the risks for mortality, stroke and intermittent claudication were significantly reduced. The authors concluded that long-term treatment with simvastatin is safe and improves survival in coronary heart disease patients.

In the PREVENT III study a total of 1404 CLI patients undergoing lower extremity bypass grafting were randomised to edifoligide vs. placebo aimed at preventing neointimal hyperplasia and vein graft failure.¹² In that trial, statin use was associated with a significant reduction of 1-year mortality in a propensity-score adjusted model.

In a Cochrane review including 18 RCTs with 10,049 participants the clinical utility of statins in PAD patients was scrutinised.¹³ Lipid-lowering medication was shown to be associated with a beneficial effect on the incidence of total cardiovascular events, primarily due to an overall reduction in coronary events (OR: 0.8; 95%CI 0.7–0.9). Statins were identified as the only type of drug for which consistent, clear evidence of a beneficial effect on total cardiovascular events, total coronary events and stroke was

available. The greatest evidence was with simvastatin in people with a blood cholesterol level of at least 3.5 mmol/L (i.e. 63 mg/dL).

At present, there is no study indicating that diet alone impacts on cardiovascular events in patients with atherosclerosis. It is recommended, however, that therapy for increased cholesterol concentrations begins with lifestyle modifications aimed at lowering elevated cholesterol.¹⁴ Thus, dietary modification and pharmacologic intervention for dyslipidaemia should be tailored to meet the current guidelines for high-risk patients.

In addition to the above-described benefits, statins may prevent plaque instability and thrombosis due to their pleiotropic effects such as improvement of endothelial function, reduction of inflammation, and stabilisation of atherosclerotic plaques.¹⁵

Current recommendations for the management of lipid disorders in PAD are to achieve an LDL cholesterol level of <100 mg/dL and to treat the pattern of increased triglyceride and low high-density lipoprotein (HDL).^{16,17}

Recommendations

In CLI patients, statins should be the primary agents to lower LDL cholesterol levels to reduce the risk of cardiovascular events. **(Level 1a; Grade B)**

For CLI patients, LDL cholesterol should be <100 mg/dL. **(Level 5; Grade D)**

Dietary modification is aimed at controlling body weight and lipid disorders. **(Level 5; Grade D)**

Statins are indicated for secondary prevention of cardiovascular events in patients with CLI. **(Level 1a; Grade B)**

3. Arterial hypertension

Arterial hypertension is a major independent risk factor for PAD. Current hypertension guidelines advocate aggressive treatment of elevated blood pressure in patients with atherosclerosis. Current treatment goals of antihypertensive therapy are arterial blood pressures of <140/90 mmHg. Moreover, blood pressure should be <130/80 mmHg if the patient also has diabetes or renal insufficiency.^{18,19} To achieve these results, all drugs capable of lowering arterial blood pressures can be considered for the prevention of vascular events. Many patients may require agents of various classes to achieve the above-mentioned blood pressure goals. Evidence for specific blood-pressure lowering drugs in PAD patients is only available for angiotensin-converting-enzyme (ACE) inhibitors and beta blockers. It has to be kept in mind, however, that an acute reduction of blood pressure may result in a further impairment of lower limb perfusion in CLI patients not undergoing revascularisation.

The specific benefit of ramipril, an ACE inhibitor, in PAD patients was documented by results from the HOPE (Heart Outcomes Prevention Evaluation) study in 4046 patients.²⁰ In the subgroup of PAD patients, there was a 22% risk reduction in the composite endpoints of myocardial infarction, stroke or cardiovascular death in patients randomised to ramipril as compared to placebo. Interestingly, this clinical benefit was independent of lowering of blood pressure. Thus, ACE inhibitors may exert beneficial effects such as plaque

stabilisation and prevention of atherosclerosis progression beyond those of lowering arterial blood pressure. However, it has to be kept in mind that this study was not carried out exclusively in CLI patients. Thus, as for other risk factor interventions, data are largely extrapolated from a general PAD but not specifically CLI population.

Based on results from initial studies with non-selective beta blockers such as propranolol, beta-adrenergic blocking drugs have previously been discouraged in PAD due to their potential to reduce cardiac output and to prevent beta-2-receptor-mediated skeletal muscle vasodilation.²¹ Two meta-analyses of studies published in patients with mild and moderate lower limb ischaemia did not confirm the intake of beta blockers to be associated with exacerbation of PAD symptoms.^{22,23} Thus, the above-mentioned concern might have been overstated, especially in patients treated with a beta-1 selective drug, especially since PAD patients with coronary disease may have additional cardiac protection with beta blockers. Therefore, beta-adrenergic-blocking agents may be considered for the treatment of arterial hypertension in PAD patients.

The clinical utility of peri-operative administration of beta blockers is controversial. Use of beta blockers was shown to be associated with significant reductions of peri-operative myocardial ischaemia and infarction in various surgical settings.²⁴ In the POISE (peri-operative ischaemic evaluation) study, a total of 8351 patients with, or at risk of, atherosclerotic disease who were undergoing non-cardiac surgery were randomised to extended-release metoprolol succinate (n=4174) vs. placebo (n=4177).²⁵ Study treatment had been started 2–4 hours before surgery and continued for 30 days. The primary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest, was more frequently observed in the beta-blocker cohort (5.8%) as compared to the placebo group (6.9%) (HR: 0.84, 95%CI 0.70–0.99; $p=0.0399$). Fewer patients in the metoprolol group experienced myocardial infarction (4.2% vs. 5.7%, HR: 0.73, 95%CI 0.60–0.89; $p=0.0017$). However, both mortality (3.1% vs. 2.3%, HR: 1.33, 95%CI 1.03–1.74; $p=0.0317$) and stroke (1.0% vs. 0.5%, HR: 2.17, 95%CI 1.26–3.74; $p=0.0053$) rates were higher in the metoprolol compared to the placebo group. Of note, the dose of beta blockers administered in the POISE trial was higher as compared to that used in earlier studies.²⁶

Recommendations

CLI patients with arterial hypertension should be treated with antihypertensive medical therapy aimed at lowering cardiovascular mortality. **(Level 1a; Grade B)**

Treatment goals for CLI patients with arterial hypertension: arterial blood pressure should be <140/90 mmHg and <130/80 mmHg in case of concomitant diabetes mellitus or renal insufficiency. **(Level 1a; Grade B)**

ACE inhibitors are recommended in CLI patients. **(Level 2a; Grade B)**

Beta-adrenergic blocking drugs are not contraindicated in CLI patients. **(Level 1a; Grade B)**

Beta-adrenergic blocking drugs may be administered to patients undergoing surgical lower limb revascularisation. **(Level 1a; Grade D)**

4. Diabetes mellitus

Diabetes mellitus is independently associated with PAD and its progression to CLI. Limb salvage rates in diabetic CLI patients have been reported to be lower as compared to those of non-diabetic patients, and diabetes was shown to be an independent risk factor for amputation and complications in CLI patients.

In the STENO-2 study, 160 diabetics were randomly assigned to either intensified or conventional therapy (control of blood glucose, statins, antithrombotic therapy, blood pressure control). After 13.3 years, intensive therapy was associated with a significant reduction of risks of all-cause death (HR: 0.54, 95%CI 0.32–0.89; $p=0.02$, risk reduction: 20%) and cardiovascular death (HR: 0.43, 95%CI 0.19–0.94; $p=0.04$, risk reduction: 13%).²⁷

In the UKPDS study (United Kingdom Prospective Diabetes study), a total of 5000 patients with newly diagnosed diabetes mellitus were randomised to conventional therapy (dietary restrictions as primary treatment approach) vs. intensified therapy (either sulfonylurea or insulin or metformin).²⁸ Although between-group differences in HbA1c levels perished after the first year, intensified therapy was associated with risk reductions for microvascular disease, myocardial infarction and death from any cause as well as for any diabetes-related endpoint.

In contrast to these findings, it has recently been called into doubt if intensive glucose lowering is truly beneficial: In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) trial, a total of 11,140 patients with type 2 diabetes were randomised to undergo either standard glucose control or intensive glucose control to achieve a glycated haemoglobin value of 6.5% or less.²⁹ In that study, rates of microvascular complications, but not macrovascular complications or cardiovascular deaths were improved by intensive diabetes therapy during a follow-up of 5 years.

Moreover, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study randomised participants with type 2 diabetes and cardiovascular disease or additional cardiovascular risk factors to receive intensive therapy (targeting a HbA1c <6.0%) or standard therapy (targeting a level of 7–7.9%).³⁰ The study was prematurely stopped after 3.4 years due to an increased mortality in the intensively treated group, although the rates of non-fatal myocardial infarction and stroke were lower in the intensively treated group by that time. At 5 years, the use of intensive therapy for 3.7 years reduced 5-year non-fatal myocardial infarctions but increased 5-year mortality.

Whether the above-mentioned benefits of thorough diabetes control yield improvements in functional lower limb outcomes such as limb salvage or freedom from repeated revascularisation in CLI patients has yet to be determined.

Recommendation

Blood glucose levels should be monitored in CLI patients with a haemoglobin A1c (HbA1c) goal of <7.0%. (Level 5; Grade D)

5. Antiplatelet therapy

While the clinical utility of antiplatelet therapy for secondary prevention of patients with atherothrombosis is

without controversy, there are currently no convincing data showing a delay or reduction of the progression of lower limb atherothrombotic lesions by antiplatelet therapy. In contrast, studies assessing antiplatelet therapy for primary prevention or peripheral vascular events are scarce and results have been conflicting so far.³¹

The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial demonstrated that the combined risk of death from vascular causes, myocardial infarction, and stroke was significantly, albeit moderately (number-needed-to-treat with clopidogrel in comparison with aspirin: 87 patients) lower with clopidogrel (75 mg/day) compared with aspirin (325 mg/day).³² Of note, the benefits of clopidogrel were most pronounced in the subgroup of PAD patients in that trial.

The Antithrombotic Trialists' Collaboration meta-analysis found a 23% reduction in serious vascular events in 9214 PAD patients within 42 trials.³³ In the primary meta-analysis, however, no significant reduction of cardiovascular events could be demonstrated for PAD patients without further atherothrombotic lesions in other arterial territories. In a subsequent summary including study data on various antiplatelet drugs such as acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole and picotamide, a 23% risk reduction of ischaemic results could be shown for all PAD patients.³⁴ Moreover, since clinically inapparent concomitant coronary heart disease is present in many PAD patients,³⁵ it might be logical to extend the administration of antiplatelet therapy to asymptomatic PAD patients, although various questions related to this issue are still pending.

The precise daily dose for aspirin remains to be determined. Low-dose aspirin (75–325 mg) is as effective as higher doses.³⁶ However, higher doses of aspirin result in increased bleeding rates³⁷ and very low doses (<75 mg) are less effective.³⁶

The daily dose of clopidogrel for secondary prevention of PAD patients is 75 mg. Ticlopidine was assessed within various PAD studies and reduces the risk for myocardial infarction, stroke and vascular death.³⁸ However, its clinical utility is limited by potential side effects such as neutropenia and thrombopenia.

In the absence of other indications for oral anticoagulation, the latter is not indicated in PAD patients. Even more so, it was shown to be associated with higher bleeding rates if added to aspirin, without lowering rates of cardiovascular events.³⁹

Two RCTs analysed whether or not antiplatelet therapy may improve patency rates subsequent to lower limb endovascular therapy. In the first study,⁴⁰ a total of 199 patients undergoing femoropopliteal angioplasty were randomised to dipyridamole (225 mg) combined with 900 mg of aspirin vs. dipyridamole (225 mg) with 300 mg of aspirin vs. placebo. Patients from both dipyridamole arms showed higher patency rates as compared to those on placebo. In the second study,⁴¹ a total of 223 patients after iliac or femoropopliteal angioplasty were randomised to placebo vs. 50 mg of aspirin plus 400 mg of dipyridamole. Primary patency was comparable in both groups. However, a substantial limitation of that study was that a significantly higher number of iliac angioplasties had been included in the placebo arm, which was shown to be associated with lower restenosis rates.

Moreover, the CASPAR study randomised a total of 425 patients undergoing below-the-knee bypass grafting to either aspirin 75–100 mg per day alone or aspirin 75–100 mg per day plus clopidogrel 75 mg per day.⁴² In that trial a combination of clopidogrel plus aspirin did not improve lower limb or systemic outcomes. However, dual antiplatelet therapy was associated with a lower rate of a composite of index-graft occlusion or revascularisation, above-ankle amputation of the affected limb, or death as compared to aspirin alone without increasing bleeding risks.

Four studies analysed whether a high dose (90–1000 mg) of aspirin is more potent in inhibiting reocclusions subsequent to endovascular therapy.^{43–45} Six months post-interventionally, there was no benefit of high-dose aspirin, whereas the rates of gastrointestinal side effects increased with higher doses.

In line with current standards in coronary endovascular revascularisation,⁴⁶ a combination of aspirin with clopidogrel is used subsequent to peripheral arterial stent implantation. However, at present there are no dedicated study data for the peripheral arteries. The CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularisation) study had been started in the USA to evaluate the combined administration of aspirin and clopidogrel in patients undergoing endovascular revascularisation of the femoropopliteal arteries. Due to insufficient numbers of patients randomised, this study was stopped prematurely.

Recommendations

Antiplatelet (aspirin or clopidogrel) therapy is indicated in patients with symptomatic peripheral arterial disease. **(Level 1a; Grade A)**

Both aspirin and clopidogrel reduce rates of cardiovascular events in patients with symptomatic peripheral arterial disease. **(Level 1b; Grade A)**

In line with recommendations for patients with coronary heart disease, an intermittent administration of dual antiplatelet therapy (aspirin plus clopidogrel) may be considered for patients undergoing stent implantation or drug-eluting balloon angioplasty of femoropopliteal or infrapopliteal arteries. **(Level 5; Grade D)**

A combination of clopidogrel and aspirin may be considered as antithrombotic regimen in patients undergoing below-the-knee prosthetic bypass grafting. **(Level 1b; Grade A)**

6. Vasoactive drugs

In patients with CLI not eligible for arterial reconstruction, prostanoids are the only vasoactive drugs with proven efficacy. The currently available data support the use of prostanoids in patients unsuitable for lower limb revascularisation or in patients in whom revascularisation attempts have failed.

Two randomised double-blind studies with prostaglandin E-1 have shown a clinical benefit with regard to the reduction of ulcer size.^{47,48} A further RCT with iloprost showed higher limb salvage and survival rates in the prostanoid group.⁴⁹

Creutzig recently concluded, in a meta-analysis of randomised placebo-controlled trials⁵⁰ including data from 7 studies totalling 643 patients, that for patients with PAD

stage III or IV PGE1 therapy not only has significant beneficial effects over placebo on ulcer healing and pain relief, but also increases the rate of patients surviving with both legs after 6 months follow-up.

A further meta-analysis has shown that a 2- to 4-week treatment with iloprost reduces rest pain and ulcer size.⁵¹ Moreover, iloprost was associated with a higher rate of amputation-free survival at 6 months. It has to be kept in mind, however, that the use of iloprost is not approved in all European countries.

Further vasoactive drugs such as naftidrofuryl, buflomedil or pentoxifylline did not show additional benefit with regard to reduction of amputations and wound healing.^{2,52}

Recommendation

Parenteral prostanoids can be used in patients with critical limb ischaemia not suitable for arterial revascularisation or after unsuccessful revascularisation. **(Level 1b; Grade B)**

7. Gene and stem-cell therapy

The clinical utility of gene and stem-cell therapy is not yet fully understood. While it has been shown that both treatment approaches are well tolerated, a significant clinical benefit has yet to be shown for either method.

Gene therapy has been clinically evaluated since 1994 within at least 6 placebo-controlled randomised clinical phase II studies and within one placebo-controlled phase III study. The four studies assessing gene therapy in CLI patients were positive for various endpoints.^{53–56} However, only amputation and mortality should be considered clinically relevant endpoints in this regard. Only the application of riferminogen pecaplasmid [non-viral gene construct for the fibroblast growth factor 1 (NV1FGF)] was shown to be associated with a reduction of the rate for major amputations and improved amputation-free survival as compared to placebo within the TALISMAN 201 study.⁵⁴ Further positive endpoints of other studies included angiographically verified improvements of arterial vascularisation during follow-up, improvements in transcutaneously measured oxygen partial pressure and further haemodynamic parameters.

Based on positive results from the above-mentioned TALISMAN 201 study,⁵⁴ the currently largest gene therapy trial was initiated including 525 CLI patients without any option for endovascular or surgical revascularisation from 30 countries and 171 hospitals. With 2-week intervals eight injections of a gene construct vs. placebo were applied into thigh and calf of the affected limb. After 12 months, there was no significant difference in amputation-free survival and time to major amputation comparing the NV1FGF with the placebo group.⁵⁷

Since progenitor cells have been identified as a participant in angiogenesis, their role in therapeutic clinical applications has been assessed. The first clinical trial investigating the use of progenitor cells in CLI patients was published in 2002.⁵⁸ Use of bone-marrow-derived mononuclear cells was associated with improvements in ABI, TcPO₂ and pain-free walking time out to 6 months. Subsequent to this trial with a small sample size, this concept was investigated in various non-randomised studies with small sample sizes.⁵⁹ To date, there are no double-blind RCTs assessing the use

of bone-marrow-derived or mobilised mononuclear cells in PAD patients. The scientific community is currently waiting for results of at least 10 randomised controlled cell therapy trials.^{59,60} Until data from these studies are available, the application of stem cells cannot be recommended outside clinical studies.

Recommendation

Neither gene nor stem cell therapy can be recommended as a treatment for CLI outside clinical trials. **(Level 5; Grade D)**

8. Exercise and lower limb rehabilitation

In contrast to patients with intermittent claudication, no data assessing the efficacy of walking exercise in CLI are available. Considering the risk of causing or worsening already present ischaemic wounds, walking exercise is contraindicated in patients with CLI not undergoing revascularisation.

Recommendation

Due to the risk of worsening pre-existing or causing new ischaemic wounds in the affected lower limb, walking exercise may be contraindicated in CLI patients not undergoing revascularisation. **(Level 5; Grade D)**

9. Treatment of co-existing disease

This section covers the management of typical co-existing diseases in patients presenting with CLI and with important impact on morbidity and mortality.

9.1. Coronary artery disease (CAD)

Patients with PAD have a high prevalence of CAD, which strongly increases the risk for cardiac mortality and morbidity.^{61,62} Therefore, all PAD patients should be considered at high risk for clinically significant ischaemic heart disease, for which guidelines exist.^{63,64} Cardiac risk is related to urgency, extent, type and duration of the intervention planned. Patients should be evaluated for evidence of CAD. Treatment decisions for coexisting CAD should be based on current practice guidelines and the intended treatment modality. Patients with unstable symptoms (acute coronary syndrome, congestive heart failure) should be referred to a cardiovascular physician for appropriate diagnosis and treatment. Most patients with severe cardiac symptoms will require coronary angiography to determine the appropriate means for revascularisation. For patients with stable CAD, management should be guided by the severity of the symptoms and comorbid conditions. All patients should be given appropriate medical therapy to treat symptoms and atherosclerotic risk factors. Cardiac assessment scores may be useful in the context of patients being considered for peripheral revascularisation.⁶⁵ In patients with a high cardiac risk assessment score, current guidelines recommend further evaluation of the patient for possible coronary revascularisation.²⁴ However, in the recent Coronary Artery Revascularization Prophylaxis (CARP) trial of patients with peripheral vascular disease who were

considered high risk for peri-operative complications and had significant CAD, coronary revascularisation did not reduce peri-operative myocardial infarction or overall mortality.⁶⁶

Delay to vascular surgery was significantly longer in patients who underwent coronary revascularisation compared to patients who did not, which in CLI patients is often counterproductive. Therefore, the strategy of a pre-emptive coronary revascularisation prior to urgent peripheral vascular surgery should not normally be pursued. In most patients, peri-operative use of beta-adrenergic-blocking agents is associated with reduced cardiovascular risks of surgery. Recent studies have shown that beta-adrenergic blockade with bisoprolol significantly decreases the risk for cardiovascular events during vascular surgery and afterwards.^{67,68} Besides controlling symptoms of myocardial ischaemia, treatment with beta-blocking agents also has the benefit of favourably influencing prognosis in these patients.⁶⁹ Starting beta-adrenergic-blocking treatment shortly before surgery (POISE), however, was not proven to be beneficial in terms of mortality and stroke as outlined above.²⁵

Recommendations

Routine treatment with beta blockers before vascular surgery is recommended. **(Level 1b; Grade B)**

Routine coronary revascularisation before vascular surgery is not recommended. **(Level 1b; Grade B)**

9.2. Carotid artery disease

The prevalence of carotid artery disease in patients with PAD is 10–30%, and there are no specific data for CLI. Since PAD patients are at an increased risk of stroke it might be reasonable to screen those patients for carotid artery disease routinely. Further evaluation and consideration for revascularisation should be based on current guidelines.⁷⁰ One must keep in mind that CLI patients with limited life expectancy will hardly benefit from carotid endarterectomy or stenting for asymptomatic carotid disease.

9.3. Renal artery disease

PAD patients are at an increased risk for renovascular hypertension. The management of patients with atherosclerotic renal artery disease and PAD is focused on preservation of renal function and control of hypertension. Patients with hypertension should be assessed by renovascular ultrasound imaging. In the presence of significant renal artery stenosis treatment should be based on current guidelines.^{2,71–74} These patients should be referred to an appropriate vascular physician. Again, one must keep in mind that CLI patients will hardly benefit from treatment of renal artery stenosis.

10. Health economics of risk-factor interventions

Unlike in PAD patients,² no literature is available on health economics of risk-factor intervention specifically in CLI patients. CLI patients differ importantly from claudicants. CLI patients are suffering from ischaemic lower

limb pain, depression, social isolation and fear of losing their limb. They tend to adhere more to their habits and changing any life style issue can be an important task.

Measuring compliance of chronic patients to risk-factor interventions is difficult since these patients are treated by numerous health professionals at the same time. Health and economic benefits are obviously worse in CLI patients than in primary preventions since life expectancy in CLI patients is significantly reduced. An additional difficulty is that health and economic benefits are delayed while resources for treatment have to be expended at once. Moreover, given that numerous interventions are performed by means of a variety of drugs, costs differ importantly between health-economic systems in different countries. Costs in health economics can be expressed as average costs for 1 year of life gained.

10.1. Cost-effectiveness of smoking cessation interventions

No publications are available for CLI patients. Although there is good evidence for smoking cessation in peripheral artery disease, cessation programmes might not be successful in CLI patients. Training and group counseling sessions may not be followed in normal range. Antidepressant therapy (bupropion) and nicotine replacement could therefore still be considered by the treating physician.⁵

10.2. Cost-effectiveness of pharmacologic interventions

Studies on diabetes, dyslipidaemia and hypertension have shown for primary intervention that compliance with guidelines is usually cost effective with a range of \$20,000 to \$30,000 per year of life gained.^{75,76} Statin drug costs represented between 45% and 68% of the overall primary preventive cost of coronary heart disease.⁷⁷ The specific costs differ depending on the guidelines used. Studies on cost-effectiveness in CLI patients are currently lacking. Considering that CLI patients would benefit from the same medication as claudicants, i.e. treatment by a combination of aspirin, a statin, a beta blocker and a diuretic,⁷⁸ the costs per additional quality-adjusted life year (QALY) would be £20,000 to £40,000. On top of that in CLI patients pain-relief medication, antibiotics, ACE inhibitors and more should be added.

Recently the term "cost per major event averted" has been created since studies have failed to show a benefit on mortality. For example, the cost effectiveness of 40 mg/day simvastatin in high-risk patients is £4500 (95% CI £2300–7400) per major vascular event averted, but the result is highly dependent on the cost of statin.⁷⁹

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None

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Chapter IV: Treatment of Critical Limb Ischaemia

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Abstract Recommendations stated in the TASC II guidelines for the treatment of peripheral arterial disease (PAD) regard a heterogeneous group of patients ranging from claudicants to critical limb ischaemia (CLI) patients. However, specific considerations apply to CLI patients. An important problem regarding the majority of currently available literature that reports on revascularisation strategies for PAD is that it does not focus on CLI patients specifically and studies them as a minor part of the complete cohort. Besides the lack of data on CLI patients, studies use a variety of endpoints, and even similar endpoints are often differentially defined. These considerations result in the fact that most recommendations in this guideline are not of the highest recommendation grade.

In the present chapter the treatment of CLI is not based on the TASC II classification of atherosclerotic lesions, since definitions of atherosclerotic lesions are changing along the fast development of endovascular techniques, and inter-individual differences in interpretation of the TASC classification are problematic. Therefore we propose a classification merely based on vascular area of the atherosclerotic disease and the lesion length, which is less complex and eases the interpretation.

Lesions and their treatment are discussed from the aorta downwards to the infrapopliteal region. For a subset of lesions, surgical revascularisation is still the gold standard, such as in extensive aorto-iliac lesions, lesions of the common femoral artery and long lesions

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of the superficial femoral artery (>15 cm), especially when an applicable venous conduit is present, because of higher patency and limb salvage rates, even though the risk of complications is sometimes higher than for endovascular strategies.

It is however more and more accepted that an endovascular first strategy is adapted in most iliac, superficial femoral, and in some infrapopliteal lesions. The newer endovascular techniques, i.e. drug-eluting stents and balloons, show promising results especially in infrapopliteal lesions. However, most of these results should still be confirmed in large RCTs focusing on CLI patients.

At some point when there is no possibility of an endovascular nor a surgical procedure, some alternative non-reconstructive options have been proposed such as lumbar sympathectomy and spinal cord stimulation. But their effectiveness is limited especially when assessing the results on objective criteria. The additional value of cell-based therapies has still to be proven from large RCTs and should therefore still be confined to a research setting.

Altogether this chapter summarises the best available evidence for the treatment of CLI, which is, from multiple perspectives, completely different from claudication. The latter also stresses the importance of well-designed RCTs focusing on CLI patients reporting standardised endpoints, both clinical as well as procedural.

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1. Introduction

Recommendations stated in the TASC II guidelines for the treatment of peripheral arterial disease (PAD) regard a heterogeneous group of patients ranging from claudicants to critical limb ischaemia (CLI) patients. However, specific considerations apply to CLI patients. CLI is characterised by multi-level disease, high burden of comorbidity and limited life span. Thus decision-making in revascularisation strategies in CLI differs substantially from that in patients with claudication as wound healing, limb salvage and maintained ambulation are different treatment aims than improved walking ability and there are often considerable time constraints. Long-term patency as such is probably of less importance. The choice of endovascular treatment may be supported by presence of major comorbidities and hence high risk for open interventions.

A minority of studies specifically addresses CLI, precluding optimal decision for this specific group of patients. Moreover, different outcome measures are reported in the scarce studies that specifically focus on CLI patients. Some studies address the success of the primary intervention, exemplified by primary patency rates, while others emphasise the clinical results, such as limb salvage rates. The former is of major importance to evaluate the success of the intervention *per se* and the latter seems to be more important from a patient's perspective. So, in our opinion both should be reported in clinical studies and in a more standardised fashion as well.¹ An important problem related to the use of limb salvage as a measure of treatment success is that it is a composite endpoint affected by a variety of factors besides the revascularisation procedure *per se*. Therefore it is a valid endpoint only in randomised controlled trials. From a larger perspective, amputation-free survival has been suggested to be the most important endpoint for therapeutic studies on CLI.²

Most publications so far have been case series, cohort studies or case-control studies. The availability of well-conducted randomised controlled trials in this field is limited and therefore most recommendations in these guidelines are based on a low level of evidence. This underlines the need for future research that specifically addresses CLI

in a prospective randomised-controlled fashion with well-circumscribed standardised reported outcomes.

2. Aorto-iliac revascularisation

Aorto-iliac arterial occlusive disease (AIOD) may lead to CLI, especially if concomitant atherosclerotic disease of infra-inguinal and/or below-the-knee (BTK) arteries is present.

Surgical repair with aorto(bi)femoral bypass grafting or aorto-iliac endarterectomy has proven effective in alleviating ischaemic pain and providing good long-term patency. Aorto(bi)femoral bypass is the most efficient procedure in case of diffuse aorto-iliac disease but carries substantial risk of peri-operative mortality, morbidity and delay in return to normal activities.

An alternative approach is represented by endovascular techniques that include angioplasty, stents, stent-grafts, and plaque debulking, which offer both good clinical and procedural results and have lower procedure-related morbidity and mortality.

There are no RCTs directly comparing surgical vs. endovascular treatment of AIOD. As a result, the selection of the optimal approach for a patient with aorto-iliac occlusive disease should be based on several variables, including an assessment of the patient's general condition and extension of the disease.

2.1. Surgical treatment of AIOD

Anatomical open surgical arterial reconstructions for treatment of AIOD are: aortofemoral bypass (AFB), iliofemoral bypass (IFB), aorto-iliac endarterectomy (AIE). In rare cases a further alternative is an extra-anatomic reconstruction by descending thoracic aortofemoral bypass (DTAF).

Aorto(bi)femoral bypass is generally the preferred treatment for diffuse aorto-iliac disease in patients who are acceptable surgical candidates. Proximal anastomosis is generally performed in an end-to-end or end-to-side fashion at the level of the infrarenal aorta, without important differences between the two techniques.³ The simplest procedure that maintains adequate pelvic and colonic blood supply, according to angiographic findings, should be selected. The use of knitted gelatine-coated

polyester, knitted collagen-coated polyester or stretch polytetrafluoroethylene (PTFE) has been reported with comparable results in terms of primary and secondary patency and long-term complication rates.⁴⁻⁶ A MEDLINE (1970–2007) and Cochrane Library search for articles that report results of different open-surgical approaches for arterial reconstruction for AIOD was recently published. Studies reporting long-term primary patency data following open anatomical repair of AIOD were included, for a total of 5738 patients treated by AFB, 778 by IFB and 1490 by AIE.⁷ The operative mortality rate for AFB, IFB and AIE was 4.1%, 2.7% and 2.7%, respectively ($p < 0.0001$), while the systemic morbidity rate was 16% for AFB, 18.9% for IFB and 12.5% for AIE ($p < 0.0001$). In a sub-analysis according to clinical presentation, the 5-year primary patency in case of CLI was 79.8%, 74.1% and 81.7% for AFB, IFB and AIE, respectively ($p = 0.06$), significantly worse in comparison to 5-year patency rates for patients with intermittent claudication ($p < 0.0001$).

All three anatomical techniques for open-surgical aorto-iliac reconstructions were equally effective in terms of primary patency rates, but AIE appears to be associated with significantly lower operative mortality and systemic and local complication rates compared to the two bypass procedures. This can probably be explained by the fact that AIE is utilised predominantly for localised aorto-iliac disease and AFB and IFB may be used for more extensive disease.

DTAF is predominantly reserved for patients in whom the aforementioned reconstructions are unsuitable and is associated with higher operative mortality and graft-related complication rates and lower 5-year patency rates than the other three techniques.⁷⁻⁹

Recommendations

Aorto(bi)femoral bypass is generally the preferred treatment for diffuse aorto-iliac disease in patients who are suitable surgical candidates. **(Level 2a; Grade B)**

Aorto-iliac endarterectomy is to be recommended for patients with suitable occlusive lesions as it appears to be associated with significantly lower operative mortality and systemic and local complication rates compared with bypass procedures. **(Level 4; Grade C)**

Descending thoracic aortofemoral bypass is to be reserved for patients that cannot be otherwise revascularised as it is associated with higher operative mortality and graft-related complication rates and lower patency rates. **(Level 5; Grade D)**

2.2. Laparoscopic repair

A variety of different techniques are encompassed in the term laparoscopic AIOD repair, including totally-laparoscopic repair, hand-assisted laparoscopic repair and robotic-assisted laparoscopic repair. These are considered together for the purposes of these guidelines. Laparoscopic repair offers patients a third option for AIOD repair that provides the durability of an "open" sutured graft with a rapid recovery and reduced length of hospital stay.^{10,11}

Currently, the role of laparoscopic repair remains limited and should be confined to centres with specific expertise in laparoscopic aortic repair. This is in part due to the requirements for advanced laparoscopic practice, and also

due to the steep learning curve for this procedure. It should be noted that the cardiac risk of laparoscopic procedures should be considered to be the same as for open repair.¹² Procedures should initially only be conducted under supervision by someone experienced in laparoscopic aortic repair. Facilities to deal with emergency surgical conversion should be available at all times.

Recommendation

The role of laparoscopic repair of AIOD remains limited, but in selected patients it might represent a third option for aorto-iliac atherosclerotic disease repair. **(Level 5; Grade D)**

2.3. Extra-anatomical bypass

Extra-anatomical arterial reconstructions such as axillo-(bi)femoral bypass and crossover femoral bypass are generally reserved for patients with increased comorbidities or a hostile abdomen. For isolated unilateral iliac artery occlusive disease, for which endovascular angioplasty failed or does not seem feasible, a crossover femoro-femoral bypass can be considered as effective as an aorto-femoral or iliofemoral bypass, but with less operative morbidity. Extra-anatomical repair also allows to preserve the autonomic nerve fibres at the aortic bifurcation and has less influence on sexual function.

Recommendation

Because of the relatively low patency rates, extra-anatomical bypass should be reserved for patients who have no other alternatives for revascularisation. **(Level 4; Grade C)**

2.4. Endovascular treatment of aorto-iliac occlusive disease

There are no RCTs directly comparing surgical vs. endovascular treatment of AIOD, and therefore there is a lack of objective grounds on which the choice between the two techniques can be made.

In clinical practice, because of its minimal invasiveness, many clinicians consider endovascular therapy to be the first-line strategy, feasible and effective for the treatment of the majority of aorto-iliac atherosclerotic lesions. The technical success rate of angioplasty of iliac stenosis is nearly 100%, and the technique is also used to treat long-segment iliac occlusion. Unfortunately, CLI is seldom caused by limited aorto-iliac lesions but rather occlusive disease affecting multiple arterial segments. If focal lesions are identified, they mostly cause an inflow problem above infrainguinal occlusions in these patients.

2.4.1. Endovascular treatment of extensive aorto-iliac occlusive disease

A recent systematic review performed by Jongkind et al.¹³ identified 19 non-randomised cohort studies reporting on 1711 patients with extensive AIOD. Although the lesions treated were described adequately, unfortunately no data on the indication were included. Technical success was achieved in 86–100% of the patients with extensive AIOD, defined as less than 30% residual diameter stenosis and/or

a residual trans-lesion pressure gradient of less than 10 mmHg. Clinical symptom improvement was observed in 83–100% of the patients, and mortality ranged from 1.2% to 6.7%. Although a number of procedural or peri-operative complications were reported, including distal embolisation, access-site haematomas, pseudoaneurysms, arterial ruptures, and arterial dissections, the majority could be treated using percutaneous or non-invasive techniques. Four- and 5-year primary and secondary patency after endovascular treatment of these extensive aorto-iliac lesions ranged from 60% to 86% and 80% to 98%, respectively.

In two studies retrospectively comparing endovascular therapy vs. open-surgical reconstruction for extensive AIOD, a significantly lower long-term primary patency was reported for endovascular therapy (69% vs. 93%, $p=0.013^{14}$ and 74% vs. 93%, $p=0.002^{15}$), while secondary patency did not differ significantly (89% vs. 100% and 96% vs. 96%). The applicability of these data on treatment decisions for CLI is affected by the low proportion of patients with CLI in these studies, 21%¹⁴ and 40%.¹⁵

Recommendations

Endovascular treatment can be considered a successful primary strategy for patients with aorto-iliac lesions, most often before or in conjunction with a distal revascularisation. Its major advantage is its less invasiveness, characterised by a lower operative morbidity-mortality. **(Level 3a; Grade C)**

Even though primary patency rates after endovascular therapy for extensive AIOD are inferior to those reported after surgery, re-interventions may be performed percutaneously. **(Level 5; Grade D)**

2.4.2. Plain balloon angioplasty vs. primary stenting

Although primary stenting has been proposed as more effective than plain balloon angioplasty for iliac atherosclerotic lesions, the evidence described in the literature does not allow clear conclusions.

The only RCT comparing the technical results and clinical outcomes of two treatment strategies (primary stenting or PTA followed by selective stenting when haemodynamic results were inadequate) concluded that patients treated with PTA and selective stent placement in the iliac artery had a better outcome for symptomatic success compared with patients treated with primary stent placement, whereas data about iliac patency, ABI, and quality of life did not support a difference between groups.¹⁶ Notably, the trial was performed in a cohort of patients with lifestyle-limiting intermittent claudication.

Nonetheless, primary stenting is now preferred in most studies for extensive aorto-iliac lesions, considering the fact that primary stenting without pre-dilatation is considered to involve less risk of causing vessel rupture and/or distal embolisation.

Recommendation

Angioplasty followed by selective stenting for PTA with inadequate result should be preferred for iliac artery occlusive disease. **(Level 2; Grade B)**

3. Infrainguinal disease

3.1. Common femoral artery (CFA)

Surgical endarterectomy of CFA lesions (CFE), isolated or within a hybrid setting, provides excellent 1- and 5-year patency rates of 93% and 91%, respectively, and secondary patency rates reaching 100%.^{17,18} Ballotta et al. confirmed the excellent long-term patency of CFE with a patch in a cohort of 117 patients (40% CLI) with 7-year primary patency rates of 96%, assisted primary patency of 100%, and 100% limb salvage.¹⁹ An advantage of surgical treatment of atherosclerotic disease of the CFA is that it provides the potential to endarterectomise adjacent diseased segments of the deep femoral artery (DFA) and the proximal superficial femoral artery (SFA) or the opportunity for hybrid iliac or SFA recanalisation. It should be noted, however, that CFE *per se* can also worsen pathology of the SFA.

There are reports on treating CFA lesions with endovascular techniques as well, although with variable results.^{20–24} In particular the early reports on angioplasty of the CFA without stenting have been associated with relatively poor results.²⁵ However, technical success rates of 100% of CFA angioplasty with primary stenting have been reported with acceptable mid-term outcome.²⁶ However, placing a stent in the CFA may increase risk of potential future surgical interventions and limit future access for endovascular revascularisation in this location. CFA stenting is likely to be an alternative for special indications and therefore RCTs comparing it with endarterectomy are hardly possible. It is further characterised by an increased risk of stent-strut fracture in this mobile segment of the arterial tree, due to repetitive hip flexion–extension and compression by the inguinal ligament.

Recommendation

Endarterectomy of atherosclerotic disease of the common femoral artery provides excellent results with limited morbidity and mortality and is the standard treatment in this location. **(Level 4; Grade C)**

3.1.1. Hybrid procedures

Concomitant disease of the external iliac artery (EIA), DFA or SFA is commonplace in CLI. In patients in whom CFE is to be performed, the direct access via the CFA can offer the opportunity to simultaneously perform endovascular treatment of the adjacent diseased EIA or SFA. These hybrid procedures have been performed with promising results and acceptable patency rates.¹⁸ Hybrid procedures of the aorto-iliac segment will be discussed here and the infrainguinal hybrid procedures will be discussed in section 3.3 on treatment of the SFA.

Aorto-iliac hybrid procedures often combine CFA surgery or infrainguinal femoropopliteal bypass surgery with aorto-iliac recanalisation, where the surgical part provides the access for the endovascular reconstruction of the diseased aorto-iliac segment. Initial technical success rates of hybrid aorto-iliac intervention generally approach 100% and peri-operative mortality rates are low.^{27–29} Reported primary patency rates after hybrid procedures for aorto-iliac occlusive disease are probably somewhat lower than for sole endovascular interventions of the aorto-iliac segment,^{29,30} with 5-year primary patency rates of 60% for hybrid

procedures²⁹ and 4-year primary patency rates of 68% (65–71%) and 77% (72–81%) for PTA and PTA with stenting, respectively.³¹ Chang et al. showed improved patency rates for stent grafts compared to bare-metal stents.²⁹ A recent report by Dosluoglu and co-workers³² reports similar results of open, endovascular and hybrid techniques for patients with similar disease complexity and even better limb salvage rates in CLI patients with complex hybrid revascularisations (TASC C or D).

Recommendations

Endovascular treatment of aorto-iliac occlusive disease in a hybrid fashion offers an acceptable alternative treatment in patients with aorto-iliac disease and concomitant common femoral artery disease that requires open surgery. **(Level 3b; Grade C)**

Stent grafts probably provide better results compared to bare-metal stents in the hybrid treatment of aorto-iliac occlusive disease. This should however be confirmed by future prospective studies. **(Level 4; Grade C)**

3.2. Deep femoral artery (DFA)

Profundoplasty is of limited value in the treatment of CLI, but can be considered in patients with stenotic lesions of the DFA and where restoration of continuous blood flow from the aorto-iliac tract to the SFA or popliteal artery is not an option. Limb salvage rates of profundoplasty have been reported to be 67% after 1 year³³ and 49% and 36% after 3 and 5 years, respectively.^{34–37} Profundoplasty is rarely performed as an isolated procedure and can be performed with or without a patch based on the intra-operative judgment by the surgeon. Besides its role for potential limb salvage profundoplasty can be of value in preserving the knee joint when amputation is deemed inevitable.³⁴

Studies on endovascular treatment of DFA obstructive disease have been mainly confined to relatively small case series, and long-term limb salvage rates are usually not reported.^{38–43} Initial technical success rates of percutaneous DFA recanalisation range from 77% to 100%,⁴⁴ but long-term results seem less favourable.^{24,43} However, more promising results of endovascular treatment of the DFA were published recently by Donas et al. in a selected group of patients (n=15) with CLI with sufficient run-off vessels, in which 3-year primary and secondary patency rates were 80% and 86.7%, respectively, and limb salvage was 93%.⁴⁵ Stenting of the DFA has also been reported,²⁶ but stenting the DFA likely hampers potential future surgical interventions in this area.

Recommendations

Revascularisation of the deep femoral artery can be considered in CLI patients without options for restoration of continuous blood flow from the aorto-iliac segment to the popliteal artery in conjunction with haemodynamically significant stenosis of the DFA. Based on currently available evidence, surgical profundoplasty is preferred over endovascular recanalisation, due to a relatively high rate of late failures of the latter. **(Level 3b; Grade C)**

Profundoplasty can be of additional value in preserving the knee joint when amputation is inevitable. **(Level 4; Grade C)**

3.3. Superficial femoral artery (SFA)

In the present guideline, lesions of the SFA are not classified according to the TASC II guidelines,⁴⁶ though these are generally regarded as the standard method of classification in treating peripheral arterial disease. The definitions of atherosclerotic lesions are changing with the rapid development of mainly endovascular techniques and devices (TASC I vs. TASC II). Furthermore, the use of the TASC classification may be problematic due to considerable inter-individual differences in interpretation.^{47–49} However, since the widespread use of the TASC classification system in the past decades most studies used this method to classify lesions under investigation. Therefore the TASC classification is still mentioned repeatedly in this guideline, but is eliminated from the treatment recommendations. For future use in research and for treatment recommendations we propose a classification system based on lesion length instead of complex loco-anatomic descriptions of lesions as provided by the TASC classification.

3.3.1. Endovascular treatment

Endovascular treatment is increasingly considered as the first-line treatment for atherosclerotic lesions of the femoropopliteal segment. Yet, the success rate of endovascular treatment of femoropopliteal lesions depends on variables such as the presence of diabetes mellitus or chronic kidney disease, stenosis vs. occlusion, lesion length and crural run-off status,⁵⁰ factors which are often unfavourable in patients with CLI.^{51,52} Despite excellent initial technical and clinical success rates of PTA of femoropopliteal artery stenoses in series studying the full range of peripheral arterial disease – most including less than 15% CLI patients – the data for CLI are far worse. This was illustrated by a meta-analysis of Muradin et al.,⁵³ which showed clearly inferior 3-year primary patency rates after recanalisation of SFA occlusions in CLI patients compared to claudicants.

Technical failure of angioplasty due to dissection or recoil has been largely reduced with the introduction of the bare metal stents,⁵⁴ but restenosis has remained a major problem precluding long-term benefit of stenting. Yet, a meta-analysis reported a 3-year patency rate of 58–68% in CLI patients.⁵³

The self-expanding nitinol stents have further improved endovascular treatment of the SFA and provide more durable results than stainless steel (balloon-expandable) stents.^{55–60} Despite the fact that these studies mainly included claudicants (proportion of CLI patients 14–89%), results of self-expanding nitinol stenting seem beneficial in CLI patients as well. Primary nitinol stenting proved beneficial compared to PTA with provisional stenting especially for longer SFA lesions (average lesion length varying from 9.8 ± 5.4 cm to 20.35 ± 9.46 cm).^{61–65} Limb salvage rates 36 months after stenting of the SFA in CLI patients have been reported to be 67–75%.^{66,67} For lesions <5.0 cm in length the benefit of primary stenting is clearly more debatable as has been shown in a meta-analysis by Kasapis and colleagues,⁶⁸ who showed no differences in restenosis rate and target vessel recanalisation, despite a higher immediate success rate for stenting compared to angioplasty alone.

Different studies have been published supporting endovascular treatment of long femoropopliteal (TASC C and D)

lesions with or without stenting. Han and co-workers published their results of endovascular treatment stratified by TASC lesion type and showed that in 243 CLI patients limb salvage rates 24 months after endovascular treatment were $81.0 \pm 12.9\%$, $81.1 \pm 6.8\%$, and $71.9 \pm 8.0\%$ for TASC A+B, TASC C and TASC D lesions of the SFA, respectively.⁶⁹ Similar limb salvage rates were obtained by Taneja and co-workers in CLI patients with long-segment occlusions (average 23.8 cm, range 10–39 cm) treated with bare nitinol stents, however primary patency rates were rather low with 61.5% and 27% after 6 and 12 months, respectively.⁷⁰ These studies suggest that endovascular treatment of long femoropopliteal lesions can be – at least clinically – successful.

The high restenosis rates of bare nitinol stents observed mainly in long atherosclerotic lesions of the SFA and the popliteal region provide the fertile soil for further technical innovations aiming at increasing patency rates. An important and promising innovation has been the stent graft (also referred to as covered stent, endograft, endoluminal bypass or thrupass). Most stent grafts are composed of nitinol stents covered with polytetrafluoroethylene (PTFE) and were developed to prevent restenosis due to intimal hyperplasia. Primary patency rates after 1 year for lesions <10 cm treated with PTFE stent grafts have been reported to be approximately 90% in CLI.^{71,72} However, lower and considerably varying 1-year patency rates have been recorded for longer lesions of the SFA treated with PTFE stent grafts, ranging from approximately 48% to 81%,^{73–78} and generally lower patency rates are observed in CLI patients and occlusive lesions. Despite a 69% primary patency rate at 3 years, Alimi et al. reported a 86% limb salvage rate in CLI patients treated with the PTFE stent graft for lesions with a mean length of 12.4 cm (range 2.6–30.2 cm).⁷⁶

Studies directly comparing stent grafts with plain PTA or PTA with bare stents are very limited. Saxon et al. compared stent grafts ($n=97$, 9% CLI) with PTA alone ($n=100$, 12% CLI) in a randomised fashion for treatment of SFA lesions (stenosis or occlusions) up to 13 cm. In the stent graft group a higher technical success rate and 1-year primary patency rate of 65% vs. 40% ($p=0.0003$) was observed.⁷⁹ The preliminary results of the VIBRANT trial that compares angioplasty of long SFA lesions with either the PTFE stent graft or bare nitinol stenting do not show any differences regarding primary patency at 1-year follow-up; however, secondary patency at 1 year was somewhat higher in the stent graft group. The official mid-term (3 years) follow-up results are not yet available but could prove superiority of one of both treatment modalities. An FDA-approved heparin-bonded version of the stent graft has been developed to improve patency rates. Future randomised trials still have to prove the efficacy and superiority of (heparin-bonded) stent grafts over bare nitinol stents.

There is one major concern of using covered stents, namely the potential loss of pre-existent collateral vessels with acute deterioration in case the stent graft occludes; however, this hypothesis is not yet confirmed by evidence.⁸⁰

Another proposed strategy to prevent intimal hyperplasia is represented by drug-eluting stents (DES). The first piloting trials (SIROCCO I & II) comparing sirolimus-coated stents with bare nitinol stents in the SFA failed to show important and significant differences between the two treatment

groups.^{81,82} Currently there are two trials, which have not yet published their results, that study the paclitaxel-coated Zilver pTX stent (Cook Medical, Bloomington, Indiana, USA) and the everolimus-eluting Dynalink-E (Abbott Vascular, Abbott Park, Illinois, USA), the Zilver pTX trial and the Strides study, respectively. In the Zilver pTX trial patients with moderate to severe symptomatic femoropopliteal artery disease (lesions up to 14 cm; average lesion length 6.6 cm) were randomised to undergo either traditional PTA or PTA plus Zilver pTX stent deployment ($n=479$). In the PTA group non-optimal ($>30\%$ residual stenosis or >5 mmHg pressure gradient) PTAs were again randomised to either subsequent deployment of a bare Zilver stent or the pTX version of the stent. The preliminary short-term results of the Zilver pTX trial are promising, with 12-month patency rates in the provisional stent group (after suboptimal PTA) of 89.9% and 73% for the Zilver pTX and bare Zilver stent, respectively ($p=0.01$). These results seem to be consistent and are confirmed by the 2-year follow-up data, where primary patency rates in the provisional stent group are 81.2% ($n=56$) and 62.7% ($n=56$) for the Zilver pTX and the bare-metal Zilver stent, respectively. On the other hand the Strides study ($n=106$; mean lesion length 9.0 ± 4.3 cm; 17% CLI patients) did not show any benefit of the everolimus-eluting Dynalink-E stent compared to historical controls treated with a similar non-everolimus-eluting stent, both showing a primary patency of between 60% and 70% at 12 months, despite a promising $94 \pm 2.3\%$ primary patency rate of the former.⁸³

Since long complex lesions are usually present in CLI patients, successful endovascular recanalisation of the SFA can sometimes only be performed with subintimal angioplasty (SIA). SIA has been associated with high limb salvage rates between 85% and 90% at 1 year, even despite a low 50% 1-year primary patency rate.⁸⁴ These results were recently confirmed by Bolia et al. and Setacci et al. with primary success rates of 80% and 83.5% and limb salvage rates of 85% and 88% at 1 year, respectively.^{85,86}

A major concern of the popularity of endovascular interventions, especially in complex lesions, is the potential alteration of the level for subsequent open procedures after failed endovascular intervention. Joels et al. have reported that the problem of alteration of the level of a subsequent open procedure after failed endovascular intervention is acceptable and even when the level alters it does not necessarily change clinical outcome.⁸⁷ They showed that only 23 out of the 276 patients subjected to endovascular recanalisation of the SFA presented with early failure of the procedure and that this altered the level of the subsequent open intervention in one third of the patients. Amputation due to early failure was necessary in only one patient (0.4%). However, they did not include TASC D lesions. In another study, by Gur et al.,⁸⁸ of the 192 patients who underwent PTA with primary stenting of the SFA, 69 stented arteries lost primary patency (over a 5-year period). In 10 patients open bypass was eventually required and the bypass level was changed in two of them. The risk of stent failure, loss of run-off vessels and necessity for open procedures was higher in the TASC C and D lesions. The fact that CLI patients are amenable to subsequent intervention (both open and endovascular) for limb salvage even after failed endovascular intervention is further supported by Ryer and colleagues.⁸⁹

3.3.2. Surgery

Bypass surgery has long been and still is the gold standard therapy in the treatment of long SFA lesions. The great saphenous vein is the best performing conduit for infra-inguinal bypass surgery. Above-the-knee femoropopliteal bypass has a patency rate of 77.2% at 5 years in claudicants and 69.4% in CLI patients, when saphenous vein is used as a conduit. Autologous great saphenous vein bypass below the knee has similar long-term patency rates compared to above the knee bypass.⁹⁰ Limb salvage rates of 86.9% ($\pm 7.6\%$) 2 years after non-reversed vein grafts in above-the-knee femoropopliteal bypasses have been reported for CLI.⁹¹ Venous conduits outperform prosthetic conduits irrespective of the material used (Dacron or PTFE). This also applies for arm vein conduits compared to prosthetic bypasses in CLI patients.⁹²

The BASIL trial is the only randomised trial comparing a PTA-first vs. a bypass surgery-first strategy in patients with severe limb ischaemia; it showed no differences in amputation-free survival between bypass surgery and PTA. However, for patients with a more than 2-year survival after the initial intervention, patients randomised to bypass surgery showed higher overall and amputation-free survival.^{93–95} The superiority of femoropopliteal bypass procedures compared to femoropopliteal PTA in CLI patients, especially in the long-term, is supported by a retrospective study by Korhonen et al. which used a propensity score analysis to minimise bias.⁹⁶ They showed considerable differences in favour of the bypass group (80.5% vein and 19.5% prosthetic graft) with 5-year limb salvage rates of 78.2% vs. 91.8% and survival rates of 49.2% vs. 57.1% for the PTA and bypass group, respectively. These results were still significant in the propensity score-matched pairs, with 5-year limb salvage rates of 74.3% vs. 88.2% ($p=0.031$) for the PTA vs. the bypass group, respectively.

Bypass surgery has also been randomly compared with stent graft procedures. Kedora et al.⁷⁵ reported on 100 patients with SFA occlusive disease and symptoms ranging from claudication to rest pain, with or without tissue loss, who were randomised to PTA with one or more self-expandable stent grafts ($n=50$) or prosthetic femoropopliteal above-the-knee bypass ($n=50$). The mean total length of artery stented was 25.6 ± 15 cm. Both 1-year primary and 1-year secondary patency rates – based on life-table analysis – were not significantly different between the two groups, with primary patency rates of 73.5% vs. 74.2% and secondary patency rates of 83.9% vs. 83.7% for the stent graft and bypass group, respectively. Neither did limb salvage between the two groups differ significantly. Severity of limb ischaemia (Rutherford classification) did not differ between the two groups; however, ischaemia showed a non-significant tendency to be more severe in the bypass group.⁷⁵ Later results from the same patient group showed a trend to lower patency rates for the stent graft group in the higher TASC II lesions (TASC C and D).⁷⁸ Less favourable results for stent graft procedures were reported by Lepäntalo and co-workers in a prematurely terminated (due to disadvantageous outcome in the stent graft group) randomised multicentre trial comparing stent graft procedures and prosthetic bypass surgery for occlusions (TASC II B and C occlusions) of the SFA.⁷³ In contrast to the two other studies, which

mainly included patients with intermittent claudication and did not clearly reveal data on concealment of treatment allocation, Lepäntalo et al. only included CLI patients based on rigorous inclusion criteria and properly reported concealment. They reported substantial lower primary and secondary 1-year patency rates for the stent graft group vs. the bypass group, 46% vs. 84% and 63% vs. 100%, respectively. Overall the results of these studies still favour the use of femoropopliteal bypass vs. stent graft procedures in CLI patients with long SFA lesions, especially long occlusions. Future RCTs comparing these treatment modalities (and the heparin-bonded endograft) in specific subgroups of CLI patients are necessary to allow definitive conclusions on these therapies.

3.3.3. Hybrid procedures

Hybrid procedures combining CFA surgery or distal origin bypass surgery with angioplasty of the SFA is another possibility to treat lesions of the SFA. Hybrid procedures studied are highly heterogeneous, therefore no exact numbers can be provided on patency rates and limb salvage rates. Patency rates after hybrid procedures vary considerably, with 3-year primary patency rates as high as 84% and primary patency rates as low as 58% after 41 months follow-up.^{32,97,98} However, reported limb salvage rates 3 years after the intervention are over 80%.^{32,97,99}

In a hybrid procedure it is also possible to perform remote superficial femoral artery endarterectomy (RSFAE). Patency rates of retrospective studies are promising so far, with patency rates of 61–69% at 18–33 months.¹⁰⁰ In the REVAS trial, RSFAE compared with above-knee bypass surgery has been studied for the treatment of TASC C and D lesions of the SFA. Primary patency rates after 1 year were 61% for RSFAE and 73% for bypass surgery, with similar secondary patency rates of 79%.¹⁰¹

3.3.4. Drug-eluting balloon, cryoplasty, cutting balloon, excimer laser

Drug-eluting balloons, successfully applied for angioplasty of coronary arteries, have not been widely studied in the femoropopliteal arteries. The available short-term data on the use of drug-eluting balloons for PTA of the femoropopliteal region are encouraging, however these studies have mainly focused on relatively short lesions and almost invariably address claudicants.^{102,103} Longer-term follow-up and larger randomised trials are needed to clarify whether drug-eluting balloons can be beneficial in the long term and should include sufficient numbers of CLI patients to draw reasonable conclusions in this subset of patients.

No data exist on the direct comparison of cryoplasty, cutting balloons and excimer laser with conventional endovascular treatment in patients with CLI. Cryoplasty seems not beneficial in the femoropopliteal area.^{104,105} Cutting balloons have a short design thereby limiting their use in long lesions of the SFA. Use of the excimer laser has been shown to be effective in CLI,^{106,107} however there is no evidence of superiority compared to conventional angioplasty or subintimal angioplasty in CLI.

Recommendations

A new and simplified classification system for peripheral arterial disease lesions is needed to improve inter-individual interpretation as this is problematic for the TASC classification. Therefore we would recommend a system based on lesion length to classify lesions for research applications and clinical management (EUSC classification; Fig. 1). Future research should prove the applicability and reproducibility of the classification and the additional value of a potential subdivision of stenotic vs. occlusive lesions. **(Level 5; Grade D)**

Short SFA lesions (<5cm) are preferably treated with angioplasty. Stenting of short lesions should only be performed when suboptimal results are obtained with PTA alone. **(Level 1a; Grade B)**

The preferred treatment of intermediate SFA lesions (5–15cm) is PTA with primary bare nitinol stenting. **(Level 1b; Grade B)**

The additional value of drug-eluting and PTFE stent grafts still has to be confirmed in CLI patients.

When autologous vein is available as a conduit, bypass surgery is the preferred treatment for long SFA lesions (>15cm), especially in younger patients. Although the outcome after an endovascular first approach is equal in the short term to prosthetic bypass surgery for long SFA lesions in CLI patients, bypass gives better results in more fit patients and should be preferred in patients with estimated longevity >2 years. **(Level 1b; Grade B)**

In long SFA lesions (>15 cm) endovascular treatment (intraluminal or subintimal) with a stent graft seems acceptable when the patient's condition precludes an open procedure. The value of the heparin-bonded stent-graft has still to be confirmed. **(Level 3b; Grade C)**

Hybrid procedures are the preferred treatment modality irrespective of lesion length in high-risk patients not suitable for open bypass surgery or when no suitable vein is available if minimally open revascularisation is mandated, such as CFE. **(Level 2b; Grade B)**

4. Infrapopliteal disease

Despite the magnitude of the problem – currently greater than ever due to the increasing diabetic and ageing population – unexpectedly little high-quality evidence exists in the literature to support a strategy paradigm in patients with CLI and infrapopliteal disease.

Several studies have demonstrated that surgical revascularisation is the standard treatment for limb salvage in patients with CLI due to atherosclerotic disease of infrapopliteal arteries, but endovascular interventions of infrapopliteal lesions represent a far less invasive option and are now considered a valid alternative to surgical bypass in many cases.

4.1. Surgical revascularisation for infrapopliteal lesions

Unfortunately, a detailed anatomical description of the disease and relative localisation of the treatment is rarely reported in RCTs and observational studies comparing

different treatments for CLI, and no specific conclusion can be drawn for patients with isolated infrapopliteal disease.

The PREVENT III study¹⁰⁸ was a prospective, randomised, double-blinded, multi-centre phase III trial of a novel molecular therapy (edifoligide; E2F decoy) to prevent vein graft failure in patients undergoing infrainguinal revascularisation for CLI, reporting a peri-operative mortality rate of 2.7%, primary and secondary graft patency rates of 61% and 80%, and 1-year limb salvage and survival rates of 88% and 84%, respectively. In the majority of the 1404 patients who underwent surgical bypass procedures (n=914, 65%) the bypass was anastomosed at the tibial or pedal/plantar vessels distally, but no separate analysis of this subgroup was provided.

In the BASIL trial,^{93–95} only 10% of distal bypass anastomoses were located distally to the popliteal artery. Moreover, the design of the trial included only patients considered suitable for both surgical and endovascular treatment, which means that very complex cases have been treated outside the scope of the trial (probably by surgical approach).

A set of suggested objective performance goals (OPG) for evaluating the results of new catheter-based treatments in CLI has recently been elaborated, based on evidence from RCTs of patients treated by surgical vein bypass. The patient-level data from three RCTs identified 838 patients with autogenous vein bypass. The primary efficacy endpoint, defined as freedom from peri-operative (30-day) death or any major adverse limb event (amputation or major re-intervention) occurring within 1 year was 76.9%, and the primary amputation-free survival at 1 year was 76.5%. The authors suggest that these data should be considered the most suitable current framework for non-randomised comparisons, especially for evaluating outcomes after endovascular treatments for CLI. They also stress that risk stratification should be incorporated in design and reporting of studies since the CLI population is heterogeneous and the OPG thresholds differ substantially between the lower- and higher-risk procedures (based on clinical, anatomical and conduit characteristics).¹⁰⁹

Although no RCTs have selectively studied the outcomes of different graft materials for the construction of bypasses to the infrapopliteal arteries, there is a large body of evidence that vein offers better results in comparison to other graft material. Both immediate and long-term patency benefit from the use of autologous great saphenous vein, whether *in situ* or reversed. Proximal (CFA, SFA or popliteal artery) and distal anastomoses (tibial and pedal arteries) of infrainguinal bypasses may vary, depending on the extent of the atherosclerotic disease. Since the proposal of the “short bypass principle” by Veith¹¹⁰ in 1981, the use of more distal sites for the origin of the bypass have been recommended (popliteal-to-distal bypasses). The advantages include the reduction of groin dissection, the use of shorter graft material, and the decrease in operative time.

A meta-analysis¹¹¹ of popliteal-to-distal vein bypass grafts reported a 5-year primary graft patency rate of 63±4%, a secondary patency rate of 70±5%, and a foot salvage rate of 78±4%.

When the great saphenous vein is unavailable or unsuitable, alternative graft materials include autologous

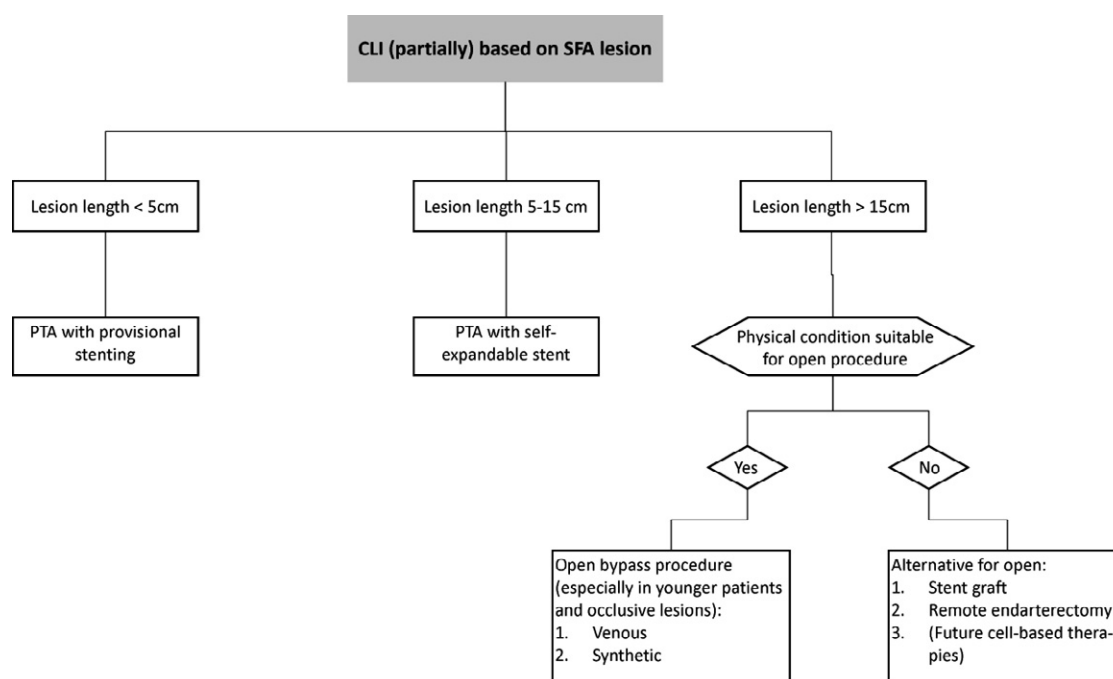


Fig. 1. EUSC classification for SFA lesions and treatment advice. In view of problems with the use of TASC guideline classification for atherosclerotic lesions – mainly poor inter-individual interpretation and hence problematic interpretation of treatment results published in the literature – we propose a simplified classification based on lesion length rather than based on complex loco-anatomic descriptions. Future research using this method has to prove its applicability and need for subclassifications, e.g., occlusive vs. stenotic lesions.

vein, allograft material (cryopreserved vein and arterial allograft) and synthetic material such as PTFE. A meta-analysis of allograft bypass grafting to infrapopliteal arteries¹¹² revealed a poor patency rate at 5 years (ranging from 19% to 30% for different grafts: cold-storage vein, cryopreserved arteries, umbilical-cord veins, and cryopreserved veins) and reduced rate of foot preservation (ranging from 55% to 60%).

Better results in cases of great saphenous vein absence come from the use of alternative autologous vein. Although this approach carries disadvantages such as the need to harvest vein from distal sites and construction of composite grafts, the meta-analysis of alternative autologous vein bypass grafts to infrapopliteal arteries¹¹³ reported results far superior to those reported for non-autologous grafts. The 5-year pooled estimates were 46.9% for primary patency, 66.5% for secondary patency, and 76.4% for foot preservation. The radial artery (or arteries) can be used for limb-salvage revascularisation when no other valuable autologous veins are available. Only short case series have been reported in the literature, almost all in diabetic patients.^{114,115}

The use of PTFE bypass to infrapopliteal arteries is associated with poor long-term outcomes. Random-effects meta-analysis¹¹⁶ yielded 5-year pooled estimates of 31% for primary graft patency, 40% for secondary graft patency, and 56% for foot preservation. Outcomes were slightly higher for a series of PTFE grafts with adjunctive procedures at distal anastomoses (composite PTFE-vein grafts, patches, cuffs and arteriovenous fistulas), compared with a series of PTFE grafts only.

Combinations of popliteal-to-distal bypass and endovascular treatment of SFA lesions have also been reported^{99,117} to improve technical success and patency rate.

Recommendations

The great saphenous vein is superior to other materials and should be preferred in bypass grafting to infrapopliteal arteries. **(Level 3b; Grade B)**

When the great saphenous vein is unavailable or unsuitable, the use of alternative autologous vein grafts (single-segment or composite) is preferable to that of allograft bypass and PTFE bypass graft. **(Level 4; Grade C)**

4.2. Endovascular revascularisation

4.2.1. Angioplasty

The primary aims of infrapopliteal angioplasty in CLI are to restore at least one straight line of blood flow to the ischaemic foot and to maintain the patency of the treated artery for as long as possible or at least as long as necessary to allow ulcer healing, pain relief and to avoid recurrence of CLI.

In the past, infrapopliteal angioplasty has been reserved for patients with short stenotic lesions or for patients who are poor candidates for bypass surgery, but in the last 5–10 years this technique has been used with increasing frequency, also for more complex lesions. Due to the evolution of techniques and the availability of dedicated materials, the endovascular first-line approach to below-the-knee (BTK) vessels should be preferred over bypass according to some authors.^{118–120}

Different endovascular approaches have been proposed, including ipsilateral, antegrade or contralateral retrograde femoral puncture, or more recently, retrograde anterior or posterior tibial puncture^{121,122} or retrograde crossing through the pedal arch (pedal-plantar loop technique).^{123,124}

Unfortunately, the level of evidence for endovascular treatment of BTK vessels is still low. Considering the absence of RCTs comparing surgical vs. endovascular techniques in patients with infrapopliteal disease, the most relevant data in the literature come from extrapolations of RCTs comparing the outcome of bypass and balloon angioplasty at different levels in patients with CLI and from the meta-analysis of retrospective case series where no biases were detected.

Another way to try to decrease bias in comparisons is to adjust differences by using propensity score analysis in large patient cohorts.^{125,126} Recently, in a study cohort comprising 1023 patients treated for CLI with 262 endovascular and 761 surgical revascularisation procedures to their crural or pedal arteries were compared. In the overall series, PTA and bypass surgery achieved similar 5-year limb salvage (75.3% vs. 76.0%), survival (47.5% vs. 43.3%), and amputation-free survival (37.7% vs. 37.3%), indicating that when feasible, infrapopliteal PTA as a first-line strategy is expected to achieve similar long-term results to bypass surgery in CLI when redo surgery is actively utilised. In a subgroup of patients who underwent isolated infrapopliteal revascularisation, PTA was associated with better limb salvage (75.5% vs. 68.0%, $p=0.042$).¹²⁷ Additionally, in 584 consecutive patients aged at least 80 years treated with either PTA ($n=277$) or bypass surgery ($n=307$) for CLI irrespective of the level of infrainguinal revascularisation, PTA achieved better results than bypass surgery after 2 years (leg salvage: 85.4% vs. 78.7%, $p=0.039$; survival: 57.7% vs. 52.3%, $p=0.014$; amputation-free survival (AFS): 53.0% vs. 44.9%, $p=0.005$). Cox regression analysis showed that increased age [relative risk (RR) 1.05, 95% confidence interval [CI] 1.02–1.08], decreased estimated glomerular filtration rate (RR 0.99, 0.99–1.00), diabetes (RR 1.30, 1.04–1.62), coronary artery disease (RR 1.36, 1.05–1.75) and bypass surgery (RR 1.55, 1.24–1.93) were associated with decreased AFS. In 95 propensity score-matched pairs, limb salvage at 2 years (88% vs. 75%; $p=0.01$) and AFS (53% vs. 45%; $p=0.033$) were significantly better after PTA. Classification and regression tree analysis suggested that PTA was associated with better 1-year AFS, especially in patients with coronary artery disease (63.8% vs. 48.9%; $p=0.008$). When feasible, a strategy of PTA first appears to achieve better results than infrainguinal bypass surgery in patients aged 80 years and older.¹²⁸

Regrettably, the only major randomised trial comparing PTA vs. surgery for peripheral arterial occlusive disease (BASIL) included patients with infrainguinal rather than isolated infrapopliteal lesions and did not report details of the anatomic segments treated and relative outcomes. Consequently, no extrapolation of data is possible, which limits analysis of the results of angioplasty vs. surgery for patients with isolated crural disease.

In a recent meta-analysis of infrapopliteal angioplasty for CLI including a large number of case series, the pooled estimate of success was $89.0\pm 2.2\%$ for immediate technical results, and the early mortality rate was 1.8%. The mid-term estimates of primary patency, secondary patency and limb salvage were assessed reliably until 36 months.¹²⁹ When compared to the results of the meta-analysis of popliteal-to-distal bypass graft, the durability of infrapopliteal angioplasty is limited, but the clinical benefit is acceptable because the limb salvage rate of 82% at

3 years is not inferior to that of surgical revascularisation, which underlines that limb salvage does not only depend on patency rates. Hence both patency rates and clinical success should be assessed when evaluating a treatment in CLI patients. Secondary interventions are much more frequent after endovascular treatment of infrapopliteal arteries. Repeated angioplasty attempts, which are not always innocuous, have some advantages over repeat bypass grafting, which is troublesome and not always feasible.

Recommendations

Endovascular treatment of infrapopliteal arteries has the potential to achieve similar limb salvage rates with less procedural morbidity and mortality than surgical bypass. Angioplasty as the first-line therapeutic modality for patients with CLI and infrapopliteal lesion is reasonable in the majority of cases, considering that the interventional procedure should not preclude future surgical intervention. **(Level 4; Grade C)**

Surgical treatment should be considered for more complex anatomical lesions of BTK vessels or in case of endovascular failure and persisting clinical symptoms of CLI. **(Level 4; Grade C)**

4.2.2. Stenting

New endovascular techniques have been proposed to improve the results of plain angioplasty, including the use of bare metal stent (balloon-expandable and self-expanding stents), drug-eluting balloon and stent, cryoplasty, laser and atherectomy. The data for these new technologies still derive predominantly from a few small RCTs and from retrospective case series, with a limited number of patients and a relatively short clinical and instrumental follow-up.

Although the first use of stents for infrapopliteal lesions was reported more than 15 years ago,¹³⁰ several concerns have been raised regarding their utilisation with respect to the risks of stent fracture, restenosis, thrombosis, and the possibly limited role of a focally acting endoprosthesis in a diffusely diseased vessel.

4.2.2.1. Balloon-expandable stent: Fering et al.¹³¹ were the first to demonstrate the safety and utility of primary stenting of infrapopliteal lesions using coronary stents, in a large retrospective series.

The first RCT on the topic was the InPeria trial published by Rand et al.¹³² The trial was a European multi-centre randomised study that investigated carbon-coated stents (a 0.014-inch coronary balloon-expandable stent with a thin coating of 0.5nm of polycrystalline carbon film to prevent thrombus formation) vs. balloon angioplasty in the infrapopliteal arteries. A total of 51 patients, with 95 lesions, were enrolled (PTA: 53 lesions in 27 patients; stent: 42 lesions in 24 patients). Inclusion criteria were isolated stenosis greater than 70% or occlusion of the tibial arteries, up to three lesions; and lesions up to 3cm with a cumulative lesion length of 9cm. Follow-up evaluation was performed with intra-arterial and/or CT angiography at 6 months by two double-blind observers. For the stent group, the cumulative primary patency at 6 months was 83.7% (70% restenosis threshold) and 79.7% (50% restenosis threshold). For PTA, the primary patency at

6 months was 61.1% (70% restenosis threshold) and 45.6% (50% restenosis threshold) ($p < 0.05$). Although the results at 6 months were superior in the stent group, 9-month clinical follow-up of an extended 88-patient group (InPeria II; 45 limbs with 69 lesions treated with PTA vs. 44 limbs with 62 lesions treated with Carbestents) showed similar levels of clinical improvement and limb salvage (96% vs. 91%, respectively) and similar 1-year patency rates of about 60%.¹³³ Until now, longer follow-up data have not been available.

Other authors reported positive results of primary stenting using coronary balloon-expandable drug-eluting stents for infrapopliteal disease in small, non-randomised, single-centre studies.^{134–138} These studies show favourable clinical results for drug-eluting stents in the early follow-up period, with significantly higher angiographic patency and less clinically driven re-interventions compared to simple angioplasty or bare-metal stent. However, these results have to be interpreted with caution because these studies were small in size and had limited follow-up. Notably most of these studies were industry-sponsored.

More recently, data from three RCTs comparing new solutions for infrapopliteal atherosclerotic disease have been presented at international meetings¹³⁹ (although manuscript publications are still awaited). These trials have found that drug-eluting stents are superior to angioplasty, or bare metal stents, in below-the-knee revascularisation. In particular, the ACHILLES trial has shown better primary patency for sirolimus-eluting balloon-expandable stents in the infrapopliteal region compared to balloon angioplasty, and the YUKON and DESTINY trials have shown a similar benefit for drug-eluting stents below the knee (respectively, a sirolimus-eluting stent and an everolimus-eluting stent) as compared to a bare metal stent. However, no significant difference in limb salvage rate was observed.

Despite the encouraging results from these RCTs for drug-eluting devices in infrapopliteal vessels, it should be noted that several inclusion criteria present in the protocols restricted study enrolment to patients with limited manifestations of tibial atherosclerotic disease, including patients with claudication (Rutherford 3) and excluding patients with severe tissue loss (Rutherford 6).

Complete longer follow-up data including clinical endpoints and wound healing assessments are expected to be published in the near future.

4.2.3. Self-expanding nitinol stents

The main restrictions of currently available bare or drug-eluting balloon-expandable stent platforms for BTK vessels are the small lengths available and the vulnerability to external compression (especially in the distal third of the anterior and posterior tibial artery). This is the reason why the majority of available studies are limited to short focal infrapopliteal lesions up to 3 cm, which are not representative of typical long BTK lesions.

Long, thin-strut, low-profile, self-expanding nitinol stents designed and engineered specifically for the infrapopliteal arteries are now commercially available, but clinical data are still limited to small non-randomised studies.^{140–142}

One RCT designed to compare PTA vs. self-expanding stent (The XXS – Balloon Angioplasty Versus Xpert Stent in CLI Patients) in patients with infrapopliteal lesions has recently completed the recruitment (180 CLI patients and

a maximum of 2 arteries with a maximum lesion length of 150 mm). Interesting data about subjects with very long BTK lesions (which might better reflect real-world cases) are expected shortly.

A collaborative systematic review and meta-analysis¹⁴³ of clinical studies focusing on BTK stenting in patients with CLI identified 18 non-randomised studies including more than 600 patients. Data showed that bailout stenting of BTK vessels, performed with either balloon-expandable or self-expanding stents for suboptimal balloon dilation, was associated with satisfactory results up to a median of 12 months after treatment: binary in-stent restenosis occurred in 25.7% (95% CI 11.6–40.0%), primary patency in 78.9% (95% CI 71.8–86.0%), improvement in Rutherford class in 91.3% (95% CI 85.5–97.1%), target vessel revascularisation in 10.1% (95% CI 6.2–13.9%), and limb salvage in 96.4% (95% CI 94.7–98.1%). Subanalyses focusing on device type showed that balloon-expandable and self-expanding stents avoiding joint segments or pedal vessels perform similarly at early and midterm follow-up. In addition, the available data suggest superiority of sirolimus-eluting stents in comparison to bare metal stents in terms of primary patency and need for re-revascularisations.

Recommendation

Short, focal infrapopliteal lesions can be treated by drug-coated or drug-eluting stents, with improved patency rate. (Level 2b; Grade B)

4.2.3.1. Bioabsorbable stent: The possibility of not having a permanent metallic implant (bioabsorbable stent scaffold technology) has emerged as an exciting technology to combine mechanical prevention of vessel recoil with the advantages of long-term perspective. The bioabsorbable stent could permit the occurrence of positive remodelling with lumen enlargement to compensate for the development of intimal hyperplasia or new lesions.

The first published data with coronary application of an absorbable polymeric everolimus-eluting stent were very promising,¹⁴⁴ revealing a nearly complete elimination of both intimal hyperplasia and the need for re-interventions at 1 year.

Unfortunately, the same promising results have not been validated for BTK vessels. The prospective multi-centre randomised trial investigating infrapopliteal absorbable magnesium stents (AMS) vs. angioplasty (AMS-INSIGHT 1 trial)¹⁴⁵ indicated that the AMS technology can be safely applied, but it did not demonstrate efficacy regarding long-term patency over standard PTA in the infrapopliteal vessels. Data from 117 patients (147 CLI limbs) showed significantly higher binary restenosis rate at 6 months (68% vs. 42%, $p = 0.01$) with a rate of lumen loss that was nearly doubled (1.4 vs. 0.7 mm, $p = 0.001$). It should be noted that the AMS stent was not drug-eluting.

Recommendation

The current-generation absorbable metal stent does not show superiority in long-term patency over standard PTA in infrapopliteal vessels. Reliable stent design modifications are required, and further clinical trials should be performed before potential widespread application of the technology. (Level 1b; Grade B)

4.2.4. Drug-eluting balloon

The concept of using a balloon catheter to directly deliver an antirestenotic drug at the site of arterial disease is of paramount interest. The plan to reduce the risk of restenosis without irreversibly modifying the structure of the vessel is a new interesting perspective, but limited clinical data are available.

Two different paclitaxel-coated balloon catheter systems are currently being compared to standard uncoated PTA balloon catheter for treatment of infrapopliteal lesion in a randomised fashion (INPACT-DEEP trial, PICCOLO trial, EURO CANAL trial).

Various angiographic and clinical efficacy measures will be evaluated to study whether paclitaxel-coated PTA balloons effectively inhibit restenosis of BTK arteries. Additionally, safety and tolerance of the drug-eluting device will be evaluated. No preliminary data are available.

It is likely that in the near future, the extent of the use of drug-coated balloons for BTK vessels in daily practice will be driven by the proof of their efficacy in reducing the restenosis rate and by the limitations of other available techniques. However, the clinical effectiveness of the drug-eluting balloons should be of crucial importance in deciding whether or not to opt for the device.

Recommendation

Drug-eluting balloon angioplasty is a promising technology for patients with CLI and infrapopliteal vessel lesions. However, prior to widespread clinical implementation, the results of pilot studies should be confirmed by RCTs with short- and long-term follow-up. **(Level 4; Grade D)**

5. Non-reconstructive option in CLI

5.1. Lumbar sympathectomy

Lumbar sympathectomy can be performed both chemically and surgically. Studies directly comparing lumbar sympathectomy to a conservative treatment in CLI patients are limited. The small number of randomised trials that have been conducted failed to show beneficial effects on hard endpoints like amputation rate, mortality or ankle-brachial pressure index.^{146,147} However, lumbar sympathectomy has a beneficial effect on subjective endpoints, such as relief of rest pain. The latter has consistently been confirmed in multiple cohort studies. These studies also suggest enhanced ulcer healing. Chemical and surgical lumbar sympathectomy seem to perform equally well¹⁴⁸ and can also be beneficial in diabetic patients.¹⁴⁹

Recommendation

Lumbar sympathectomy, either surgical or chemical, should not be considered an option to prevent amputation. However, chemical lumbar sympathectomy can be considered in CLI patients not amenable to revascularisation in order to relieve symptoms. **(Level 2a; Grade B)**

5.2. Spinal cord stimulation (SCS)

Spinal cord stimulation involves a technique where an implanted pacemaker activates the dorsal columns of the spinal cord with an epidural lead. Early studies have

reported a potential role for the device in limb salvage in patients with CLI. However, a recent meta-analysis of randomised trials that have studied the effects of SCS failed to show a beneficial effect on amputation rate or mortality.¹⁵⁰ It has been suggested that some subgroups could potentially benefit from SCS, but this could not be confirmed in the meta-analysis. Most randomised studies showed pain relief in the group treated with SCS compared to standard care.¹⁵¹ However, complication rates are considerable (12%) and treatment costs are high.^{150,152}

Recommendation

Evidence is insufficient to recommend spinal cord stimulation in the treatment of CLI. **(Level 1a; Grade A)**

5.3. Gene and cell therapy

Regenerative medicine has raised much interest as a potential therapeutic strategy in patients with peripheral arterial disease, especially critical limb ischaemia. Both angiogenic gene and cell therapy have been studied in clinical context after promising results in animal experiments. Early piloting trials have been carried out for different gene-based therapies involving vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and hepatocyte growth factor (HGF), and showed promising results. The subsequently performed larger trials have generally failed to confirm the promising findings of the pilot trials, therefore gene therapy is still confined to research settings.¹⁵³ For example, the large TAMARIS trial randomised 525 patients with CLI unsuitable for revascularisation to treatment with non-viral FGF1 or placebo (8 intramuscular injections in the ischaemic leg, four times with 2-week intervals).¹⁵⁴ The trial could not prove that FGF is effective in reducing major amputation or death and amputation in these patients.

Studies that investigate the potential use of cell-based therapies in CLI are very heterogeneous, with varying amounts of cells administered, different administration routes, different cell sources and cell types used. Recently, Fadini et al.¹⁵⁵ performed a meta-analysis of clinical studies using cell-based therapies in patients with peripheral arterial disease. These studies almost invariably show improvement of both objective and subjective endpoints; however, conclusions based on these studies are largely limited by the small size and mainly non-randomised design of these studies. Large randomised placebo-controlled trials focusing on clinically relevant endpoints are needed to confirm the promising results and to clarify the remaining questions surrounding cell therapy, such as preferred administration route and cell source.

Recommendation

There are data to suggest promising potential of cell-based therapies in patients with CLI. However, prior to widespread clinical implementation, the results of pilot studies should be confirmed by large-scale randomised placebo-controlled trials. Until then, both cell and gene therapy should be confined to the research setting. **(Level 5; Grade D)**

Conflict of Interest/Funding

None

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Chapter V: Diabetic Foot

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KEYWORDS

Diabetic foot;
Ischaemia;
Neuroischaemia;
Vascular impairment;
Ulcer healing;
Revascularisation

Abstract Ulcerated diabetic foot is a complex problem. Ischaemia, neuropathy and infection are the three pathological components that lead to diabetic foot complications, and they frequently occur together as an aetiological triad. Neuropathy and ischaemia are the initiating factors, most often together as neuroischaemia, whereas infection is mostly a consequence. The role of peripheral arterial disease in diabetic foot has long been underestimated as typical ischaemic symptoms are less frequent in diabetics with ischaemia than in non-diabetics. Furthermore, the healing of a neuroischaemic ulcer is hampered by microvascular dysfunction. Therefore, the threshold for revascularising neuroischaemic ulcers should be lower than that for purely ischaemic ulcers. Previous guidelines have largely ignored these specific demands related to ulcerated neuroischaemic diabetic feet. Any diabetic foot ulcer should always be considered to have vascular impairment unless otherwise proven. Early referral, non-invasive vascular testing, imaging and intervention are crucial to improve diabetic foot ulcer healing and to prevent amputation. Timing is essential, as the window of opportunity to heal the ulcer and save the leg is easily missed.

This chapter underlines the paucity of data on the best way to diagnose and treat these diabetic patients. Most of the studies dealing with neuroischaemic diabetic feet are not comparable in terms of patient populations, interventions or outcome. Therefore, there is an urgent need for a paradigm shift in diabetic foot care; that is, a new approach

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and classification of diabetics with vascular impairment in regard to clinical practice and research. A multidisciplinary approach needs to be implemented systematically with a vascular surgeon as an integrated member. New strategies must be developed and implemented for diabetic foot patients with vascular impairment, to improve healing, to speed up healing rate and to avoid amputation, irrespective of the intervention technology chosen. Focused studies on the value of predictive tests, new treatment modalities as well as selective and targeted strategies are needed. As specific data on ulcerated neuroischaemic diabetic feet are scarce, recommendations are often of low grade.

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1. Introduction

Diabetic foot ulcers are a major healthcare problem. In 2011, 350 million people worldwide (6.6% of the population) and more than 55 million in Europe suffer from diabetes mellitus,¹ and estimates for 2025 cite a total of over 65 million patients.¹ Complications of foot ulcers are the leading cause of hospitalisation and amputation in diabetic patients. Indeed, 20–40% of the healthcare resources spent on diabetes are related to diabetic feet.^{2,3}

Individuals suffering from diabetes and neuropathy with no other confounders will develop an ulcer in 7–10% of the cases annually, whereas the rate for patients with additional risk factors – such as peripheral arterial disease (PAD), foot deformity, previous ulcers or previous amputation – is 25–30%.^{2–4}

Major amputation will be needed within 1 year in 5–8% of patients with diabetic ulcers.^{5–7} Of all amputations on diabetic patients, 85% are preceded by a foot ulcer which subsequently deteriorates to a severe infection or gangrene.^{2–4} Diabetes increases the risk of amputation 8-fold in patients aged >45 years,⁸ 12-fold in patients aged >65 years and 23-fold in those aged 65–74 years.⁹

2. Neuropathy

Ischaemia, neuropathy and infection are the three pathological components that lead to diabetic foot complications, and they frequently occur together as an aetiologic triad.¹⁰ Neuropathy and ischaemia are the initiating factors, with a different weight in different patients (Fig. 1), and infection is mostly a consequence.¹¹

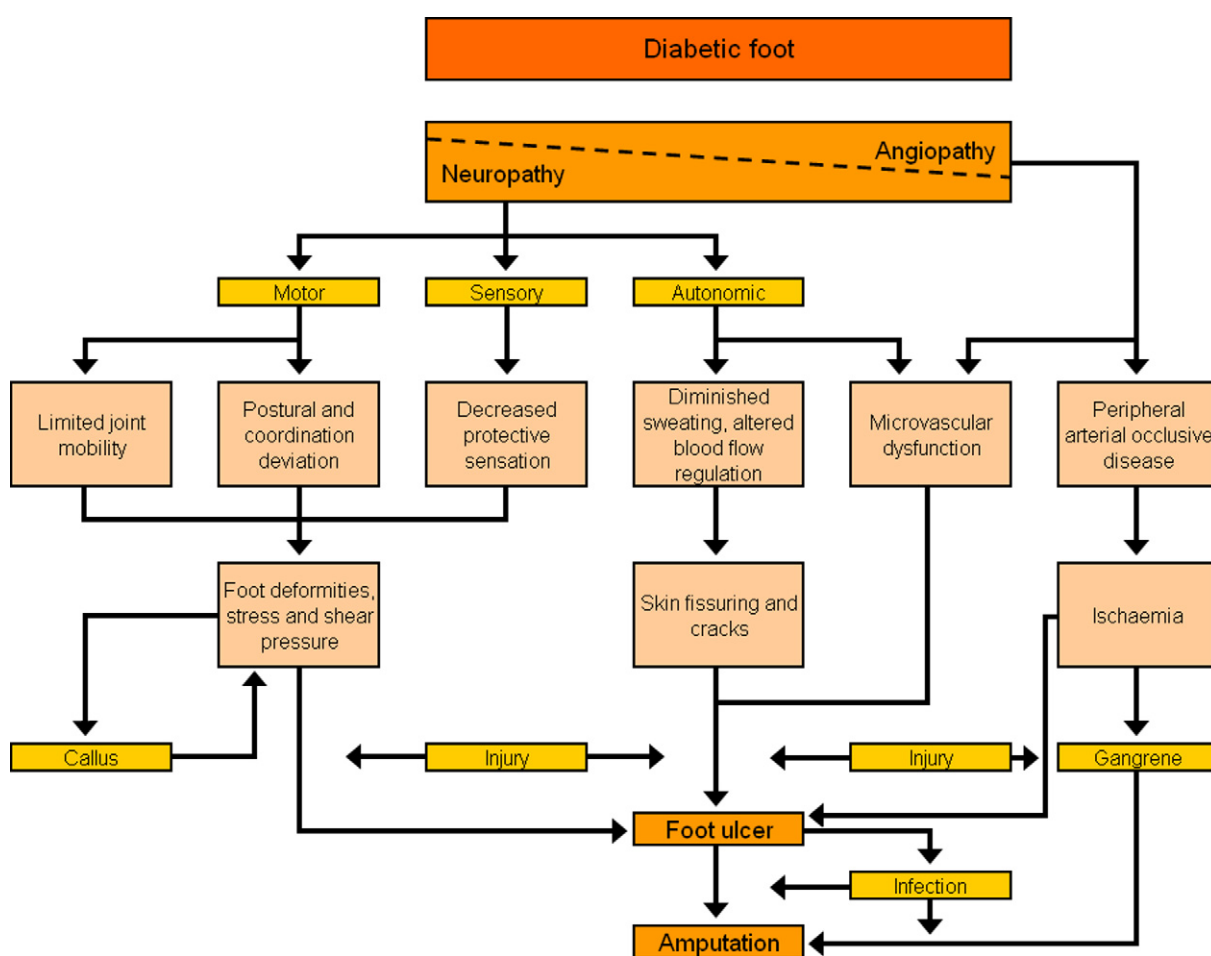


Fig. 1. Pathway to diabetic ulcer. Modified from the International Working Group on the Diabetic Foot, International Consensus on the Diabetic Foot, 1999, with permission.

Due to the lack of protective sensation, the foot is vulnerable to unattended minor injuries caused by excess pressure, mechanical or thermal injury. Motor neuropathy alters the biomechanics and, gradually, the foot anatomy. Foot deformities, limited joint mobility and altered loading of the foot are obvious consequences from these disarrangements. The most important feature of the treatment of any ulcer with neuropathy is to restrict weight bearing, irrespective of the presence of ischaemia.

The treatment of purely neuropathic ulcers is beyond the scope of these guidelines, and neuropathy is further dealt with only in conjunction to ischaemia – i.e. as neuroischaemic ulcers. For the purposes of this chapter, the term diabetic foot refers to an ulcerated diabetic foot with vascular impairment.

3. Ischaemia and neuroischaemia of the diabetic foot

3.1. Underestimation of the role of ischaemia

Poor glucose control accelerates the manifestation of PAD. For every 1% increase in haemoglobin A1c (HbA1c), there is a corresponding increase of 25–28% in the relative risk of PAD.¹² Diabetes increases the prevalence of symptomatic PAD 3.5-fold in men and 8.6-fold in women.¹³ Recent large European cohort studies of individuals with diabetes and foot ulcers confirm that at least half are of neuroischaemic or ischaemic origin.^{14–16} Yet the strategy of prevention and treatment of the diabetic foot has predominantly been focused on neuropathy and its consequences,^{2,17} although ischaemia is the most important factor preventing healing.¹¹ PAD in diabetics is often multisegmental, typically infrapopliteal and poorly collateralised.^{18–20} Ischaemia has been reported to be at least a contributing factor in 90% in diabetics undergoing major amputation.²¹

Recommendation

Ischaemia should not be excluded as a cause of a diabetic foot ulcer unless proven absent.^{22,23} **(Level 5; Grade D)**

3.2. Inadequate understanding of neuroischaemia

Neuroischaemia is the combined effect of diabetic neuropathy and ischaemia, impairing the oxygen delivery to meet metabolic tissue demands in a synergetic way. Macrovascular disease and microvascular dysfunction both impair perfusion in a diabetic foot.²⁴ Peripheral autonomic neuropathy, or auto-sympathectomy, causes deficient sweating and altered blood flow regulation with an opening of arteriovenous shunts and precapillary sphincter malfunction, which decreases nutritive blood flow and manifests as warm, dry skin, increasing the likelihood of skin breakdown.²⁵

The microvascular dysfunction is further characterised by the subsequent capillary leakage and venous pooling as well as hormonal activity in the vessel and inflammation in the wall, all indicating that decreased perfusion in the diabetic foot is more complex and not only related to PAD.^{26–28} Yet PAD is the most important cause of vascular impairment of diabetic foot.²⁴

Recommendation

In neuroischaemic legs, healing is primarily affected by the severity of ischaemia.¹¹ Therefore, from a practical point of view, neuroischaemic and ischaemic lesions should be considered together as both may require revascularisation. **(Level 2b; Grade C)**

3.3. Assessment of vascular impairment beyond ischaemia

The use of rigid non-invasive methods is mostly based on the haemodynamic changes in the macrovascular arterial tree, and criteria applicable to non-diabetic legs are not good enough to predict the healing of diabetic foot lesions.²³ There is a clear need to recognise decreased perfusion or vascular impairment as an indicator for the need for revascularisation in the diabetic foot in order to achieve and maintain healing and to avoid or delay a future amputation.^{4,6,16,23,29–31}

Recommendation

The International Working Group for the Diabetic Foot recommends further vascular studies in case the ulcer has not healed with proper treatment in 6 weeks even if initial diagnostics have suggested only questionable or mild disease.²² **(Level 5; Grade D)**

Critical issue

Criteria for impaired perfusion should be established.

3.4. Delay in revascularisation

As less than 25% of diabetics with PAD report intermittent claudication, and rest pain is far less common than in non-diabetics, the diagnosis of ischaemia is often delayed.² The obvious consequence has been that a vascular consultation is arranged too late for diabetics. Indeed, 30–50% of their foot ulcers are already gangrenous, and, therefore, vascular surgeons are too often not consulted at all.^{2,4}

Recommendation

To prevent a delay in vascular consultation and revascularisation, early non-invasive vascular evaluation is important in identifying patients with poor ulcer healing and a high risk for amputation.^{2,4,6,17,29–31} **(Level 2b; Grade B)**

3.5. Ischaemia, infection and tissue damage

Neuroischaemic ulcers are susceptible to infection. Infection is seldom the direct cause of an ulcer but strongly related to the probability of amputation, especially in combination with ischaemia (PAD).¹¹ Deep infections are manifested either as osteomyelitis or a soft tissue infection spreading along the tendons in the compromised foot. A deep infection is a limb-threatening condition and the immediate cause of amputation in 25–50% of diabetic patients.^{2,4,32–34} In several studies, the outcome of deep foot infection has been related to the extent of tissue involved, comorbidity and co-existing PAD.^{2,4,14,16}

Recommendation

The combination of ischaemia and infection always necessitates urgent treatment, as “time is tissue”.²² (Level 2c; Grade C)

4. Clinical examination from the vascular perspective

4.1. History

4.1.1. General

The primary evaluation with regard to the diabetic foot should include information on the presence of concomitant diseases and their medications; cardiovascular risk factors; occupation and hobbies; lifestyle; smoking as well as the use of alcohol, drugs and other intoxicants; in addition to diabetes-related complications, especially nephropathy, retinopathy and neuropathy. Special attention should also be paid to impaired vision, renal replacement therapy, previous foot education, social isolation and poor access to healthcare.²

4.1.2. Foot-specific history

The main aim of the examination of a diabetic foot is to assess the risk factors for foot ulceration and, in case there already is an ulcer, to evaluate its specific aetiology and duration to allow targeted treatment.^{17,25}

4.2. Inspection

A clinical examination of the foot of a diabetic patient should be performed at least once a year and more frequently in the presence of risk factors. The role of a regular inspection of the diabetic foot cannot be emphasised enough.^{3,11,35} As Andrew Boulton has put it, “For one mistake made for not knowing, ten mistakes are made for not looking.” A neuropathic foot frequently has a characteristic appearance upon inspection.¹⁰

4.3. Vascular clinical examination

Pulse palpation is the cornerstone of vascular examination although it is not necessarily a method of good reproducibility.³⁶ Therefore, clinically significant arterial disease can most often be ruled out only if both dorsalis pedis and posterior tibial pulses are palpable with certainty. Yet, in diabetics even this may not suffice to exclude impaired perfusion.³⁷ Furthermore, the arteria dorsalis pedis pulse is missing in 8% and tibialis posterior pulse in 3% of healthy individuals.³⁸

An ischaemic foot may appear pink and relatively warm even with impaired perfusion due to arteriovenous shunting. Delayed discolouration (rubor) or venous refilling >5s on dependency may indicate poor arterial perfusion.³⁹ Slow capillary refilling time has little diagnostic value.³⁹

Recommendation

Every foot ulcer should be examined for the presence of ischaemia.² (Level 5; Grade 4)

4.4. Neurological clinical examination

Sensory loss tested by pressure perception with a 10-gram (5.07) Semmes–Weinstein monofilament is the most important single test.^{2,17} Vibration perception using a 128 Hz-tuning fork, pinprick discrimination and tactile sensation testing with cotton wool on the dorsum of the foot, as well as testing Achilles tendon reflexes, belong to the neurological examination in addition to looking for foot deformities or bony prominences.²

Recommendation

Every foot ulcer should be examined for the presence of neuropathy.² (Level 5; Grade 4)

4.5. Ulcers

The diabetic foot ulcer is not a disease of the skin but a sign of abnormal loading and impaired perfusion. A systematic classification of foot ulcers would be helpful for the comparison of data, but only few scoring systems have been validated.⁴⁰ The most frequently used systems include perfusion, the extent and size of tissue involvement as well as infection.^{29,41}

Critical issue

The validity of scoring systems needs to be evaluated specifically in ischaemic diabetic ulcers.

4.6. Infection

Ulcer infections are diagnosed clinically on the basis of local signs and symptoms of inflammation. These include purulent secretion in the ulcer or at least two of the following signs or symptoms: redness, warmth, swelling, pain, delayed improvement or bad odour. The clinical signs of infection can be reduced due to diminished leucocyte function, PAD, poor metabolic control and neuropathy.⁴² Occasional systemic signs are fever and poor general condition.^{34,43} In almost 50% of patients with diabetes and deep foot infections, signs such as increased white blood cell count, erythrocyte sedimentation rate, C-reactive protein concentration and fever have been found absent, resulting in a delay in diagnosis.^{32–34} Some patients with a diabetic foot infection also have a worsening in their glycaemic control. A swollen foot with a long-lasting ulceration or a red swollen digit should always arouse suspicion of an infection extending to deep tissue. The most common sign of a diabetic foot infection with an ulcer is increased exudation rate.^{32,44} Unroofing a superficial eschar may reveal deeper abscesses.¹⁰ Indeed, the severity of infection should be assessed after debridement, based on its extent and depth as well as the presence of any systemic findings.²² Tissue specimens should be obtained by biopsy, curettage or aspiration, preferable to wound swab specimens, prior to starting empirical antibiotic therapy.^{45–47}

A continuous extension of a soft tissue infection to the underlying bone poses both diagnostic and therapeutic challenges.^{32–34,48} Imaging studies may help detect pathological findings in the bone.⁴⁹ Plain radiographs of the foot may be of value in revealing the presence of a foreign body, gas, osteolysis or joint effusion. Radiological diagnosis is often

difficult because changes suggesting osteomyelitis usually take several weeks to become visible on X-ray.

Fever as well as an increased erythrocyte sedimentation rate (ESR), white cell count and C-reactive protein concentrations (CRP) are usually helpful in recognising soft tissue infections or abscess. An MRI, bone scan or CT scan can be of value in evaluating the presence and extent of a deep foot infection.

Recommendation

Every diabetic foot ulcer should be examined for the presence of infection.² (Level 5; Grade D)

4.7. Non-invasive vascular studies – special considerations related to the diabetic foot

In the case of any uncertainty as to foot perfusion, the measurement of ankle pressure, the ankle-brachial systolic pressure index (ABI) and toe pressures should be included. Normal ABI values range between 0.9 and 1.3, as high values suggest non-compressible arteries (pseudohypertension) characteristic of advanced mediasclerosis, which is typical in diabetes. Less severe calcification may result in a normal ABI despite clinically significant PAD.⁵⁰ In a series of 554 diabetics with vascular impairment, ankle pressures could not be measured in 35% of the patients.⁵¹ An ABI <0.4–0.45, absolute systolic ankle pressure <55 mmHg and toe pressure <30 mmHg have most frequently been used to indicate the need for revascularisation.^{10,52,53} Pseudohypertension may be revealed by pulse volume recording (PVR),⁵⁴ but there are not enough data to support the use of methods such as the pole test.⁵⁵ In hand-held Doppler examination, an absent or monophasic flow velocity signal from a foot artery indicates occlusion or collateral flow.

Recommendation

Trust ABI when low but not when high. An ABI <0.6 indicates significant ischaemia in respect to wound healing potential, whereas an ABI >0.6 has little predictive value and, therefore, at least the toe pressure should be measured.²² (Level 5; Grade D)

Toe pressure may give more reliable information on the level of distal flow capacity but, as reported in one study, it could not be measured in 16% of cases due to a previous amputation or gangrene of the big toe.⁵¹ Vascular intervention has been suggested feasible for diabetics with an ulcer as well as ankle pressures <80 mmHg⁵⁴ and toe pressure <55 mmHg.⁵⁶ The probability of ulcer healing is clearly related to available perfusion pressures and, regardless of the method used, follows a sigmoid curve (Fig. 2).¹⁷

Recommendation

An ulceration of the foot in diabetes will generally heal if the toe pressure is >55 mmHg, whereas healing is usually severely impaired when toe pressure is <30 mmHg.²² (Level 2b; Grade B)

Transcutaneous oxygen pressure (TcPO₂) <30 mmHg has been considered to predict that the infection will not

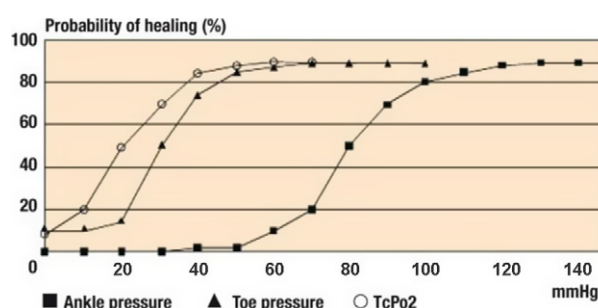


Fig. 2. Probability of ulcer healing as related to different levels of systolic ankle pressure, toe pressure and TcPO₂. From the International Consensus on the Diabetic Foot, 1999, with permission.

resolve itself and the ulcer will not heal.⁵² The accuracy of these measurements in patients with critical leg ischaemia has been questioned, especially in the presence of tissue oedema.^{53,57} Nevertheless, TcPO₂ may be a useful method of identifying tissue lesions that may heal with conservative treatment.^{58,59} TcPO₂-values >40 mmHg support conservative treatment alone as the first approach as >90% of the ulcers healed.^{59,60}

Recommendation

Ulceration of the foot in diabetes will generally heal if the TcPO₂ is >50 mmHg. Healing is usually severely impaired when TcPO₂ is <30 mmHg.²² (Level 2b; Grade B)

Low ABI, ankle pressure, toe pressure and TcPO₂ suggest that a diabetic ulcer may not heal, but the limitations of each technique should always be considered.

4.8. Vascular imaging – special considerations related to the diabetic foot

Extensive calcification of the infrapopliteal arterial tree may prevent proper duplex diagnostics as well as computed tomography angiography, although the use of multislice devices decreases interpretation difficulties caused by arterial wall calcifications.^{61–64} MRA may have limited spatial resolution and the images may be distorted by previous stents, implants and flow disturbances. The use of the paramagnetic contrast material gadolinium has been reported to cause nephrogenic systemic fibrosis typically in patients with renal failure.^{65–67}

Recommendation

Any of the techniques are useful for mere imaging as the accuracies of the different techniques in diagnosing stenosis of >50% in the infrapopliteal segment are acceptable and similar when using DSA as the reference.⁶¹ (Level 2b; Grade B)

A systematic angiographic classification of infrapopliteal occlusive lesions would be valuable in order to have comparable data for future comparisons of different revascularisation techniques. At present, at least three classifications are in use,^{19,23,68} each with different degrees of validation and inter-observer agreement.^{19,69–71} None of them has gained larger acceptance in the practice of assessing angiographic patterns of ulcerated diabetic feet.

Chronic renal failure is increasingly common in diabetics with a foot ulcer. Metformin treatment should be discontinued before angiography as it may cause lactic acidosis.⁷² Renal insufficiency influences the choice of imaging method, because contrast media are nephrotoxic agents. In the case of mild chronic renal failure, regular DSA and CTA can be performed, but intravenous hydration of the patient is recommended before and after the examination.^{72,73} In more severe cases, selective angiography with a minimal amount of contrast media, preferably diluted non-ionic iso-osmolar, can produce excellent imaging when focused on the target lesion.⁷³ Alternatively, duplex ultrasound can be used for imaging and sometimes also for guiding the endovascular procedure.⁷⁴

Recommendation

Detailed visualisation of infrapopliteal arteries, including the arteries of the foot, is necessary for a complete evaluation of diabetic patients.²² (Level 5; Grade D)

Critical issue

The risks of gadolinium-enhanced MRA for imaging diabetic patients with kidney failure should be considered and further evaluated.

5. Treatment of ulcerated neuroischaemic diabetic feet

5.1. Multifactorial approach mandatory

The complexity of diabetic foot ulcers necessitates in-depth knowledge of the underlying pathophysiology and a multifactorial approach in which aggressive management of ischaemia and infection is of major importance (Table 1).

Recommendation

Patients in need of revascularisation to improve perfusion and achieve healing should be identified by an extensive clinical examination and non-invasive, vascular testing.^{22,23} (Level 5; Grade D)

Metabolic control also plays an important role in comprehensive treatment. Blood glucose control may be difficult because of infection. If the patient is on oral antidiabetic drugs, a temporary switch to insulin may be necessary. On the other hand, high blood glucose worsens infection and is associated with poorer operative results, morbidity and mortality. The recommended target level of HbA1c should be <7.0–7.5% but higher if hypoglycaemic episodes are a problem, and the LDL level should be <1.8 mmol/L and blood pressure <130/80 mmHg, while less stringent goals should be accepted for elderly and multimorbid patients.⁷⁵

Recommendation

Intensive management of diabetes, including glycaemic and platelet aggregation control, treatment of hypertension and dyslipidaemia as well as non-pharmacological interventions, decreases vascular complications in the long run.⁷⁶ (Level 1a; Grade A)

5.2. Management of infection

Antibiotic therapy is necessary for virtually all infected wounds, but it is not beneficial for non-infected ulcers and is insufficient without appropriate wound care. In long-standing ulcers or ulcers with delayed healing and ischaemia or necrotic tissue, polymicrobial flora with an unknown causative agent is frequently present. Broad-spectrum empirical therapy is not routinely required but is indicated for moderate to severe infections.^{34,77} Antibiotic therapy is continued until there is evidence that the infection has been resolved but not necessarily until the wound has healed.⁴⁹

Patients with uncontrolled or limb-threatening infections require immediate hospitalisation, immobilisation and intravenous antibiotics. Infections accompanied by a deep abscess, extensive bone or joint involvement, crepitus, substantial necrosis or gangrene, or necrotising fasciitis, need prompt surgical intervention. Infections can spread extremely rapidly in a diabetic foot, which may lead to a life-threatening general septic infection if treatment is delayed. Urgent evaluation of lower limb circulation, treatment of infections and surgical procedures, including debridement and revascularisations, are often needed as first-line leg salvage strategies.^{48,50,78}

Recommendation

Surgical intervention for moderate or severe infections is likely to decrease the risk of major amputation.²² (Level 2c; Grade B)

5.3. Infringuinal revascularisation

The crucial issue is to decide whether revascularisation is needed for a certain lesion in a certain patient.¹⁰ Although non-invasive evaluation is helpful, the decision to intervene is made according to the symptoms and clinical findings.¹⁰ Anatomical imaging should be considered only as strategic.⁷³

If both an endovascular and a bypass procedure are possible with an equal outcome to be expected, endovascular treatments should be preferred.⁷⁹ Especially patients with chronic neuroischaemic ulcers, borderline toe pressures and short lesions are candidates for endovascular treatment. However, continuous surveillance and a low threshold for secondary imaging, percutaneous transluminal angioplasty (PTA) or bypass are basic principles when treating diabetic ulcers with an endovascular procedure.⁸⁰ Bypass grafting is to be used for long occlusions. Patency rates after crural and pedal bypasses are similar in diabetics and non-diabetics.⁸¹ (For femoropopliteal reconstructions, see Chapter IV, Treatment of Critical Limb Ischaemia, pp. S43–S59.)

5.4. Infrapopliteal endovascular procedures

Endovascular therapy for infrapopliteal arterial disease is gaining acceptance as a first-line revascularisation method to improve ulcer healing and limb salvage.⁷⁹ The angioplasty of isolated crural arterial lesions in diabetic patients with an unhealed ulcer is also considered an effective and safe therapeutic modality to avoid limb loss.⁸² There are several studies showing good results and patency rates after endovascular treatment of PAD with critical ischaemia.^{82–86} An important task for any revascularisation is to achieve

Table 1 Multifactorial treatment of a diabetic foot ulcer

Goal	Treatment
Improvement of perfusion	Endovascular revascularisation (PTA) Reconstructive vascular surgery (bypass) Vascular drugs Reduction of oedema Hyperbaric oxygen
Treatment of infection	Antibiotics (oral or parenteral) Incision, drainage Resection
Reduction of oedema	External compression therapy Intermittent compression (pumps) Diuretics
Pain control	Analgesic drugs (local or systemic) Immobilisation, offloading, relief of anxiety and fear, TNS
Improvement of metabolic control	Insulin treatment Necessary nutritional support
Offloading	Protective and therapeutic footwear Insoles, orthosis Total contact cast, walkers Crutches, wheelchair, bed rest
Wound bed preparation	Debridement, removal of debris Topical treatment, dressings Control of exudation, moist wound healing, GCSF infection control, NPWT Tissue engineering, growth factors, matrix modulation
Removal of dead tissue	Incision, drainage, amputation
Correction of foot deformities	Corrective foot surgery, skin transplant, amputation
Improvement of general condition	Fluid and nutrition replacement therapy Aggressive treatment of concomitant disease, antiplatelet drugs, antihypertensive agents, lipid decreasing agents Cessation of smoking Physiotherapy
Implementation of systematic care	Patient and staff education Support and follow-up Multidisciplinary coordination, communication, staggered treatment chains Improvement of concordance process oriented approach

GCSF, granulocyte colony-stimulating factor; NPWT, negative-pressure wound therapy; PTA, percutaneous transluminal angioplasty; TNS, total neuropathy score.

at least one open infrapopliteal artery down to the foot, preferably the artery that supplies the anatomical region of the ulcer.⁸⁰ The revascularisation of the plantar arch and branches of the peroneal artery has been suggested recently.^{87–89} The role of revascularisation of the specific angiosome feeding the ulcer area has not been settled.^{90–93}

5.5. Distal bypass procedures

If proximal vessels are free of major wall changes, inflow to the graft can be taken from the superficial femoral or popliteal artery. Distal outflow vessels in diabetics are often heavily calcified, making the distal anastomosis challenging.

Clamping of vessels should be avoided to prevent any lesions distal to the anastomosis. In such cases, gentle obstruction balloons or tourniquet ischaemia provide better visibility while the anastomosis is performed.⁹⁴

The best graft material in distal bypasses is an autogenous vein as it has better patency and resistance to infection than a prosthetic graft. In a retrospective study, the Boston Deaconess Hospital Group reported results from 1032 limb salvage bypasses on the dorsalis pedis artery in 865 patients, mostly diabetics.⁹⁵ The patency of saphenous vein grafts was better than all other conduits, with a secondary patency rate of 67.6% vs. 46.3% at 5 years.⁹⁵

5.6. Immediate outcome after revascularisation

Several conditions, such as chronic renal failure requiring long-term dialysis, an arterial graft of poor quality or severe foot infection may indicate problems in leg salvage.⁹⁶ Diabetes along with coronary artery disease, foot gangrene and an urgent operation have been found to be independent predictors of 30-day post-operative mortality and/or major lower limb amputation after revascularisation for CLI.⁹⁶ Systemic complications are encountered in approximately 10% of patients.⁹⁷

5.7. Endovascular intervention or surgical bypass

There is not a single randomised controlled trial available comparing endovascular and surgical revascularisation in the treatment of impaired perfusion or critical ischaemia in diabetics.^{97,98} A literature search revealed only seven case series on revascularisations exclusively for diabetic feet, provided that all patients were diabetics, had an ulcer and were treated with an infrainguinal revascularisation (Table 2).

As the infrapopliteal region is strongly affected by diabetic PAD, current interest is increasingly targeted on infrapopliteal revascularisations. New endovascular techniques are rapidly evolving, despite the lack of RCTs comparing open and endovascular revascularisations below the knee. However, a recent meta-analysis is available for both infrapopliteal surgery and infrapopliteal endovascular interventions,^{106,107} with 29 and 30 studies included, respectively. As 88% of the patients were diabetics and 88% had tissue loss in the bypass group with 2320 grafts studied, the results may be accepted to be indicative of a diabetic population. Unfortunately, only 61% of the patients in the endovascular group were diabetics and only 76% of them suffered from tissue loss, and the group therefore rather represented a mixed group. No distal pressure data were available. Primary and secondary mid-term patency rates were better after bypass, but there was no difference in limb salvage. The so-called patency/leg-salvage gap seemed wider in the endovascular than in the surgical series – i.e. occlusion of the revascularised segment was less likely to lead to amputation after an endovascular procedure than surgical bypass. It is unclear whether bypass patients had more severe ischaemia pre-operatively or whether open surgery caused more leg morbidity. As the BASIL trial showed, only 29% of patients are suitable for both treatment methods, and patient populations are thus bound to be different in endovascular and surgical series.¹⁰⁸ Bypass surgery and endovascular interventions are therefore complementary techniques for revascularisation in diabetic patients with non-healing ulcers.⁵⁶ Indeed, an analysis of infrapopliteal revascularisations in 611 diabetics with 417 open and 194 endovascular revascularisations showed a comparable outcome in terms of amputation-free survival.⁷⁹

Recommendation

The choice between different methods of revascularisation – open, endovascular or hybrid – depends on comorbidity, severity and extension of the arterial lesions as well as the expertise of the centre. **(Level 2c; Grade B)**

5.8. Microvascular flaps

Microvascular free flaps may be used to cover large tissue defects and ulcers overtaking tendons and bones in diabetic feet. In a recent review there were 17 case series, the largest with 79 patients, 85% of whom were diabetics and 66% of whom underwent a procedure combining revascularisation and free flap transfer.¹⁰⁹ Revascularisations of ischaemic diabetic feet combined with free flap transfer represent only a small fraction – 4% at most – of all interventions to improve diabetic foot perfusion.¹¹⁰

Recommendation

When ischaemia coincides with a large diabetic foot defect, major amputation may be prevented in an ambulatory patient by combining revascularisation with microvascular flap transfer.¹⁰⁹ **(Level 4; Grade C)**

5.9. Timing of the treatment of infection vs. revascularisation

The most important step in controlling deep infection is urgent incision and drainage of an abscess as well as radical debridement of all infected, nonviable necrotic tissue.^{32–34} The debridement should be done first and revascularisation thereafter.^{32–34,48} Distal bypass, when needed, is usually delayed 2–5 days to control the infection.^{94,111,112} Simultaneous revascularisation, preferably endovascularly, in patients without systemic sepsis allows maximising blood flow at the initial debridement. Those having a minor amputation before bypass have been reported to fare worse than those who were revascularised first.¹¹³ Common sense is essential in this setting since purulent lesions necessitate an amputation first whereas mummified gangrene allows revascularisation first.

In situations with no limb-threatening infection, the blood supply to the wound/extremity should be optimised before surgical debridement to ensure that potentially viable tissue is not unnecessarily removed. This may take weeks.

Recommendation

The severity of infection guides the decision whether to debride, to revascularise or to use a simultaneous approach first. **(Level 2c; Grade C)**

5.10. Debridement

Debridement after the damage control phase has been studied extensively. A large review comprising surgical debridement, surgical excision, the use of hyperbaric oxygen, negative-pressure wound therapy, skin grafting, bioactive local therapy products as well as electrical, magnetic, ultrasound and laser therapies¹¹⁴ showed no evidence to prove that one method was better than the others with regard to the probability of healing according to Cochrane Database.^{114–116}

Recommendation

No single method is outstanding in terms of enhancing diabetic ulcer healing. **(Level 1c; Grade A)**

Table 2 Case series including exclusively infrainguinal revascularisations for ischaemic ulcerated diabetic feet

Author	Patients; N/gender/ age (mean/median)	Comorbidity	Intervention	Infra- popliteal distribution	30-day complications	Follow-up (fu)	Outcome
Rosenblum, 1994 ⁹⁹	39/M33, F6/62.3 yrs	NA	Infrapopliteal bypass grafts	79%	Major amputation 3%, mortality NA	21.2 months (mean), range 2–64	83% primary ulcer healing with graft patency during fu
Wölfle, 2000 ¹⁰⁰	125/NA/70 yrs	CAD 57%, ESRD 25%	Infrapopliteal bypass grafts	100%	Major amputation NA, mortality 2%	24 months (mean)	Leg salvage 80% and patency 76% at 1 yr, mortality 51% during fu
Schneider, 2001 ¹⁰¹	84/NA/68 yrs	CAD 48%, ESRD 42%	Infrapopliteal PTA (mostly stenoses)	100%	Major amputation NA, mortality 6%	24 months (mean)	Leg salvage 82% at 1 yr, mortality 35% during fu
Schneider, 2001 ¹⁰¹	110/M67, F43/69 yrs	CAD 43%, ESRD 69%	Revascularisation using either fem-distal bypass, combined SFA PTA and distal bypass grafting or short distal bypass graft	100%	NA	23 months (mean)	Leg salvage 89%, patency 78% at 2 yrs, mortality NA
Faglia, 2002 ¹⁰²	219/NA/NA	CAD 55%, ESRD 4%	Femorodistal and infrapopliteal PTA (of stenoses >50%)	94%	Major amputation 5%, mortality 0%	12 months (median), range 5–30	Leg salvage NA, mortality 5.3% at 1 yr
Dorweiler, 2002 ¹⁰³	46/M36, F10/69 yrs	CAD 46%, ESRD 13%	Pedal bypass grafts	100%	Major amputation 7%, mortality 2%	28 months (median), range 1–70	Leg salvage 87% at 2 yrs
Bargellini, 2008 ¹⁰⁴	60/M41, F19/69.4 yrs	CAD 42%, CVD 25%	Multi-level subintimal PTA in patients unfit for surgery	43%	Major amputation 5%, mortality 5%	23 months (mean), range 0–48	Leg salvage 93.3%, mortality 10% at 1yr
Ferraresi, 2009 ¹⁰⁵	101/M85, F16/66 yrs	CAD 28%, ESRD 3%	Infrapopliteal PTA	100%	NA	35 months (mean)	Leg salvage 93%, mortality 9% during fu

As to hyperbaric oxygen therapy, a recent double-blind RCT demonstrated a significantly improved outcome in the intervention group as the treated patients were more likely to heal within 12 months: 25/48 (52%) vs. 12/42 (27%); $p=0.03$.¹¹⁷ Notably, a favourable outcome seems to be connected to moderate rather than severe ischaemia.^{117–119} A recent systematic review by the NICE Guidelines Development Group in the UK concluded that the available data were insufficient to demonstrate that the intervention was cost-effective.¹²⁰

Recommendation

Hyperbaric oxygen therapy may be indicated for a selected group of diabetic ulcers, but it is not clear which patients are likely to benefit and what is the optimal duration. **(Level 1b; Grade A)**

Negative-pressure wound therapy (NPWT) is used to accelerate healing and to ease local wound therapy. The prerequisite for optimal effect is that there is sufficient blood supply for ulcer healing. Armstrong et al. used a $TcPO_2 \geq 50$ mmHg or toe pressure ≥ 30 mmHg as inclusion criteria in their large multicentre trial.⁵⁸ NPWT does not replace surgical wound debridement and measures to improve blood circulation. There must be no significant infection or gangrene in the wound when NPWT is initiated.

Recommendation

Negative-pressure wound therapy appears to be as effective and, under certain circumstances, more effective than other available local wound treatments in patients without significant infection.^{121,122} **(Level 1a; Grade A)**

5.11. Foot surgery and correction of deformities

There are surgical techniques to offload non-infected ulcers, including surgical excision, arthroplasties, metatarsal head resections and Achilles tendon lengthening. These procedures seem to expedite healing and reduce ulcer recurrence after revascularisation or if tissue perfusion is adequate.¹²³ Elective surgery should be considered to correct structural deformities that cannot be accommodated by therapeutic footwear.

Recommendation

Foot surgery to offload pressure areas may be beneficial to prevent ulcer recurrence after revascularisation for neuroischaemic diabetic foot ulcers. **(Level 4; Grade 5)**

5.12. Minor amputation and removal of necrotic tissue

Minor amputations can be performed under ankle blockade. Minor amputations should be left open whenever skin viability is compromised. Patients with restricted acral gangrene or dry lesions usually benefit from revascularisation first. Patients frequently need several debridements and care lasting several months before ulcers have healed even after successful bypass.¹¹¹ Heel ulcers are especially vulnerable as poor perfusion in the heel fat pad and the danger of debriding into the calcaneus may expose the area to deep infection. Once the ulcer bed infection has subsided,

healing per second intention, or covering of the wound should be discussed.

Recommendation

Toe, ray and transmetatarsal amputations are preferred whenever possible as they enable a broader distribution of weight during ambulation.¹⁰ **(Level 4; Grade 5)**

5.13. Amputations

Amputations are urgent or curative.¹²⁴ Indications for an amputation include the removal of infected or gangrenous tissue, controlling infection and creating a functional foot or stump that can accommodate footwear or a prosthesis. The preservation of leg length aids ambulation and decreases energy expenditure. Yet the surgical site should heal primarily. A closed toe and metatarsal amputation typically leave the patient with a functional foot for walking.^{10,125–127}

If the healing of a toe is in doubt, metatarsal amputations should be used liberally after revascularisation. Piecemeal amputations should be avoided. In situations involving extensive tissue loss and precluding a functional foot, as well as when there are non-healing wounds despite patent revascularisation and for controlling sepsis, amputation below the knee is necessary.¹²⁸

Recommendation

Bedridden patients, poor ambulation that is not worsened by amputation, life expectancy less than 1 year, and a non-revascularizable leg are indications for performing a major amputation, even above the knee when necessary. **(Level 4; Grade D)**

6. Outcomes

6.1. Ulcer healing

As an example of the recent positive trend in healing rates, it has been observed that 50–60% of ulcers had healed at 20 weeks of observation and more than 75% had healed at 1 year.¹¹ Yet it is difficult to obtain reliable data on ulcer healing rates in diabetic populations. Furthermore, the definition and observation time may cause problems in the assessment of wound healing. Typically, heel ulcers heal slowly. The completeness of revascularisation seems important as shown by the predictive value of post-procedural $TcPO_2$ measurements by Faglia et al.⁵⁹ Complete tissue healing after infrainguinal bypass, including the healing of ischaemic tissue lesions and surgical wounds, was 26% at 6 months and 63% at 1 year, which was slower than in non-diabetics.¹²⁹ The median time to complete tissue healing was 213 days in diabetics and 159 days in non-diabetics.¹²⁹ In a large study by Apelqvist et al., 801 patients underwent angiography, and 297 were treated medically, 314 by an endovascular technique, and 190 by open surgical revascularisation. Revascularisations improved ulcer healing, whereas the number of ulcers and severity of PAD as well as congestive heart failure and renal function impairment were associated with poor ulcer healing.¹³⁰ Renal failure has been reported to independently predict non-healing of neuroischaemic foot lesions (OR 3.04).⁶

6.2. Leg salvage

Leg salvage is a composite endpoint and only an indirect measure of successful revascularisation – only half of the diabetic patients with CLI were observed to undergo major amputation within 6 months if they were not candidates for revascularisation.¹³¹ Occlusion of all three crural arteries, dialysis, wound infection, multiple ulcers, oedema and non-compliance to treatment increase the risk of major amputation.^{16,51} Leg salvage rates of approximately 80% at 1 year and roughly 70% at 3 years have been reported after revascularisations.⁹⁷ Diabetic patients with end-stage renal disease (ESRD) and gangrene are at high risk of losing their leg despite successful infrapopliteal revascularisation.^{132,133}

Proper patency data on revascularisations for ulcerated diabetic feet are not available as almost all series mix diabetics and non-diabetics as well as different indications and levels of disease.⁹⁷

6.3. Mortality

Diabetic patients with CLI have been observed to have 53% mortality at 6 months if not suitable for revascularisation.¹³¹ ESRD and coronary heart disease increase mortality.^{51,130} Peri-operative mortality in reported revascularisation series tends to be mostly below 5%.⁹⁷ Mortality is roughly 10–20% at 1 year and 40–50% at 5 years after open surgery; long-term data are missing in endovascular series.⁹⁸

6.4. Quality of life

Successful revascularisation for critical ischaemia improves the quality of life for diabetics.^{134,135} Concurrent diseases limit the chances of improving quality of life. Indeed, diabetics with impaired ambulatory status and gangrene at presentation had an 83% probability (OR 10.5) of not benefiting from the intervention, and for those also with end-stage renal disease and prior vascular surgery, the probability of failure was 93% (OR 23.7).¹³⁶

Recommendation

Comorbidities, especially renal failure and impaired ambulatory status, at presentation are major factors for poor outcome in diabetics with ischaemic ulcers. These comorbidities should be taken into consideration when deciding whether or not to revascularise. **(Level 2a; Grade B)**

7. Multidisciplinary team approach

7.1. Multidisciplinary team

Diabetic foot ulcers should be managed by a multidisciplinary team, comprising individuals who can deliver all the necessary and wide-ranging skills: medical and surgical as well as podiatric, nursing and orthotic experts.¹²³ Using a protocol-driven and multidisciplinary approach will lower the number of diabetics suffering from numerous foot complications. Education, presented in a structured and organised manner, also plays an important role in the prevention of foot problems when combined with podiatry

and the use of adequate preventive footwear and offloading techniques.

The associated systemic factors that impair wound healing need to be treated; these include hyperglycaemia, cardiovascular disease, peripheral vascular disease, increased incidence of bacterial infections, and plantar pressure redistribution.¹³⁷ The medical management of ulcers includes offloading, treatment of infection (local, cellulitis, osteomyelitis or sepsis), debridement, wound bed preparation and dressings. Surgery is often needed to revascularise the limb, to treat the infected ulcers and to achieve offloading.

A multidisciplinary approach is supported by the complexity of the disease in patients with diabetic foot ulcers as most of them present with multi-organ disease. Comparative cohort studies with regard to healing and amputations, epidemiological studies on incidence and diabetic-foot-related amputations as well as health economic studies strongly support this approach.

Vascular diagnostics and intervention are an integral part of the strategy but are implemented conservatively, the main reason being a poorly functioning treatment chain with delayed referrals to vascular centres.^{2,17} To improve amputation prevention, this window of opportunity should not be missed.^{4,6,16,29,30} According to the most optimistic view, up to 85% of amputations may be prevented by a multidisciplinary approach.¹⁷

Recommendation

Early referral and intervention are crucial for to improve diabetic foot ulcer healing and to prevent amputation:

- Do non-invasive vascular testing to all individuals with diabetes and a foot ulcer.
- Image if non-invasive tests indicate ischaemia or when mild or questionable ischaemia is diagnosed and conservative treatment (Table 1) does not promote ulcer healing (in 4–8 weeks)
- Revascularise to repair distal perfusion to promote ulcer healing whenever feasible.

(Level 2b; Grade B)

8. Summary

The incidence of diabetes is increasing, and diabetic foot ulcers continue to be a growing challenge for healthcare as well as for vascular services. A neuroischaemic diabetic foot is far more common than is usually thought. From a practical point of view, diabetics with neuroischaemic feet and the small group of diabetics with purely ischaemic ulcerated diabetic feet should be lumped together. A diabetic foot ulcer should always be considered to have vascular impairment unless otherwise proven.

There is a paucity of data on how to diagnose and treat these diabetic patients in the best possible way. Most of the studies dealing with neuroischaemic diabetic feet are not comparable in terms of patient populations, interventions or outcome. Therefore, there is an urgent need for a paradigm shift in diabetic foot care – i.e. a new approach and classification of diabetics with impaired perfusion with regard to clinical practice and research. A multidisciplinary approach needs to be implemented systematically so as to

intervene with a diabetic foot with impaired arterial supply to improve healing and to avoid amputation irrespective of the technique chosen.

Conflict of Interest/Funding

None

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Chapter VI: Follow-up after Revascularisation

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KEYWORDS

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Abstract Structured follow-up after revascularisation for chronic critical limb ischaemia (CLI) aims at sustained treatment success and continued best patient care. Thereby, efforts need to address three fundamental domains: (A) best medical therapy, both to protect the arterial reconstruction locally and to reduce atherosclerotic burden systemically; (B) surveillance of the arterial reconstruction; and (C) timely initiation of repeat interventions. As most CLI patients are elderly and frail, sustained resolution of CLI and preserved ambulatory capacity may decide over independent living and overall prognosis. Despite this importance, previous guidelines have largely ignored follow-up after CLI; arguably because of a striking lack of evidence and because of a widespread assumption that, in the context of CLI, efficacy of initial revascularisation will determine prognosis during the short remaining life expectancy. This chapter of the current CLI guidelines aims to challenge this disposition and to recommend evidentially best clinical practice by critically appraising available evidence in all of the above domains, including antiplatelet and antithrombotic therapy, clinical surveillance, use of duplex ultrasound, and indications for and preferred type of repeat interventions for failing and failed reconstructions. However, as corresponding studies are rarely performed among CLI patients specifically, evidence has to be consulted that derives from expanded patient populations. Therefore, most recommendations are based on extrapolations or subgroup analyses, which leads to an

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almost systematic degradation of their strength. Endovascular reconstruction and surgical bypass are considered separately, as are specific contexts such as diabetes or renal failure; and critical issues are highlighted throughout to inform future studies.

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1. Introduction

Follow-up after revascularisation for chronic critical limb ischaemia (CLI) should ensure not only best clinical results including survival, limb salvage and resolution of chronic CLI with sustained functional improvement and improved quality of life, but also timely amputation in case of failure and improved cost-efficiency by structured outcome analysis.¹ Appropriate endpoints for assessment of these goals, however, are still used inconsistently, which handicaps comparisons.²

Follow-up after revascularisation needs to address three main issues: (A) best medical therapy, (B) surveillance of arterial reconstruction and (C) indication of repeat revascularisation or timely amputation. As patients with CLI are usually elderly and frail, preserved ambulatory capacity will often decide over independent living, but efforts at limb salvage need to be balanced realistically against the likelihood of continued independence. An associated challenge is the implementation of structured follow-up, which is difficult to achieve even in solid studies with rigorous record-keeping.³ Most studies are retrospective and use inconsistent reporting standards, and only a few are stratified for presence of CLI. This explains why high-level evidence is scarce, particularly for follow-up after endovascular reconstruction;² and why follow-up after revascularisation for CLI has largely been ignored in previous guidelines.^{4,5}

Critical issue

There is a need for well-designed clinical studies evaluating follow-up strategies and indications for specific prognostic, diagnostic or therapeutic interventions during follow-up after revascularisation for CLI.

2. Best medical care

Best medical treatment and smoking cessation advice are considered a mainstay of care for all vascular patients, even though this has not been explored specifically in the context of CLI. Monitoring of patient compliance is of paramount importance and an effective way to involve primary care providers into a general therapeutic concept.

2.1. Best medical treatment and cardiovascular risk reduction

The evidence for best medical treatment and systemic cardiovascular risk reduction is addressed in Chapter III (Management of Cardiovascular Risk Factors and Medical Therapy, pp. S33–S42) and should be applied independently of the type of local revascularisation that has been achieved.

A *post hoc* analysis of the PREVENT III cohort⁶ investigated the efficacy of statins, beta blockers and antiplatelet agents during follow-up in 1404 patients with CLI undergoing venous bypass grafting. Use of statins was independently associated with a statistically significant survival advantage at 1 year

(HR 0.67; 95%CI 0.51–0.90; $p=0.001$), but none of the drug classes taken separately was associated with a better graft patency in this study. In contrast, daily use of statins in addition to acetylsalicylic acid (ASA) almost halved rates of both restenosis (42% vs. 22%) and lower limb amputation (21% vs. 11%) at 1 year after percutaneous transluminal angioplasty in patients with severe claudication or CLI.⁷ A similar favourable effect of statins on graft patency (OR 3.7; 95%CI 2.1–6.4) and amputation rate (OR 0.34; 95%CI 0.15–0.77) has also been observed at 1.5 years after venous bypass grafting (70% CLI patients) in other studies.^{8,9}

2.2. Platelet inhibition and antithrombotic therapy

Venous grafts used as arterial bypass suffer the loss of their endothelial layer within days after implantation,¹⁰ which triggers increased expression and exposure of tissue factor within the vein graft. The ensuing thrombogenic process is led primarily by the activated coagulation system, although activated platelets may also play a role.¹¹ In contrast, introduction of a prosthetic surface such as polyethylene terephthalate (PET), PTFE or endovascular stents initiates a thrombogenic process that is led predominantly by activated platelets.

This may explain consistent observations of a differential efficacy of antiplatelet vs. antithrombotic agents regarding prevention of thrombotic occlusion of vascular reconstructions,^{11–13} although none of these Cochrane meta-analyses was stratified for CLI. However, reconstructions for CLI can be assumed particularly prone to thrombotic occlusion due to low flow, suggesting that findings as shown in Table 1 remain pertinent to patients with reconstructed CLI.

2.2.1. Surgical reconstruction

After lower limb bypass, antiplatelet treatment (i.e. ASA alone or in combination with dipyridamole) improves primary patency at 1-year follow-up.¹² However, the size of this effect differs when patients with prosthetic and venous grafts are considered separately. In patients with PTFE or PET bypass, antiplatelet drugs are more efficient and improve primary patency as early as 1 month after surgery with a durable effect thereafter. In contrast, patients with venous bypass benefit less from platelet inhibition and the effect becomes statistically significant only at 1-year follow-up.¹² Ticlopidine, another antiplatelet agent, may be more effective. In a multicentre RCT comparing ticlopidine vs. placebo, ticlopidine significantly improved primary venous graft patency rates at 6, 12 and 24 months but not at 3 months.¹⁴

In contrast, vitamin K antagonists (VKA) have a strong but time-limited protective effect occurring early on venous graft patency at 3 and 6 months, but disappearing at 1, 2 and 5 years.¹¹ Attempts to improve venous graft patency with heparin have produced conflicting results: although daily administration of 2500 international units (IU) of low-molecular-weight heparin (LMWH) for 3 months after bypass surgery did not confer any benefit as compared to 300 mg ASA across a single-institution RCT, stratified analysis of the

Table 1 Summary table of randomised controlled trials assessing efficacy of antithrombotic and antiplatelet treatment after revascularisation for CLI^a

Comparison	(meta)analysis of	No. of patients	Study group	Control group	Effect of intervention
Vein bypass (evidence not stratified for chronic CLI)					
Vitamin K antagonist vs. no vitamin K antagonist	Arfvidsson et al., <i>Am J Surg</i> 1990;159:556–60 Johnson et al., <i>J Vasc Surg</i> 2002;35:413–21 Kretschmer et al., <i>Arch Surg</i> 1992;127:1112–5 Sarac et al., <i>J Vasc Surg</i> 1998;28:446–57	235	Vitamin K antagonist (target prothrombin time <30%, or INR 1.4 to 3.5) with or without acetylsalicylic acid	No vitamin K antagonist, administration of acetylsalicylic acid possible	Positive effect of vitamin K antagonists on primary patency. OR for restenosis/occlusion at 6 months was 0.41 (95% CI 0.17 to 0.96).
Acetylsalicylic acid/dipyridamole vs. nothing/placebo	Clyne et al., <i>Br J Surg</i> 1987;74:246–8. McCollum et al., <i>J Vasc Surg</i> 1991;13:150–62 Kohler et al., <i>Surgery</i> 1984;96:462–6	723	2–3×325 mg acetylsalicylic acid/2–3×75 mg dipyridamole	Placebo	Moderately positive effect of acetylsalicylic acid on restenosis/occlusion rates with overall OR of 0.69 (95% CI 0.48 to 0.99)
Acetylsalicylic acid vs. vitamin K antagonists	BOA Study Group, <i>Lancet</i> 2000;355:346–51 Schneider et al., <i>Angio</i> 1979;2:73–7	1637	80 to 1000 mg acetylsalicylic acid	Vitamin K antagonist (aim for Quick 25–30%; or INR 3.0–4.5)	Sustained favourable effect of vitamin K antagonists on primary patency. OR for restenosis/occlusion at 24 months was 0.59 (95% CI 0.46 to 0.76).
Ticlopidine vs. placebo	Becquemini et al., <i>NEJM</i> 1997;337:1726–31	243	250 mg ticlopidine	Placebo	Sustained favourable effect of ticlopidine on primary patency. OR for restenosis/occlusion at 24 months was 0.37 (95% CI 0.21 to 0.64).
Acetylsalicylic acid/dipyridamole vs. low molecular weight heparin	Edmondson et al., <i>Lancet</i> 1994;334:914–8	56	3×300 mg acetylsalicylic acid/3×75 mg dipyridamole for 3 months	2500 IU low molecular weight heparin for 3 months	Positive but statistically nonsignificant effect of low molecular weight heparin
Low molecular weight vs. unfractionated heparin	Samama et al., <i>Ann Vasc Surg</i> 1995;9:S45–53 Swedenborg et al., <i>Eur J Vasc Endovasc Surg</i> 1996;11:59–64	153	Low molecular weight heparin twice daily for 10 days	Unfractionated heparin	Beneficial effect of low molecular weight heparin: OR for early graft thrombosis at 30 days was 0.41 (95% CI 0.20 to 0.85). Not stratified for graft type.

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Table 1 (continued)

Comparison	(meta)analysis of	No. of patients	Study group	Control group	Effect of intervention
Prosthetic bypass (evidence predominantly for intermittent claudication)					
Acetylsalicylic acid/dipyridamole vs. nothing/placebo	Green et al., Surgery 1982;92:1016-26 Goldman et al., Vasc Surg 1984;18:217-21 Kohler et al., Surgery 1984;96:462-6 Donaldson et al., Vasc Surg 1985;19:224-30 Clyne et al., Br J Surg 1987;74:246-8.	261	2-3×325 mg acetylsalicylic acid/2-3×75 mg dipyridamole	Placebo	Protective effect of acetylsalicylic acid: OR for restenosis/occlusion at 12 months 0.22 (95%CI 0.12 to 0.38).
Vitamin K antagonist vs. no vitamin K antagonist	Arfvidsson et al., Am J Surg 1990;159:556-60 Johnson et al., J Vasc Surg 2002;35:413-21	661	Vitamin K antagonist (target prothrombin time <30%, or INR 1.4 to 3.5) with or without acetylsalicylic acid	No vitamin K antagonist, administration of acetylsalicylic acid possible	No statistically significant effect of vitamin K antagonist on primary patency at 24 months (OR 0.72; 95%CI 0.40 to 1.29). Moderate but significant effect at 5 years (OR 0.43; 95%CI 0.26 to 0.73)
Acetylsalicylic acid vs. vitamin K antagonists	BOA Study Group, Lancet 2000;355:346-51	1104	80 mg acetylsalicylic acid	Vitamin K antagonist (aim for INR 3.0-4.5)	Advantage for acetylsalicylic acid regarding primary patency. OR for restenosis/occlusion at 24 months was 1.41 (95%CI 1.11 to 1.80).
Acetylsalicylic acid/dipyridamole vs. low molecular weight heparin	Edmondson et al., Lancet 1994;334:914-8	144	3×300 mg acetylsalicylic acid/3×75 mg dipyridamole for 3 months	2500 IU low molecular weight heparin for 3 months	Positive but statistically nonsignificant effect of low molecular weight heparin
Low molecular weight vs. unfractionated heparin	Sanama et al., Ann Vasc Surg 1995;9:S45-53	64	Low molecular weight heparin twice daily for 10 days	Unfractionated heparin	Beneficial effect of low molecular weight heparin: OR for early graft thrombosis at 30 days was 0.41 (95%CI 0.20 to 0.85). Not stratified for graft type.

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Table 1 (continued)

Comparison	(meta)analysis of	No. of patients	Study group	Control group	Effect of intervention
Infrainguinal endovascular intervention (evidence predominantly for intermittent claudication)					
Acetylsalicylic acid vs. placebo	Heiss et al., <i>Angiology</i> 1990;41:263–9 Study Group, <i>Eur J Vasc Surg</i> 1994;8:83–8	356	50 mg to 330 mg acetylsalicylic acid	Placebo	OR for occlusion at 6 months 0.69 (95% CI 0.44 to 1.10), significant only for 330 mg
Acetylsalicylic acid high dose vs. low dose	Heiss et al., <i>Angiology</i> 1990;41:263–9 Minar et al., <i>Circulation</i> 1995;91:2167–73 Weichert et al., <i>Vasa</i> 1994;23:57–65 Ranke et al. <i>Clinical Investigator</i> 1994;72:673–80.	930	330 mg to 1000 mg acetylsalicylic acid	50 mg to 300 mg salicylsalicylic acid	No positive effect regarding occlusion for high dose at 6 months (OR 0.99, 95% CI 0.71 to 1.38). Similar for other time points up to 24 months. However, more side effects
Acetylsalicylic acid/dipyridamole vs. vitamin K antagonist	Pilger et al., <i>Circulation</i> 1991; 83:141–7 Do et al., <i>Radiology</i> 1994;193:567–71	289	75 mg to 3×330 mg acetylsalicylic acid/75 mg to 200 mg dipyridamole	Vitamin K antagonist	No difference regarding occlusion up to 12 months: OR 0.65 (95% CI 0.40 to 1.06)
Ticlopidine vs. vitamin K antagonist	Schneider et al., Hans Huber, <i>Fortschr Angiol</i> 1987): 355–6	197	2×500 mg ticlopidine	Vitamin K antagonist	Statistically non-significant advantage of ticlopidine, OR for occlusion at 12 months 0.71 (95% CI 0.37 to 1.36)
Low molecular weight vs. unfractionated heparin	Schweizer et al., <i>Angiology</i> 2001;52:659–69	172	Low molecular weight heparin at therapeutic dose (7 days), 6 months 200 mg acetylsalicylic acid	Unfractionated heparin at therapeutic dose (7 days), 6 months 200 mg acetylsalicylic acid	Significant advantage of low molecular weight heparin, OR for restenosis/reocclusion at 6 months 0.35 (95% CI 0.19 to 0.65)
Abciximab vs. placebo	Dörffler et al., <i>Radiology</i> 2005;237:1103–9	98	Abciximab perfusion for 12h	Placebo	Positive effect of peri-interventional abciximab on primary patency, OR at 6 months 0.43 (95% CI 0.19 to 0.98)

^a Adapted from Sasaki et al.,¹⁰ Dörffler-Melly et al.¹¹ and Brown et al.¹²

subset of CLI patients suggested markedly improved patency rates at 6 and 12 months.¹⁵ However, addition of LMWH to ASA failed to improve primary graft patency in a RCT of 284 CLI patients.¹⁶

In a comparison of VKA and ASA alone or in combination with dipyridamole, VKA was superior in 1637 patients with venous grafts, whereas antiplatelet agents had a stronger effect on 1104 prosthetic grafts at 2 years.¹¹

Finally, the multicentre CASPAR trial¹⁷ randomly assigned 851 patients receiving below-the-knee bypass surgery to ASA alone or to ASA plus thienopyridine (clopidogrel). Endpoints of the study were bypass patency, absence of restenosis, major amputation or death. No difference was observed in this trial among the two groups, but a subgroup analysis suggested a benefit of dual antiplatelet therapy for patients receiving prosthetic grafts (HR 0.65; 95% CI 0.45–0.95; $p=0.025$). This was achieved without a significant increase of the risk of major bleeding.

The therapeutic range of vitamin K antagonism needs consideration as improved anticoagulation control seems to halve the risk of adverse events.¹⁸ In a general population, the optimum risk–benefit range lies between an international normalised ratio (INR) of 2 and 3,¹⁹ with moderately higher INR still safe. For peripheral artery bypass surgery, patients spending most time during follow-up in an INR range between 3 and 4 had fewest thrombo-embolic or haemorrhagic events in a *post hoc* analysis of the Dutch BOA trial cohort.²⁰

To summarise the current literature, it appears that platelet inhibitors improve graft patency rates as compared to placebo. Patients with a prosthetic graft are likely to benefit more from platelet inhibitors than those with a venous graft. On the other hand, patients with a venous bypass appear to benefit more from vitamin K antagonists than platelet inhibitors, particularly following below-the-knee bypass. But these results should be interpreted with caution due to the heterogeneity of the studies including different proportions of patients with CLI and several types of reconstructions.

2.2.2. Endovascular reconstruction

Administration of ASA combined with dipyridamole appears to reduce the incidence of restenosis or occlusion after superficial femoral artery (SFA) endovascular intervention by 60% at 1 year.¹³ However, this result could be confounded by a high proportion of claudicants as platelet inhibitors might be less effective in patients with CLI. A meta-analysis of four trials comparing high-dose (300–1000 mg) to low-dose (50–300 mg) ASA regimens indicated that higher doses did not significantly improve patency rates but increased gastrointestinal side effects.¹³

Although platelet inhibitors seem generally superior to VKA, single pathway inhibition may be insufficient to protect extensive endovascular reconstructions.^{13,21} According to a small single-centre RCT, GPIIb/IIIa inhibitors such as abciximab are promising to prevent early thrombotic occlusions in high-risk situations.²¹ However, abciximab has to be administered intravenously and its long-term effects are unclear.

Another single-centre RCT involved 275 patients undergoing peripheral artery angioplasty to compare the effect of 2500 IU of LMWH in addition to ASA vs. ASA alone for 3 months. Although no effect was observed across the trial,

a subgroup analysis of patients with CLI showed a risk reduction from 72% to 45%.²²

To summarise these findings, there is no high-level evidence regarding the optimum antithrombotic strategy after endovascular interventions for CLI (Table 1). Long-term platelet inhibitors (50–300 mg ASA) appear to be the preferred drug therapy compared to vitamin K antagonists. Platelet inhibitors should be given prior to intervention. Evidence from coronary interventions suggests that more potent platelet inhibitors such as thienopyridines (clopidogrel) or dual antiplatelet therapy might confer additional benefits; however, specific data for CLI are lacking. Finally, time-limited subcutaneous administration of LMWH may improve primary patency following peripheral artery angioplasty.

2.3. Exercise training

There is conclusive evidence that exercise training is beneficial for patients suffering from claudication,²³ particularly if supervised.²⁴ However, no study has addressed the potential value of supervised exercise training in CLI patients recovering from revascularisation. One reason may be that these frail patients often present with co-existent morbidity, which may compromise compliance with a structured exercise programme or make it impractical. Nonetheless, exercise training may be assumed beneficial in CLI patients who become asymptomatic or with a mild claudication remaining after arterial revascularisation.

Recommendations

Following vein bypass surgery for CLI, ASA or ASA combined with dipyridamole, is efficient in lowering the incidence of thrombotic occlusions (**Level 1b; Grade B**); however, vitamin K antagonists are superior when closely monitored and should be preferred in suitable patients during early follow-up, particularly for below-the-knee bypass. (**Level 1b; Grade B**)

Ticlopidine is efficient in protecting vein bypass from occlusion (**Level 1b; Grade B**) and may be used as an alternative to vitamin K antagonists. (**Level 3; Grade D**)

Daily administration of 2500 IU of low molecular weight heparin during 3 months after venous bypass may be beneficial (**Level 2b; Grade C**) and is superior to unfractionated heparin. (**Level 1b; Grade B**)

After prosthetic bypass or endovascular revascularisation, ASA, or ASA combined with dipyridamole, should be given daily at low dose (50 to 300 mg) to lower the incidence of bypass or angioplasty occlusions (**Level 1b; Grade B**). Additional use of thienopyridine (clopidogrel) may be beneficial without increasing the risk of major bleeding. (**Level 2b; Grade C**)

In general, vitamin K antagonists do not seem efficient for prosthetic bypasses (**Level 1b; Grade B**); however, they may be considered additionally to platelet inhibitors for low-flow (<45 cm/s) prosthetic grafts. (**Level 4; Grade C**)

Vitamin K antagonists should be closely monitored to lower the risk of adverse events (**Level 2b; Grade B**). An INR between 2 and 4 is efficient for patients receiving surgical bypass, but values between 3 and 4 seem most efficient and are probably safe. (**Level 2b; Grade C**)

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Recommendations (cont'd)

Continued use of statins is associated with improved patency rates and limb salvage after venous bypass and endovascular reconstruction. **(Level 2b; Grade C)**

Whenever possible, patients with CLI should be motivated to undergo supervised exercise training following a successful revascularisation. **(Level 5; Grade D)**

Critical issues

- Several studies have suggested an adverse effect of increased homocysteine serum levels on progression of atherosclerosis.^{25,26} Homocysteinaemia-lowering therapy is theoretically available; however, its clinical value is still unknown²⁵ and should be addressed in RCTs.
- Similarly, the value of (supervised) exercise training after revascularisation of CLI should be established.
- In current practice, many vascular centres give platelet inhibitors to patients with a venous bypass, although, regarding graft patency, available evidence favours VKA.¹¹ Probable reasons are concerns regarding compliance of these elderly patients and anticipated difficulties to ensure safe VKA levels. Besides, local benefits may be considered less important than systemic protective effects of platelet inhibitors, which are detailed in Chapter III. Therefore, it would be interesting to compare a dual antiplatelet regimen to VKA in CLI patients. On any account, optimum duration of VKA after venous bypass needs to be established as protective early effects may be time-limited.
- Similarly, the role of clopidogrel, or clopidogrel in combination with ASA, needs to be evaluated in prosthetic grafts and endovascular reconstructions as does the optimal therapeutic range of VKA and its duration.
- New antithrombotic agents including direct thrombin inhibitors, mega-pentasaccharides, tissue factor/factor VIIa complex inhibitors and oral factor Xa inhibitors might be promising perspectives and should be properly evaluated. Particularly factor Xa inhibitors may be safer and easier to use than vitamin K antagonists, but approval for use outside prevention of thromboembolism is pending.
- For CLI patients, RCTs should not only concentrate on primary patency rates but also integrate other clinically meaningful endpoints such as limb salvage, resolution of CLI and survival.²

3. Surveillance

The goal of arterial reconstructions is to improve arterial blood flow. Therefore, surveillance of sustained treatment success usually concentrates on monitoring patency (Table 2). However, sustained patency may not always be needed to achieve limb salvage or to obtain resolution of CLI.^{29,36} Conversely, around 10% of patent reconstructions eventually fail despite improved macro-circulation.^{37–39} Pre-operative factors such as independency and mental capacity may be important independent predictors of functional recovery.^{39–41} Therefore, primary patency alone may not be the ideal surrogate measure for treatment success,²⁹ and other efficacy measures should also be considered.²

Prospective analyses suggest that the quality of life of CLI patients depends directly on sustained patency of the reconstruction.⁴² As revisions for failing grafts are far more successful than revisions for failed grafts and generate less cost,^{43–45} surveillance programmes have been recommended to detect failing grafts and to prevent graft occlusion.²⁷ But no study has ever examined the value of surveillance programmes as such by comparing surveillance to no surveillance (Table 2). There is also a controversy regarding the best and most cost-effective surveillance method.⁴⁶ Regular clinical revaluations including interval patient history, clinical examination and non-invasive assessment of perfusion using ankle-brachial pressure index (ABI) are generally accepted. The controversy exists on whether additional routine screening by duplex ultrasound confers any clinical benefit (Table 2).¹

3.1. Surveillance of surgical reconstruction**3.1.1. Autologous vein bypass**

Venous grafts are prone to stenoses during follow-up precipitating reduced blood flow and graft failure.⁴⁷ Most stenoses occur within the first year, and about 25–30% of vein grafts are affected.⁴⁴ Nature of failure varies according to its timing.²⁹ Failure within 30 days is usually attributed to a technical surgical error, whereas failure between 30 days and 1 year is usually due to developing stenosis. Both are obvious targets of surveillance efforts. In contrast, late failure often follows progression of the disease and is conceptually addressed by best medical care.

Duplex ultrasound scanning is the preferred non-invasive method for detecting stenotic lesions (see Chapter II, Diagnostic Methods, pp. S13–S32). A systematic review of 6649 vein grafts concluded that colour duplex (CD) surveillance significantly reduced the total number of occluded grafts as well as the incidence of graft occlusions after 30 days;^{27,33} However, overall limb salvage was not improved by CD screening.²⁷

Although there is no RCT exploring the potential benefit of CD surveillance specifically among CLI patients, four RCTs have investigated CD in a large population receiving surgical bypass.¹ Three RCTs concentrated on venous bypass,^{3,28,29} and one RCT also included prosthetic grafts.³¹ The latter randomly assigned 156 patients to either CD screening every 3 months for 2 years or to clinical surveillance including ABI measurements at yearly intervals. At 3 years, assisted primary and secondary patency rates were significantly improved by CD screening (78% vs. 53% and 82% vs. 56%, respectively; $p < 0.05$); however, amputation rates were not affected.³¹ In contrast, no difference was found in another trial between CD and ABI measurements at 3-month intervals regarding patency and limb salvage at 1 year even though more grafts had been revised under CD screening.²⁸ This finding was essentially confirmed by the largest RCT²⁹ that involved 594 patients receiving vein bypass and demonstrated that CD surveillance failed to confer a clinical benefit in terms of limb salvage or quality of life, but incurred additional costs.

None of these trials was stratified for CLI. Moreover, only patients with a patent graft at 4–6 weeks after surgery were randomised. However, a likely key benefit of CD is the early identification of silent lesions; therefore exclusion of the patients with early graft abnormalities may have missed one

Table 2 Summary table of studies assessing postprocedure duplex surveillance^a

Study (year)	Study type	No. of patients (limbs)	% with CLI (with prosthetic bypass)	Surveillance strategy	Control group	Outcome measure	Mean follow-up (mo)	Findings	Conclusion
Golledge et al. (1996) ²⁷	Systematic review of observational studies (n = 43), including uncontrolled studies	Not given (6257 limbs undergoing bypass)	72 (0)	Duplex and clinical surveillance	Clinical follow-up	Rates of graft occlusion, mortality and limb salvage	40–49	Total number of deaths, occluded grafts and occlusions after 30 days were significantly greater in control group. Peri-operative occlusion rates were not significantly different. The numbers of amputations were not significantly different between the two groups	Comparison of surveillance and non-surveillance studies. The patency of infrainguinal vein grafts is improved by surveillance, no improvement can be demonstrated with respect to limb salvage rates.
Ihlberg et al. (1998) ³	Randomised controlled trial, single centre	179 (185 limbs undergoing bypass)	84 (0)	Duplex and clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Rates of primary patency, assisted primary patency, secondary patency and limb salvage	12	56% primary patency in surveillance group vs. 68% in control group; 65% assisted primary patency in surveillance group vs. 74% in control group; 71% secondary patency in surveillance group vs. 84% in control group; 81% limb salvage in surveillance group vs. 88% in control group.	This study failed to show any beneficial effect of duplex scanning in a surveillance program. However, occluded grafts and amputees at 1 month were excluded and the main difference in outcome appeared during this first postoperative month, i.e. before the commencement of the surveillance program.
Ihlberg et al. (1999) ²⁸	Randomised controlled trial, single centre	344 (362 limbs undergoing bypass)	83 (0)	Duplex and clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Clinical surveillance including ABI measurement at 1, 3, 6, 9 and 12 months	Rates of assisted primary patency, secondary patency and limb salvage	12	78% assisted primary patency in surveillance group vs. 77% in control group; 83% secondary patency in surveillance group vs. 87% in control group; 93% limb salvage in surveillance group vs. 94% in control group.	Includes patients of 1998 publication and reconfirms its findings: intensive surveillance with duplex scanning did not improve the results of any outcome criteria examined
Davies et al. (2005) ²⁹	Randomised controlled trial, multicentre	594 (594 limbs undergoing bypass)	66 (0)	Duplex and clinical surveillance including ABI measurement at 6 weeks, 3, 6, 9, 12 and 18 months	Clinical surveillance including ABI measurement at 6 weeks, 3, 6, 9, 12 and 18 months	Rates of major amputation, vascular mortality and primary patency	18	7% amputations in surveillance group vs. 7% in control group; 3% vascular mortality in surveillance group vs. 4% in control group; 69% primary patency in surveillance group vs. 67% in control group	Intensive surveillance with duplex scanning 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. However, occluded grafts at 1 month were excluded.

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Table 2 (continued)

Study (year)	Study type	No. of patients (limbs)	% with CLI (with prosthetic bypass)	Surveillance strategy	Control group	Outcome measure	Mean follow-up (mo)	Findings	Conclusion
Mofidi et al. (2007) ³⁰	Explorative cohort study, single centre	352 (364 limbs undergoing bypass)	77 (0)	Duplex and clinical surveillance at 6 weeks, 3, 6 and 12 months. Clinical follow-up afterwards	No control group	Rates of primary patency, stenosis progression and major amputations according to degree of flow disturbance at initial scan.	23	82% cumulative patency and 93% limb salvage at 40 months for initially normal grafts; 38% lesion progression/10% occlusion for initially mild stenosis; 56%/16% for initially intermediate stenosis; and 52%/38% for initially critical stenosis	Flow abnormalities at 6 weeks can be used to select grafts for continued duplex surveillance. However, for grafts without any flow abnormality, the yield from continuing with duplex surveillance is likely to be low and probably little better than what is achievable by simple clinical follow-up.
Lundell et al. (1995) ³¹	Randomised controlled trial, single centre	156 (156 limbs undergoing bypass)	94 (32)	Duplex and clinical surveillance including ABI measurement at 1, 3, 6, 9, 12, 15, 18, 24, and 36 months	Clinical surveillance including ABI measurement at 1, 12, 24, and 36 months	Rates of assisted primary patency, secondary patency and repeat procedures	36	Vein grafts: 78% (82%) assisted primary (secondary) patency in surveillance group vs. 53% (56%) in control group. Prosthetic grafts: 57% (67%) assisted primary (secondary) patency in surveillance group vs. 50% (54%) in control group.	Intensive surveillance identified failing vein grafts leading to a significantly higher assisted primary and secondary patency compared with controls. The patency of prosthetic and composite grafts was not influenced by intensive surveillance.
Dunlop et al. (1996) ³²	Explorative case series, single centre	65 (69 limbs undergoing bypass)	61 (100)	Duplex and clinical surveillance including ABI measurement at 3 monthly intervals	No control group	Detection of treatable lesions before graft failure	12	55% 1 year patency (both assisted primary and secondary); 10% detection rate; 86% of failed grafts not identified by surveillance.	Surveillance appears to be of limited benefit in the maintenance of patency of prosthetic grafts.
Fasih et al. (2004) ³³	Cohort study, single centre	97 (106 limbs undergoing bypass)	48 (47)	Duplex and clinical surveillance at 3, 6 and 12 months	Clinical follow-up in 6 monthly intervals	Rates of graft occlusions and major amputations	15	22% occlusions in surveillance group vs. 69% in control group; 2% amputations in surveillance group vs. 38% in control group	Surveillance of vein grafts helped to improve patency by identifying the correctable lesions

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Table 2 (continued)

Study (year)	Study type	No. of patients (limbs)	% with CLI (with prosthetic bypass)	Surveillance strategy	Control group	Outcome measure	Mean follow-up (mo)	Findings	Conclusion
Brumberg et al. (2007) ³⁴	Explorative case series, single centre	121 (130 limbs undergoing bypass)	86 (100)	Duplex and clinical surveillance including ABI measurement at 1, 3 and 7 months and at 6 monthly intervals thereafter	No control group	Rates of assisted primary patency, secondary patency and limb salvage	17	43% assisted primary patency; 59% secondary patency; 75% limb salvage at 3 years	Low graft flow was a more common mode of prosthetic bypass failure than development of duplex scan-detected stenotic lesions during follow-up. Early duplex scanning may be more important for characterising midgraft velocity and related thrombotic potential and selecting patients for chronic anticoagulation.
Carter et al. (2007) ⁸	Explorative case series, single centre	197 (212 limbs undergoing bypass)	38 (23)	Duplex and clinical surveillance at 0, 1, 3, 6, 12, and 18 months	No control group	Rates of stenosis, graft occlusion, and major amputations	18	22% occurrences overall. 88% of femoro-popliteal vein grafts preceded by detectable stenosis vs. 34% of femoro-crural vein grafts and 4% of prosthetic grafts.	Graft surveillance is a valid method for detecting the presence of significant stenoses in vein grafts at high risk of failure without intervention. Despite the intensive follow-up, the program failed to detect lesions prior to occlusion in a large percentage of prosthetic and femorocrural grafts.
Humphries et al. (2011) ³⁵	Explorative case series, single centre	156 (198 limbs undergoing endovascular intervention)	100 (-)	Duplex and clinical surveillance including ABI measurement at 3 to 6 monthly intervals	No control group	Rates of primary and secondary patency and amputation-free survival according to degree of flow disturbance at initial scan (30 day).	24	20% major amputations for abnormal early scans vs. 5% for normal early scans (significant). However, amputation-free survival not significantly different between groups. In 56% of abnormal early duplex stenosis had been missed during intervention.	Abnormal duplex scan within the first 30 days postprocedure was associated with an increased risk of amputation suggesting a possible role for routine early duplex, close clinical follow-up, and consideration of re-intervention for residual abnormalities in patients treated for CLI.

^a Adapted from Lane et al.¹

important advantage of CD. Thus, despite lacking Level 1 evidence, CD screening has a role and should probably be focused on patients with a high risk of graft failure and be initiated immediately after revascularisation.^{44,48}

3.1.2. Duplex screening for failing revascularisations

A significant proportion of patients (around 25%) has an abnormal early CD^{1,29,49} (i.e. peak systolic velocity of less than 45 cm/s; peak systolic velocity increase to more than 150 to 300 cm/s; or velocity ratio across a suspected stenosis of more than 2.0 to 3.5). This might be occurring despite a normal intraoperative completion angiogram. Half of these patients will eventually need repeat interventions,^{8,50} whereas the other half will see these abnormalities on CD remaining stable or even regressing.⁴⁹

Thus, an abnormal initial CD could, together with other risk factors, help to identify patients at a high risk of graft failure who might benefit from continued CD screening.^{51–53} The most important additional predictors include falling serial ABI (by more than 0.1 to 0.2), composite or small diameter (<3 mm) vein bypass, redo-bypass grafts, long grafts (>50 cm in length) and alternative autologous venous conduits (i.e. arm or small saphenous veins).⁵⁴ Interestingly, absolute ABI was not predictive of failure in a *post hoc* analysis of a large multicentre RCT.⁵¹

In contrast, patients with normal CD scans at 6 weeks to 6 months had a very low risk for subsequent graft occlusion if clinical surveillance remained normal.^{30,55} Others found that the incidence of graft stenosis does not decline significantly during the first year.⁵⁶ Therefore, selective CD surveillance for less than 1 year could miss about 30% of lesions eventually leading to revision.

3.1.3. Prosthetic bypass grafts

Although evidence regarding efficacy of CD surveillance for prosthetic bypass is weak,¹ consistent estimates indicate that occlusions of prosthetic grafts are rarely preceded by a detectable stenosis (Table 2). Thus, even intensive surveillance programmes failed to detect salvageable lesions prior to occlusion in a large percentage of prosthetic grafts.⁸ If anything, low flow (<45 cm/s midgraft velocity) rather than high flow seems a more common mode of presentation, and early CD may be useful to identify these prosthetic grafts at increased risk, which might benefit from combined antiplatelet and anticoagulant therapy.³⁴ However, in one RCT that involved prosthetic bypass grafts, no benefit was shown for CD surveillance during 1 year.³¹

3.1.4. Cost

The mean cost for 5-year surveillance including CD has been estimated to be that of the initial bypass graft procedure, whereas the cost of bypass procedure plus surveillance for 5 years approaches the total cost of primary amputation.⁴³ But revision of a stenotic but patent bypass identified by CD is significantly less expensive than revision for graft occlusion which is also followed significantly more often by a major amputation (33% vs. 2%). Therefore, limb salvage-related expenses⁵⁷ appear to be justified in CLI patients.⁵⁸ In fact, CD needs to prevent only 5% of patients from an amputation to be economically viable.²⁹ On the other hand, repeated unsuccessful attempts to revascularise a leg will disproportionately increase the cost without any profit for the patient.⁵⁸

3.2. Surveillance of endovascular reconstruction

A fundamental difference of surveillance for endovascular interventions comes from the obvious challenge to localise the treated arterial segment precisely and not to confound restenosis or re-occlusion with progressive arterial disease elsewhere on the same artery. This is reflected by the distinction between target lesion re-intervention and target extremity re-intervention as important endovascular outcomes.² The preservation of collateral vessels during endovascular recanalisation may attenuate the clinical impact of restenosis or reocclusion. Therefore CD could be of less value in an endovascular context. So far, no RCT has investigated the use of routine CD after endovascular interventions. However, by extrapolation, close post-interventional follow-up and timely repeat interventions are generally accepted,^{59,60} but the same result could probably be achieved by clinical surveillance alone with similar effectiveness. As with surgical bypass, selective early CD screening may be beneficial after interventions as early duplex is able to detect a residual stenosis missed on completion angiography in up to half of patients. Such stenosis is known to be associated with a higher amputation rate when compared to normal early CD (20% vs. 5%).³⁵

3.2.1. Expected ulcer healing

It is important to note that, even after successful revascularisation, ischaemic tissue lesions may heal only slowly. Important therapeutic adjuncts include appropriate removal of ischaemic tissue, dedicated wound management including ultrasound and negative-pressure wound therapy, targeted antibiotic therapy of infections with abscess, and any measure to improve immune-deficient states of any origin. These measures are dealt with in great detail in Chapter V (Diabetic Foot, pp. S60–S74) of these guidelines. Expected median time to complete healing is in the range of 190 days.^{61,62} Diabetes and insufficient diabetes control are the most important predictors of delayed healing; these are dealt with in Chapters III and V. Female gender is a risk factor for wound complications after bypass surgery in patients with CLI.⁶³ However at 1 year, 75% of ulcers can be expected to have healed.^{61,62} Lesions at mid- or hindfoot level are the most critical to heal, whereas duration of ulceration before revascularisation is not predictive of healing time. Foot care, mechanical unloading and stump healing (for prosthetic accommodation of amputation) are critical to retain tissue integrity and ambulatory capacity, and are detailed in Chapter V.

Recommendations

An early (30 day) colour duplex scan should be done for venous bypass grafts in CLI patients. However, best level evidence does not support the use of routine long-term colour duplex surveillance for venous bypass grafts that are undisturbed at 1 month (**Level 1b; Grade B**). Instead, 3- to 6-monthly clinical review with ankle-brachial pressure index measurements should be utilised for at least 2 years. (**Level 2a; Grade B**)

Clinical deterioration and a drop in ankle-brachial pressure index of 0.1–0.2 indicate a failing infrainguinal vein bypass and should trigger focused colour duplex examination. (**Level 1b; Grade B**)

continued on next page

Recommendations (*cont'd*)

A colour duplex scan at 6 weeks to 6 months helps predicting which venous graft is likely to fail and should benefit from surveillance. **(Level 2b; Grade C)**

Other reconstructions with a likely benefit from colour duplex surveillance include composite vein bypass, redo-bypass grafts, small diameter (<3 mm) venous grafts, long vein bypass (>50 cm) and alternative autologous venous conduits. **(Level 2b; Grade C)**

An early colour duplex scan is useful after endovascular revascularisation for CLI to identify those at risk for failure **(Level 3b; Grade C)**. However, there is no evidence supporting routine long-term colour duplex surveillance after endovascular revascularisation.

Best level evidence does not support the use of colour duplex imaging compared to clinical follow-up with ankle-brachial pressure index measurements every 3 months in patients with prosthetic bypass. **(Level 1b; Grade B)**

Critical issues

- More studies are needed to ensure general applicability of the above findings to patients with CLI, including the preferred duration of CD and/or clinical surveillance.
- The role and duration of CD surveillance after endovascular revascularisation including use of stents, subintimal recanalisation and endarterectomy devices should be better evaluated as compared to clinical surveillance with ABI measurements.
- Cost-effectiveness analyses are lacking regarding preferred surveillance modalities after bypass or endovascular revascularisation in patients with CLI.
- There is a need for stratified analyses comparing prophylactic measures, surveillance or repeat interventions during follow-up between above- and below-the-knee bypass in CLI patients. Available evidence pertains predominantly to below-the-knee reconstructions, but differential outcomes should be explored.

4. Repeat revascularisation

Approximately 40% of CLI patients undergoing vein bypass will need a secondary intervention during follow-up; and in a third of them the contralateral limb will be involved.^{52,64} Around 20% of bypass procedures result in graft occlusion or amputation.^{53,54,65,66} Overall, this rate corresponds to an estimated average of 1.75 repeat interventions per patient for a 3-year period.⁶⁴

The success rate of secondary procedures for endovascular and surgical techniques is generally high, as long as the bypass or the angioplasty segment is not occluded. In contrast, once a graft has failed long-term patency is poorer after revision and limb salvage rate is moderate.⁶⁷ Timing of bypass failure is an important indicator of prognosis: the risk of amputation increases five-fold for early bypass failure (<30 days) as compared to failure after 30 days, as half of patients with early failure will develop untreatable critical ischaemia and immediate amputation.⁶⁵ Similarly, early repeat intervention (<120–180 days) is associated with impaired outcome as compared to late re-intervention.^{68,69}

4.1. Failing bypass

Stenotic vein bypass can be salvaged with similar success by endovascular or surgical techniques,^{54,59,68,70} even though surgical revisions are more durable and necessitate fewer subsequent re-interventions.⁷¹ Midgraft stenoses are more benign than anastomotic stenoses,⁷⁰ and late-appearing short lesions have a favourable prognosis as compared to early and extensive stenoses.⁶⁸ Overall revision failure is in the range of 30% and is similar between surgical and endovascular approaches.⁷¹

For stenoses located within the main body of the graft, surgical patch angioplasty and interposition grafting using autologous vein are equally effective in prolonging assisted primary patency. Alternatively, endovascular angioplasty may be used with comparable early results,^{71,72} although results are not as good as primary endovascular interventions for native CLI lesion.⁷³ Thus, the choice of the technique depends on anatomical characteristics and accessibility of the lesion.⁴⁷

Outcome of recurrent stenosis is markedly inferior with endovascular angioplasty, and such lesions probably benefit from surgical revision.⁷⁴ Other types of lesions for which surgical repair should be preferred based on its durability include early lesions and lesions within anastomoses.⁷⁰ Endovascular revision is probably best suited for short (<2 cm) and late-appearing lesions (>3–4 months) involving the mid-graft, where it reaches similar durability as surgical revision.^{58,68–70}

4.2. Failed bypass

Bypass occlusion is a critical event and should undergo urgent revision if the bypass is to be maintained. However, graft salvage attempts fail in up to 65% of patients;^{57,65} and about half of graft occlusions will eventually lead to amputation.^{34,65}

For occluded vein grafts, surgical revision including placement of a new bypass is preferred, since endovascular revision is less durable.⁷¹ For occluded prosthetic bypasses, graft salvage surgery is associated with acceptable long-term results only for above-the-knee or extra-anatomic grafts. Occluded below-the-knee grafts are preferably replaced by a new bypass to a new outflow artery using an autologous vein.⁶⁶

In some cases, catheter-directed thrombolysis is an appealing alternative. In a recent RCT, a mixed cohort of 124 patients with bypass occlusion was assigned to either surgical revision or intra-arterial thrombolysis.⁷⁵ Catheter placement failed in almost 40% of cases and composite clinical outcome at both 30 days and 1 year favoured surgical revision with new graft placement for chronically (>14 days) occluded grafts. However, patients with acute graft thrombosis (<14 days) had a lower amputation rate after successful thrombolysis at 1 year. Other authors have confirmed intra-arterial thrombolysis as a favourable strategy for acute graft occlusions and that it seems to give best results in above-the-knee prosthetic grafts in place at least for 1 year.⁷⁶ However, half of these grafts re-occlude within 1 month, particularly if thrombolysis fails to unmask an underlying correctable stenosis.^{76,77}

4.2.1. Endovascular reconstruction

In 35% of cases a repeat intervention is needed within 1 year after endovascular revascularisation for CLI.^{59,60} Although technical success of second-time endovascular angioplasty is in the range of 95%, its mid-term patency may be limited,⁶⁹ particularly in diabetic patients.⁵⁹ Therefore, multiple re-interventions may be needed for sustained limb salvage.⁵⁹ Early failure (<180 days) of initial endovascular intervention is a predictor of poor success of secondary intervention⁶⁹ and indicates that surgical alternatives should be considered. Overall, similar proportions of failed endovascular reconstructions are amenable to surgical or endovascular revision with comparable results.^{59,60} Therefore, attempts at revision should be tailored individually.

Recommendations

In venous bypass, an early (<4 months) stenosis or one that involves the anastomosis may benefit from surgical revision (**Level 2b; Grade C**). In this setting, patch angioplasty using autologous vein and interposition vein grafts are equally effective. (**Level 2b; Grade B**)

Late-appearing and short (<2 cm) stenosis located within the main body of a vein graft can be treated with equivalent efficacy using endovascular intervention or surgical revision (**Level 2b; Grade B**). However, recurrent stenosis has an inferior outcome when treated by angioplasty and is likely to benefit from surgical revision. (**Level 4; Grade C**)

Following vein graft revision, ongoing clinical and colour duplex surveillance is recommended as the risk of new restenosis appears to be high. (**Level 4; Grade C**)

Following graft occlusion, intra-arterial thrombolysis may be an option in patients without acute critical ischaemia and a recent occlusion (<14 days) of a prosthetic or vein bypass above the knee and in place for at least 1 year, provided that there are no contraindications and that lysis can be accomplished safely. Surgical revision with a new graft using an autologous vein remains the preferred salvage procedure for other types of graft occlusion. (**Level 2b; Grade C**)

Failing or failed endovascular revascularisations can be treated with similar efficacy by endovascular or surgical revision (**Level 2b; Grade C**). However, early repeated endovascular interventions (<180 days) are associated with a poor outcome. In these cases, a surgical alternative may be preferable. (**Level 4; Grade C**)

Critical issues

- There is a need to study the best available treatment for in-stent restenosis and after graft failure.
- A RCT is needed to evaluate the role of drug-eluting stents for restenosis after angioplasty and for venous graft stenosis.

5. Follow-up in specific contexts

5.1. Diabetic patients

A large proportion of CLI patients are diabetic⁵⁹ and may be challenging to manage. Expected clinical outcomes

are supposedly similar between surgical and endovascular reconstruction,⁵⁹ but as diabetic patients tend to present with an advanced stage of peripheral vascular disease, they may demonstrate reduced primary patency rates.^{59,78} However, with timely and repeated use of salvage re-interventions, acceptable secondary patency and limb salvage rates can be reached.^{78,79} Therefore, diabetic patients are a subset likely to benefit from close long-term surveillance during follow-up.⁵⁹

5.1.1. Patients with end-stage renal disease

The proportion of patients with both CLI and chronic renal failure is increasing. But with an aggressive repeat revascularisation approach, peri-operative mortality and graft patency rates as well as expected 4-year survival rates tend to approach those of patients with normal renal function.⁸⁰ The risk of amputation is however markedly increased in dialysis patients.⁸⁰⁻⁸³ Major amputation despite a patent graft occurs in 10% of patients with end-stage renal disease,^{37,39} particularly when prosthetic graft material has been used in non-ambulatory patients with extensive tissue loss.^{37,38,80,82,84} In addition, secondary salvage procedures after bypass occlusion have a poor prognosis in patients with end-stage renal disease, and most will need a major amputation within 1 year of graft failure.⁶⁷

5.1.2. Elderly and functionally impaired patients

In elderly patients (≥ 80 years), quality of care for CLI is not solely determined by the traditional measures of patency and limb salvage but particularly by functional outcomes. The most important predictor of preserved ambulatory capacity is the patient state at presentation, including mental state, pre-operative ambulatory capacity and independent living status.^{40,85} General outlook after open or endovascular revascularisation is fair for aged ambulatory patients with CLI,^{86,87} even for below-the-knee reconstructions.⁸⁸ At 1 year, 88% of survivors are ambulatory, 85% live at home, and 80% do both, whereas at 5 years, 71% are still ambulatory, and 81% live independently.⁴⁰ Therefore, those who were ambulatory and lived at home pre-operatively almost invariably continue to do so. Those with poor ambulatory function or who required assistance pre-operatively, however, are unlikely to improve their status after revascularisation even if technically successful.^{40,85,88} These findings question the appropriateness of revascularisation in functionally impaired and chronically ill patients.

Recommendations

Diabetic patients are likely to benefit from close clinical and colour duplex-scan surveillance as primary patency rates are low and ankle-brachial pressure index may be unreliable. (**Level 2b; Grade C**)

Patients with end-stage renal disease and patients who are not ambulatory or are mentally incapacitated are unlikely to profit from any kind of continued limb salvage efforts. This is particularly true if tissue loss is extensive and no adequate autologous vein is available. (**Level 2b; Grade C**)

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None

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