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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 ***or*** extrapolations from Level 1 studies
C	Level 4 studies ***or*** extrapolations from Level 2 or 3 studies
D	Level 5 evidence ***or*** 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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