

# Critical Limb Ischemia: Current Trends and Future Directions

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**C**ritical limb ischemia (CLI), which is at the end of the peripheral artery disease (PAD) spectrum, is associated with excessively high risk for cardiovascular events, including myocardial infarction, and death.<sup>1–3</sup> Mortality rates as high as 20% within 6 months from diagnosis and exceeding 50% at 5 years have been reported for CLI,<sup>4–6</sup> whereas 1-year mortality rates in nonrevascularizable, so-called no-option CLI patients range from 10% to 40%.<sup>7,8</sup> The high mortality rates exceed those for every other form of occlusive cardiovascular disease, including symptomatic coronary artery disease (CAD),<sup>9,10</sup> and reflect the systemic atherosclerotic burden associated with CLI. Besides poor survival rates, prognosis with respect to limb preservation in CLI patients is poor,<sup>11</sup> particularly in no-option CLI patients, where 6-month major amputation rates have been reported to range from 10% to 40%.<sup>6–8</sup> Additionally, CLI is associated with poor quality of life<sup>12</sup> and high treatment costs,<sup>13</sup> especially when amputation is inevitable.<sup>13,14</sup> With an estimated yearly incidence of 500 to 1000 new cases per million individuals in Western society,<sup>7</sup> which is ever increasing in concert with the increase in cardiovascular risk factors,<sup>15–17</sup> CLI poses a substantial burden on patients, healthcare providers, and resources.

In the current review we will describe how management strategies in CLI have evolved over the past decades and discuss issues that could facilitate more rapid and evidence-based improvements in CLI management and care. Focus will be on factors that may have limited evidence-based management and on actions that could promote progress in this field, especially with respect to clinical research.

## Definition of CLI

Essential for the interpretation of study results is a widely accepted definition of the disease under study. Variable definitions have been and are used to classify CLI, which complicate the evaluation of available evidence with regard to CLI.<sup>18</sup> The first formal definition of CLI was proposed by Fontaine et al in 1954,<sup>19</sup> as being the existence of rest pain or tissue loss due to severe PAD, without including any hemodynamic criteria. In 1986, the first Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ISCVS) standards for reporting on lower limb ischemia were published, which included a classification currently known as the Rutherford classification.<sup>20</sup> This classification—in its original form—added objective hemodynamic parameters (ie, pulse volume recordings and ankle and toe pressure measurements) to the clinical presentation in order to enhance homogeneity and objectivity of the definition. While hemodynamic parameters have remained part of subsequent international consensus guidelines on PAD and CLI,<sup>7,8,21,22</sup> these strict hemodynamic criteria are often not part of routine use in clinical as well as research practice. As the definitions used to define CLI in clinical reports vary from merely clinical criteria,<sup>4</sup> clinical criteria combined with a variety of objective parameters,<sup>23</sup> and definitions based on hospital discharge information,<sup>24</sup> research reporting on CLI is inherently variable. Recent consensus statements have proposed stricter definitions that include ankle and toe pressures,<sup>7,22</sup> aiming to improve standardized reporting on CLI, which will be discussed in more detail in the last paragraph of this article.

## Changing Prognosis in CLI

Prognosis with respect to limb salvage and survival in CLI patients, and the PAD population as a whole, has improved over the years.<sup>24–31</sup> In a large population-based study in a heterogeneous PAD population >65 years of age, the adjusted odds ratio of lower extremity amputation per year between 2000 and 2008 was 0.95 (95% CI: 0.95–0.95,  $P < 0.001$ ).<sup>31</sup> Consistently, Goodney et al showed a reduction of major amputation rates of 263 to 188 per 100 000 Medicare beneficiaries between 1996 and 2006 (relative risk 0.71; 95% CI: 0.6–0.8).<sup>28</sup> A similar pattern was suggested for

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the CLI population in a study by Egorova et al showing a reduced proportion of the surgical interventions in a US CLI population being major amputations (decrease from 42% to 30% between 1998 through 2007).<sup>24</sup> Since amputations in a PAD population are likely performed in case of CLI, these data suggest a decrease in major amputation rates in the CLI population over the past 2 decades, while a decrease of CLI incidence might also partially explain these observations. The aforementioned studies also show a trend towards more endovascular as compared to surgical revascularization procedures<sup>24,26,28–31</sup> and suggest a potential causal relationship between the increased number of endovascular procedures and reduced amputation rates.<sup>24,30</sup> However, Benoit et al have shown significant improvement of 1-year amputation-free survival (AFS) from  $\approx$ 28–40% in trials performed during the period 1996–1999 to 48–81% during the period 2006–2010 for patients with nonrevascularizable CLI<sup>32</sup> and a tendency for major amputation rates to decline from 20–50% to 10–38% during the same period. Improvements in prognosis over time in this no-option CLI population suggest a role for factors other than increased frequency of endovascular interventions, such as increased public awareness, better medical therapy, improved wound care,<sup>33</sup> and secondary prevention.

## Trends in Medical Therapy for PAD

### Current Guidelines

In 2000, the first international guideline for the management of PAD was published, the TransAtlantic Inter-Society Consensus I (TASC-I).<sup>22</sup> Since then, several international guidelines have been published that include secondary prevention in PAD, such as smoking cessation, management of hypertension and diabetes, lipid lowering, and antiplatelet therapies.<sup>7,22,34,35</sup> All PAD and CLI guidelines consider the effectiveness of statins, antiplatelet therapy, and ACE inhibitors to reduce cardiovascular events and mortality proven in the PAD population.<sup>7,22,34,35</sup> Recommendations for CLI are often, as a result of lacking CLI-specific evidence,<sup>35,36</sup> extrapolated from other populations.

### Temporal Changes in Secondary Prevention

The ultimate goal of guidelines is to enhance uniform and evidence-based treatment in a specific patient population in order to improve outcome and quality of care. It takes time before guideline-based therapy finds its way to the clinic and treatment conforms to these guidelines. Over the past decade the use of antiplatelet therapy, statins, and antihypertensive drugs in PAD patients has been evaluated in several reports,<sup>37,38</sup> but no CLI specific data are available. In general

an increase in the use of secondary prevention has been observed over time.<sup>39–42</sup> For instance, Subherwal et al reported, in a large population-based study in Denmark, an increase in the use of antiplatelet therapy in patients with the incident diagnosis of PAD,<sup>42</sup> without a history of CAD, from 29% in 2000 to 59% in 2007 ( $P<0.0001$ ). The increase in statin use was even more pronounced from 9% in 2000 to 56% in 2007 ( $P<0.0001$ ), and for use of ACE inhibitors a significant increase was also observed ( $P<0.0001$ ); however, its use remained below 20%. Subherwal and co-workers also compared the use of cardioprotective drugs in PAD patients with that of CAD and observed that patients with PAD were approximately half as likely to be treated with cardioprotective drugs for the period from 2000 to 2007. This could be related to the fact that the introduction of guidelines in CAD preceded those in PAD more than a decade.<sup>22,43</sup> The differences between the CAD and PAD population declined over the period from 2000 to 2007 from 28% in 2000 to 19% in 2007 for antiplatelet therapy and 22% in 2000 to 9% in 2007 for statin therapy. The underuse of cardioprotective medication in the PAD population in comparison to patients with CAD has been published previously.<sup>38,39</sup> The underuse of cardioprotective drugs in the PAD population does not seem limited to PAD patients with relatively mild symptoms. The The Project or Ex-Vivo vein graft Engineering via Transfection III (PREVENTIII) and BASIL-trial, which included patients with CLI between 2001 and 2003 and 1999 and 2004, respectively, show that 88% and 46% and 54% and 34% were treated with antiplatelet drugs and statins, respectively.<sup>4,23</sup> However, also in the CLI population, adherence to secondary prevention strategies seems to improve over time. For example, 70% (almost all of the remaining patients were on anticoagulants) and 84% of patients included in the recently published Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial were on antiplatelet and statin therapy, respectively.<sup>44</sup> The relatively poor incorporation of PAD guidelines probably results from a relative lack of public awareness about PAD, its unappreciated implications on overall cardiovascular risk, and the fact that the benefits of treatment are not well appreciated.<sup>45–47</sup> Furthermore, overestimation of the treatment given by others, lack of education, training, and organizational facilities to implement guidelines properly play a role,<sup>48</sup> as well as the beliefs of the physician themselves.<sup>49</sup> Cacoub et al showed that the extent of risk factor management was significantly associated with the type of doctor that treated the PAD patient.<sup>50</sup> Hackam et al calculated in a systematic review and modeling study that more widespread implementation of antiplatelet therapy, statins, and ACE inhibition (85% use of each) in the PAD population may prevent more than 200 000 cardiovascular events each year (myocardial infarction, stroke, and cardiovascular death; 212 166 events; 95% CI

95 823–310 392) in North America and Western Europe alone.<sup>51</sup>

While evidence for secondary prevention on cardiovascular events and mortality in general is not in doubt, there is less evidence whether it can reduce limb-specific events. It has been reported that statin therapy is associated with improved infrainguinal autogenous venous graft patency, with a 3.2-fold increased risk of graft failure in patients not on statins.<sup>52</sup> Additionally, statin therapy is associated with reduced restenosis rates after endovascular intervention,<sup>53,54</sup> and reduced rates of symptom recurrence after revascularization for intermittent claudication.<sup>54</sup> Aiello et al showed in a retrospective study in 646 CLI patients that statins can improve limb salvage rates after endovascular interventions for CLI (limb salvage 83% versus 62% at 24 months).<sup>55</sup> The temporal trend of increasing AFS and reducing amputation rates reported by Benoit et al in no-option CLI patients may also partly reflect a relation between improved secondary prevention and limb-related outcomes.<sup>32</sup> For viable conclusions on the effect of specific secondary prevention measures on limb-related outcomes, amputation rates in particular, larger, and well-designed studies should be conducted, based on large patient registries and properly designed clinical trials.

## Current Status of Non- and Minimal Invasive Treatment Options in CLI

### Cell- and Gene-Based Therapies

Initial pilot studies for both gene and cell therapy that aim at inducing angiogenesis and neovascularization showed promising results in CLI with respect to surrogate outcomes, such as improved ankle/brachial index, transcutaneous oxygen measurement, walking distance, and pain scores, and also for the hard clinical outcomes such as reduction in amputation rates. However, the larger and especially randomized placebo-controlled trials did not confirm these promising results.<sup>44,56–58</sup> Different types of gene therapies have been studied (ie, fibroblast growth factor 1, vascular endothelial growth factor, and hepatocyte growth factor), of which the latter currently seems the most promising.<sup>57,59</sup> The phase III AnGes trial (ClinicalTrials.gov: NCT02144610) has been initiated, which will study the efficacy of hepatocyte growth factor (DNA plasmid with hepatocyte growth factor gene) in a double-blind randomized controlled trial (RCT) that has planned to include 500 Rutherford 4 and 5 patients in North America, South America, and Europe. The effect of several types of cell therapy (eg, bone marrow-derived mononuclear cells, CD34+ bone marrow cells, and mesenchymal stromal cells) has been studied in CLI, and to date none of these therapies has convincingly shown clinical efficacy with

respect to outcomes such as AFS or reduction in amputation rates; the larger placebo-controlled RCTs especially showed no effect on these hard clinical outcomes, and emphasize the essential role of an adequate placebo-controlled randomized design for these studies in CLI.<sup>58,60</sup> A potential explanation for the discrepancy between the preclinical and the clinical results of cell therapy in CLI is the potential role of disease-mediated stem cell dysfunction, which may limit the effects of these autologous cell therapies. Evidence exists that mesenchymal stem cells are less sensitive to this disease-mediated dysfunction and can be a promising target for future cell therapy in CLI patients.<sup>61</sup>

### Other Nonsurgical Treatment Options

Several other medical devices or pharmaceutical agents have been studied for the treatment of CLI patients, such as iloprost, sympathectomy, and spinal cord stimulation, all with insufficient evidence to support their routine use in the treatment of CLI patients.<sup>62</sup>

### Revascularization Strategies in CLI

Endovascular interventions have significantly evolved over the past decades. Since the initial application of plain balloon or percutaneous transluminal angioplasty, several novel endovascular approaches and devices have been released on the market (for example, bare metal stents, cryoplasty, atherectomy devices, stent-grafts, drug-eluting stents, and drug-eluting balloons). In general these devices have been studied in relatively small and selected patient populations, often not including CLI patients.<sup>62</sup> The only RCT directly comparing open bypass surgery with endovascular therapy (ie, plain balloon angioplasty) in CLI patients is the BASIL trial, which overall showed no differences between the treatment groups with respect to AFS at 1 and 3 years of follow-up based on an intention-to-treat analysis.<sup>4</sup> Patients allocated to the open bypass surgery group surviving for more than 2 years after the initial procedure had improved AFS (adjusted HR 0.37; 95% CI 0.17–0.77;  $P=0.008$ ) and reduced all-cause mortality (adjusted HR 0.34; 95% CI 0.17–0.71;  $P=0.004$ ). Patients who had no useable vein graft and hence underwent prosthetic bypass and patients who initially underwent endovascular treatment, but crossed over to the bypass group fared worse compared to those undergoing initial open bypass surgery using a vein graft.<sup>63,64</sup> Although this study was not specifically designed with this purpose, it suggests a benefit of bypass surgery in specific subgroups of CLI patients. To date no other randomized studies have compared bypass surgery with endovascular therapy in CLI. However, a tendency to an endovascular-first strategy has evolved over

the past 2 decades, fueled by results of nonrandomized comparisons, reports in milder and selected PAD populations, and a perceived short-term favorable balance of an endovascular-first approach in the high-risk CLI population.<sup>24,28,29,65</sup>

In line with the BASIL-trial, indirect comparisons of endovascular procedures<sup>66,67</sup> and open bypass surgery using a vein graft<sup>11</sup> show similar results with respect to 1-year limb salvage and mortality rates in CLI, both ranging from 85% to 90%, but a higher need for reinterventions after endovascular therapy.<sup>68</sup> This increased reintervention rate corresponds with an increase in the number of endovascular interventions in both claudication and CLI over the years that outnumbers the decline in open surgical interventions. Goodney et al reported that over 3 endovascular interventions were performed for every one procedure declined in lower extremity bypass surgery.<sup>28</sup> It is unlikely that this increase in endovascular procedures is merely the result of more reinterventions after endovascular intervention. It may also be due to a lowering threshold for endovascular interventions as reflected by an increase of hospital admissions for endovascular interventions for claudication (ie, increase from 10–31% to 26–43% of the PAD-related hospital admissions in 2001 and 2008, respectively).<sup>69</sup> The larger need for reinterventions in endovascular therapy also becomes apparent from cost-effectiveness analyses that focused on the comparison of endovascular strategies with open surgery.<sup>70,71</sup> These studies show an early benefit of endovascular strategies over open procedures but this benefit is lost after ≈1 year, due to reinterventions in the endovascular group. Moreover, a recent study by Goodney et al showed that in regions in the United States with a high-spending profile for vascular care perform a significantly higher number of endovascular interventions, without any benefit with respect to amputation rates; on the contrary these regions have even higher amputation rates, which suggests that an increased number of endovascular interventions does not result in improved outcome per se.<sup>72</sup>

Based on the available literature, it is not easy to defend either an endovascular- or bypass-first strategy in CLI.<sup>73</sup> An argument that is often used to choose for an endovascular-first strategy is that after failure of an endovascular therapy, bypass surgery is often still feasible;<sup>62</sup> however, this is not based on objective data and there is also evidence that bypass surgery after an initial endovascular intervention has a worse prognosis than initial bypass surgery.<sup>63,74,75</sup> Furthermore, the relatively late superiority of open surgery over endovascular intervention is sometimes considered irrelevant in CLI due to the perceived high mortality rates. This argument is challenged by the relatively favorable 1-year survival rate of 85% in the PREVENTIII-trial,<sup>23</sup> which studied the effect of edifoligide after bypass surgery in CLI, and 70% 2-year survival rate of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial.<sup>4</sup> The researchers of the PREVENTIII-trial

developed an easy-to-use and highly reliable tool to stratify CLI patients who undergo bypass surgery in low-, medium-, and high-risk categories, providing a reliable estimate of the 1-year AFS after surgical revascularization.<sup>76,77</sup> The variables that comprise this risk score include dialysis dependence, tissue loss, advanced age (>75 years), presence of coronary artery disease, and low hematocrit (<30%). Patients in the highest risk group have a 1-year AFS after open bypass surgery of ≈45%, and bypass surgery is therefore not preferred in this high-risk population. Other studies also identified risk factors for bypass surgery,<sup>36</sup> and showed that the conduit used is a major procedural factor influencing prognosis after bypass surgery.<sup>62,78</sup>

The initial choice of treatment in CLI patients is not easily made and depends on patient- and procedure-specific factors, such as age and comorbidity, the severity of limb ischemia, presence of a useable vein graft, and the vascular anatomy, which influences the available options for bypass anastomosis and the potential success of endovascular interventions as well. Well-designed RCTs investigating novel devices and factors influencing treatment success in CLI would be highly valuable to determine which patients are eligible for an endovascular-first strategy. It is likely that revascularization in CLI patients will become more individualized in the future, based on multifactorial decision models, at least including systemic risk, severity of limb ischemia, and vascular anatomy.<sup>79</sup>

## Key Issues and Important Steps to Improve Evidence-Based Management of CLI

High-level evidence, typically level I, to guide evidence-based clinical decision making in CLI is limited in contrast to coronary artery, carotid artery, and aortic aneurysm disease.<sup>7,18,35,36,62</sup> Well-designed prospective studies and RCTs in CLI patients are sparse.<sup>80</sup> This may be related to the fact that studies in this specific population are not easy to conduct, due to the lower incidence of CLI compared to milder forms of PAD, and issues with respect to follow-up of CLI patients. Furthermore, partially related to the aforementioned issues, there seems to be less interest from the pharmaceutical industry to initiate trials in this specific population. High-quality epidemiological data on incidence, prevalence, and prognosis of CLI, particularly more recent data, are also sparse.<sup>7,8</sup>

Essential to a meaningful comparison and interpretation of study data is a more comprehensive definition and stratification of CLI. An important step towards such a more strict and meaningful stratification has been made by the Society of Vascular Surgery Lower Extremity Guidelines Committee, which proposed a novel classification system for the threatened lower limb.<sup>81</sup> This classification system is based on 3 major factors that impact amputation risk and clinical



management: Wound, Ischemia, foot Infection (WIFI) and combines clinical factors with perfusion parameters. The ultimate goal of this new classification system is to provide more meaningful analyses of outcomes from various therapies among the heterogeneous limb ischemia population. Initial validation studies of this novel classification system have been promising and showed that the classification system nicely predicted wound healing and amputation risk.<sup>81,82</sup>

Given the temporal changes discussed above, along with the considerable heterogeneity of the CLI population, one should be careful when considering historical controls and nonrandomized cohorts in clinical research in CLI. Recently, the SVS-CLI Working Group published Objective Performance Goals that provide benchmark values for various end points in CLI, AFS, and limb salvage, among others.<sup>11</sup> If these benchmark values are to be used as comparator in future CLI trials, it should be realized that these values can gradually change over time due to factors not related to the intervention per se, such as secondary prevention measures. It is advisable to regularly update the Objective Performance Goals to provide contemporary benchmark values. Additionally, the decline in event rates in clinical trials makes it more difficult to demonstrate superiority of a novel intervention,<sup>83</sup> which requires exponentially larger study sizes or are at risk to be underpowered.

It is encouraging that the importance of developments and high-quality evidence in severe limb ischemia seems to get more attention in recent years, which is reflected by 3 important RCTs in both the United States and Europe, the BEST-CLI and BASIL-2 and -3 trials, respectively. In short, the BEST-CLI (ClinicalTrials.gov: NCT02060630), Best Endovascular versus Best Surgical Therapy in patients with CLI, trial is a pragmatic, multicenter, open label, randomized trial in 2100 subjects in 120 sites in North America that compares best endovascular versus best surgical therapy in CLI patients eligible for both treatments.<sup>84</sup> Subjects will be stratified in Rutherford 4 versus Rutherford 5 or 6 patients, which likely influences outcome substantially. The trial is funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health by a \$24.9 million grant. BASIL-2 (ISRCTN.com: ISRCTN27728689), Bypass versus Angioplasty in Severe Ischemia of the Leg-2, funded by the National Health Service (NHS), investigates venous bypass first versus best endovascular first strategy in 600 patients with severe limb ischemia due to infrapopliteal atherosclerotic disease in a 1:1 randomized fashion, while BASIL-3 (not yet initiated) will be a 3-armed trial that will compare plain balloon angioplasty, drug-eluting balloon, and drug-eluting stents in severe limb ischemia patients due to femoropopliteal lesions. These trials will also include several of the recently defined Objective Performance Goals as outcome measures.<sup>11</sup> These large and ambitious trials will provide very essential information on characteristics and prognosis of severe limb ischemia and

more current evidence to guide therapy for this challenging pathology.

There are some pertinent questions that need to be answered in future clinical studies, which will—at least partially—be addressed by the abovementioned trials. The most important issues are the following: First, which clinical staging system is useful to predict outcome in severe limb ischemia patients and is it reproducible? Second, can we improve secondary prevention in PAD patients, with respect to both the number of patients prescribed medication to prevent future cardiovascular events and also in providing a more personal-based medication profile (eg, based on antiplatelet testing)? Third, what is the actual incidence of CLI and what is the prognosis of the contemporary CLI patient? Fourth, can we identify patients who are best treated with a surgical or an endovascular approach? Fifth, can gene or cell therapy provide an alternative option in the therapeutic armamentarium of (no-option) severe limb ischemia patients? And sixth and foremost, can we identify patients at risk for and prevent them from advancing to CLI?

Addressing these issues and further improving treatment and outcomes of PAD patients worldwide and in all socioeconomic segments of the population requires collaborative international, national, and local efforts. As funding strategies for PAD are uncommon, public or private initiatives are essential,<sup>85</sup> which could be enhanced by increased public awareness of PAD and its implications for public health, such as cardiovascular risk, influence on quality of life, and expenditure of healthcare resources.

## Recommendations for the Future

Practically, we identified several recommendations with respect to research and clinical management in CLI.

- 1 Initiatives should be taken to enhance widespread use of a generally accepted definition and staging scheme of CLI that includes both hemodynamic as well as detailed clinical staging criteria (eg, the SVS Threatened Limb Classification system [WIFI]). Moreover, we should consider a novel and more comprehensive 3-dimensional approach to stratify CLI patients and guide treatment decisions, based on the clinical severity of the disease (WIFI), the overall physical condition and comorbidities, and anatomic characterization of the vascular pathology.
- 2 Clinical trials in CLI patients, implementing separately powered distinct trial arms that consider disease severity and related prognosis (ie, tissue loss versus rest pain), according to the design of the BEST-CLI trial (ClinicalTrials.gov: NCT02060630), should be stimulated.
- 3 Appropriate end points should be selected in studies that focus on CLI, considering that, for instance, AFS only partly

embraces true interventional effects, since AFS does not separate limb from life loss. End points that include reinterventions and early intervention-related complications may be preferable, such as major adverse limb event (MALE), one of the Objective Performance Goals defined by the SVS-CLI Working Group, and ideally a measure of hemodynamic success should be incorporated.

- 4 Study populations should reflect the CLI population encountered in vascular clinics' daily practice and not a particular selection of patients that is not generalizable to the total CLI population. Comparative effectiveness studies should incorporate a staging scheme such as the SVS Threatened Limb Classification system (WIFI) to allow for meaningful interpretation and comparisons of outcomes.
- 5 Transatlantic or large continental collaborative efforts, as have been done in carotid disease, may be needed to guarantee sufficiently powered trials, with room for stratification. Treatment of cardiovascular risk factors in CLI patients should be given a central role on international conferences. Increased recognition of data on prevalence, management, outcomes, and treatment costs of PAD and CLI by public and governmental authorities will promote further evidence-based treatment of these patients, enhance detection of PAD, and improve funding resources for essential research in this specific patient population.

If we are able to fulfill these recommendations by joining international forces, we might be able to optimize evidence-based treatment of the CLI patient, hence offer a relief of the burden on healthcare providers and resources, but foremost the patient.

## Disclosures

None.

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