American Heart Association | American Stroke Association®

Critical Limb Ischemia: Current Trends and Future Directions

Martin Teraa, MD, PhD; Michael S. Conte, MD; Frans L. Moll, MD, PhD; Marianne C. Verhaar, MD, PhD

Critical 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.[1–3] Mortality rates as high as 20% within 6 months from diagnosis and exceeding 50% at 5 years have been reported for CLI,[4–6] whereas 1-year mortality rates in nonrevascularizable, so-called no-option CLI patients range from 10% to 40%.[7,8] The high mortality rates exceed those for every other form of occlusive cardiovascular disease, including symptomatic coronary artery disease (CAD),[9,10] and reflect the systemic atherosclerotic burden associated with CLI. Besides poor survival rates, prognosis with respect to limb preservation in CLI patients is poor,[11] particularly in no-option CLI patients, where 6-month major amputation rates have been reported to range from 10% to 40%.[6–8] Additionally, CLI is associated with poor quality of life[12] and high treatment costs,[13] especially when amputation is inevitable.[13,14] With an estimated yearly incidence of 500 to 1000 new cases per million individuals in Western society,[7] which is ever increasing in concert with the increase in cardiovascular risk factors,[15–17] 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.[18] The first formal definition of CLI was proposed by Fontaine et al in 1954,[19] 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.[20] 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,[7,8,21,22] 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,[4] clinical criteria combined with a variety of objective parameters,[23] and definitions based on hospital discharge information,[24] research reporting on CLI is inherently variable. Recent consensus statements have proposed stricter definitions that include ankle and toe pressures,[7,22] aiming to improve standardized reporting on CLI, which will be discussed in more detail in the last paragraph of this article.

From the Departments of Vascular Surgery (M.T., F.L.M.), Surgery (M.T.), and Nephrology & Hypertension (M.T. M.C.V.), University Medical Center Utrecht, Utrecht, The Netherlands; Division of Vascular and Endovascular Surgery, University of California, San Francisco, San Francisco, CA (M.S.C.).

Correspondence to: Martin Teraa, MD, PhD, Departments of Vascular Surgery, Surgery, and Nephrology & Hypertension, University Medical Center Utrecht, HP G. 04.129, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands. E-mail: m.teraa@gmail.com

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.[24–31] 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, $P<0.001$).[31] 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).[28] A similar pattern was suggested for

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).[24] 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[24,26,28–31] and suggest a potential causal relationship between the increased number of endovascular procedures and reduced amputation rates.[24,30] However, Benoit et al have shown significant improvement of 1-year amputation-free survival (AFS) from ≈28–40% in trials performed during the period 1996–1999 to 48–81% during the period 2006–2010 for patients with nonrevascularizable CLI[32] 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,[33] 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).[22] 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.[7,22,34,35] 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.[7,22,34,35] Recommendations for CLI are often, as a result of lacking CLI-specific evidence,[35,36] 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,[37,38] but no CLI specific data are available. In general

an increase in the use of secondary prevention has been observed over time.[39–42] 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,[42] 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.[22,43] 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.[38,39] 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.[4,23] 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.[44] 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.[45–47] Furthermore, overestimation of the treatment given by others, lack of education, training, and organizational facilities to implement guidelines properly play a role,[48] as well as the beliefs of the physician themselves.[49] Cacoub et al showed that the extent of risk factor management was significantly associated with the type of doctor that treated the PAD patient.[50] 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.[51]

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.[52] Additionally, statin therapy is associated with reduced restenosis rates after endovascular intervention,[53,54] and reduced rates of symptom recurrence after revascularization for intermittent claudication.[54] 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).[55] 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.[32] 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.[44,56–58] 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.[57,59] 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.[58,60] 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.[61]

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.[62]

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.[62] 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.[4] 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.[63,64] 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.[24,28,29,65]

In line with the BASIL-trial, indirect comparisons of endovascular procedures[66,67] and open bypass surgery using a vein graft[11] 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.[68] 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.[28] 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).[69] 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.[70,71] 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.[72]

Based on the available literature, it is not easy to defend either an endovascular- or bypass-first strategy in CLI.[73] 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;[62] 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.[63,74,75] 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,[23] 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.[4] 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.[76,77] 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,[36] and showed that the conduit used is a major procedural factor influencing prognosis after bypass surgery.[62,78]

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.[79]

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.[7,18,35,36,62] Well-designed prospective studies and RCTs in CLI patients are sparse.[80] 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.[7,8]

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.[81] 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.[81,82]

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.[11] 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,[83] 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.[84] 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 (ISRTCN.com: ISRTCN27728689), 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.[11] 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,[85] 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.

References

1. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *Am Heart J*. 2002;143:961–965.

2. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381–386.

3. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis*. 1991;87:119–128.

4. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, Fowkes FG, Gillepsie I, Ruckley CV, Raab G, Storkey H. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005;366:1925–1934.

5. Stoyioglou A, Jaff MR. Medical treatment of peripheral arterial disease: a comprehensive review. *J Vasc Interv Radiol*. 2004;15:1197–1207.

6. Abu Dabrh AM, Steffen MW, Undavalli C, Asi N, Wang Z, Elamin MB, Conte MS, Murad MH. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg*. 2015;62:1642–1651.

7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45(suppl S):S5–S67.

8. Becker F, Robert-Ebadi H, Ricco JB, Setacci C, Cao P, de Donato G, Eckstein HH, De Rango P, Diehm N, Schmidli J, Teraa M, Moll FL, Dick F, Davies AH, Lepantalo M, Apelqvist J. Chapter I: definitions, epidemiology, clinical presentation and prognosis. *Eur J Vasc Endovasc Surg*. 2011;42(suppl 2):S4–S12.

9. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Rother J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, Pencina MJ, Goto S. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–1206.

10. Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord*. 2005;5:14.

11. Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, Nehler MR, Powell RJ, Sidawy AN. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg*. 2009;50:1462–1473.

12. Sprengers RW, Teraa M, Moll FL, de Wit GA, van der Graaf Y, Verhaar MC. Quality of life in patients with no-option critical limb ischemia underlines the need for new effective treatment. *J Vasc Surg*. 2010;52:843–849.

13. Barshes NR, Chambers JD, Cohen J, Belkin M. Cost-effectiveness in the contemporary management of critical limb ischemia with tissue loss. *J Vasc Surg*. 2012;56:1015–1024.

14. Peters EJ, Childs MR, Wunderlich RP, Harkless LB, Armstrong DG, Lavery LA. Functional status of persons with diabetes-related lower-extremity amputations. *Diabetes Care*. 2001;24:1799–1804.

15. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med*. 2008;13:209–215.

16. Makdisse M, Pereira AC, Brasil DP, Borges JL, Machado-Coelho GL, Krieger JE, Nascimento Neto RM, Chagas AC. Prevalence and risk factors associated with peripheral arterial disease in the Hearts of Brazil Project. *Arq Bras Cardiol*. 2008;91:370–382.

17. Eraso LH, Fukaya E, Mohler ER III, Xie D, Sha D, Berger JS. Peripheral arterial disease, prevalence and cumulative risk factor profile analysis. *Eur J Prev Cardiol*. 2014;21:704–711.

18. Conte MS. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) and the (hoped for) dawn of evidence-based treatment for advanced limb ischemia. *J Vasc Surg*. 2010;51:69S–75S.

19. Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders. *Helv Chir Acta*. 1954;21:499–533.

20. Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg*. 1986;4:80–94.

21. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, Jones DN. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.

22. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg*. 2000;31:S1–S296.

23. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Seely L, Lorenz TJ, Namini H, Hamdan AD, Roddy SP, Belkin M, Berceli SA, DeMasi RJ, Samson RH, Berman SS. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg*. 2006;43:742–751.

24. Egorova NN, Guillerme S, Gelijns A, Morrissey N, Dayal R, McKinsey JF, Nowygrod R. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. *J Vasc Surg*. 2010;51:878–885.

25. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. *J Vasc Surg*. 2003;38:279–288.

26. Nowygrod R, Egorova N, Greco G, Anderson P, Gelijns A, Moskowitz A, McKinsey J, Morrissey N, Kent KC. Trends, complications, and mortality in peripheral vascular surgery. *J Vasc Surg*. 2006;43:205–216.

27. Eskelinen E, Eskelinen A, Alback A, Lepantalo M. Major amputation incidence decreases both in non-diabetic and in diabetic patients in Helsinki. *Scand J Surg*. 2006;95:185–189.

28. Goodney PP, Beck AW, Nagle J, Welch HG, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J Vasc Surg*. 2009;50:54–60.

29. Rowe VL, Lee W, Weaver FA, Etzioni D. Patterns of treatment for peripheral arterial disease in the United States: 1996–2005. *J Vasc Surg*. 2009;49:910–917.

30. Hong MS, Beck AW, Nelson PR. Emerging national trends in the management and outcomes of lower extremity peripheral arterial disease. *Ann Vasc Surg*. 2011;25:44–54.

31. Jones WS, Patel MR, Dai D, Subherwal S, Stafford J, Calhoun S, Peterson ED. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000–2008. *J Am Coll Cardiol*. 2012;60:2230–2236.

32. Benoit E, O'Donnell TF Jr, Kitsios GD, Iafrati MD. Improved amputation-free survival in unreconstructable critical limb ischemia and its implications for clinical trial design and quality measurement. *J Vasc Surg*. 2012;55:781–789.

33. Chung J, Modrall JG, Ahn C, Lavery LA, Valentine RJ. Multidisciplinary care improves amputation-free survival in patients with chronic critical limb ischemia. *J Vasc Surg*. 2015;61:162–169.

34. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr, White CJ, White J, White RA, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)—summary of recommendations. *J Vasc Interv Radiol*. 2006;17:1383–1397.

35. Diehm N, Schmidli J, Setacci C, Ricco JB, de Donato G, Becker F, Robert-Ebadi H, Cao P, Eckstein HH, De Rango P, Teraa M, Moll FL, Dick F, Davies AH, Lepantalo M, Apelqvist J. Chapter III: management of cardiovascular risk factors and medical therapy. *Eur J Vasc Endovasc Surg*. 2011;42(suppl 2):S33–S42.

36. Schanzer A, Conte MS. Critical limb ischemia. *Curr Treat Options Cardiovasc Med*. 2010;12:214–229.

37. Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. *Circulation*. 2011;124:17–23.

38. Rodriguez F, Cannon CP, Steg PG, Kumbhani DJ, Goto S, Smith SC, Eagle KA, Ohman EM, Umez-Eronini AA, Hoffman E, Bhatt DL. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherothrombotic disease: findings from the REACH Registry. *Clin Cardiol*. 2013;36:721–727.

39. Gasse C, Jacobsen J, Larsen AC, Schmidt EB, Johannesen NL, Videbaek J, Sorensen HT, Johnsen SP. Secondary medical prevention among Danish patients hospitalised with either peripheral arterial disease or myocardial infarction. *Eur J Vasc Endovasc Surg*. 2008;35:51–58.

40. van Hattum ES, Tangelder MJ, Huis in 't Veld MA, Lawson JA, Algra A, Moll FL. Medical treatment after peripheral bypass surgery over the past decade. *Eur J Vasc Endovasc Surg*. 2011;41:805–813.

41. Hogh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Secondary medical prevention after primary vascular surgery between 1996 to 2006: a shift towards more evidence-based treatment. *Eur J Prev Cardiol*. 2013;20:763–770.

42. Subherwal S, Patel MR, Kober L, Peterson ED, Jones WS, Gislason GH, Berger J, Torp-Pedersen C, Fosbol EL. Missed opportunities: despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. *Circulation*. 2012;126:1345–1354.

43. Secondary prevention in survivors of myocardial infarction. Joint Recommendations by the International Society and Federation of Cardiology, Scientific Councils on Arteriosclerosis, Epidemiology and Prevention, and Rehabilitation. *Br Med J (Clin Res Ed)*. 1981;282:894–896.

44. Teraa M, Sprengers RW, Schutgens RE, Slaper-Cortenbach IC, van der Graaf Y, Algra A, van der Tweel I, Doevendans PA, Mali WP, Moll FL, Verhaar MC. Effect of repetitive intra-arterial infusion of bone marrow mononuclear cells in patients with no-option limb ischemia: the randomized, double-blind, placebo-controlled Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial Supplementation (JUVENTAS) trial. *Circulation*. 2015;131:851–860.

45. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton JD, Gavin JR III, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med*. 2003;163:884–892.

46. Hirsch AT, Halverson SL, Treat-Jacobson D, Hotvedt PS, Lunzer MM, Krook S, Rajala S, Hunninghake DB. The Minnesota Regional Peripheral Arterial Disease Screening Program: toward a definition of community standards of care. *Vasc Med*. 2001;6:87–96.

47. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317–1324.

48. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, Miller CD, Ziemer DC, Barnes CS. Clinical inertia. *Ann Intern Med*. 2001;135:825–834.

49. Dijkstra RF, Braspenning JC, Uiters E, van Ballegooie E, Grol RT. Perceived barriers to the implementation of diabetes guidelines in hospitals in The Netherlands. *Neth J Med*. 2000;56:80–85.

50. Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS, Goto S, Rother J, Steg PG, Hirsch AT. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Atherosclerosis*. 2009;204:e86–e92.

51. Hackam DG, Sultan NM, Criqui MH. Vascular protection in peripheral artery disease: systematic review and modelling study. *Heart*. 2009;95:1098–1102.

52. Abbruzzese TA, Havens J, Belkin M, Donaldson MC, Whittemore AD, Liao JK, Conte MS. Statin therapy is associated with improved patency of autogenous infrainguinal bypass grafts. *J Vasc Surg*. 2004;39:1178–1185.

53. Iida O, Soga Y, Kawasaki D, Hirano K, Yamaoka T, Suzuki K, Miyashita Y, Yokoi H, Takahara M, Uematsu M. Angiographic restenosis and its clinical impact after infrapopliteal angioplasty. *Eur J Vasc Endovasc Surg*. 2012;44:425–431.

54. Siracuse JJ, Giles KA, Pomposelli FB, Hamdan AD, Wyers MC, Chaikof EL, Nedeau AE, Schermerhorn ML. Results for primary bypass versus primary angioplasty/stent for intermittent claudication due to superficial femoral artery occlusive disease. *J Vasc Surg*. 2012;55:1001–1007.

55. Aiello FA, Khan AA, Meltzer AJ, Gallagher KA, McKinsey JF, Schneider DB. Statin therapy is associated with superior clinical outcomes after endovascular treatment of critical limb ischemia. *J Vasc Surg*. 2012;55:371–379.

56. Belch J, Hiatt WR, Baumgartner I, Driver IV, Nikol S, Norgren L, Van Belle E. Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia. *Lancet*. 2011;377:1929–1937.

57. Ko SH, Bandyk DF. Therapeutic angiogenesis for critical limb ischemia. *Semin Vasc Surg*. 2014;27:23–31.

58. Peeters Weem SM, Teraa M, de Borst GJ, Verhaar MC, Moll FL. Bone marrow derived cell therapy in critical limb ischemia: a meta-analysis of randomized placebo controlled trials. *Eur J Vasc Endovasc Surg*. 2015;50:775–783.

59. Powell RJ, Simons M, Mendelsohn FO, Daniel G, Henry TD, Koga M, Morishita R, Annex BH. Results of a double-blind, placebo-controlled study to assess the safety of intramuscular injection of hepatocyte growth factor plasmid to improve limb perfusion in patients with critical limb ischemia. *Circulation*. 2008;118:58–65.

60. Teraa M, Sprengers RW, van der Graaf Y, Peters CE, Moll FL, Verhaar MC. Autologous bone marrow-derived cell therapy in patients with critical limb ischemia: a meta-analysis of randomized controlled clinical trials. *Ann Surg*. 2013;258:922–929.

61. Gremmels H, Teraa M, Quax PH, den Ouden K, Fledderus JO, Verhaar MC. Neovascularization capacity of mesenchymal stromal cells from critical limb ischemia patients is equivalent to healthy controls. *Mol Ther*. 2014;22:1960–1970.

62. Setacci C, de Donato G, Teraa M, Moll FL, Ricco JB, Becker F, Robert-Ebadi H, Cao P, Eckstein HH, De Rango P, Diehm N, Schmidli J, Dick F, Davies AH, Lepantalo M, Apelqvist J. Chapter IV: treatment of critical limb ischaemia. *Eur J Vasc Endovasc Surg*. 2011;42(suppl 2):S43–S59.

63. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: analysis of amputation free and overall survival by treatment received. *J Vasc Surg*. 2010;51:18S–31S.

64. Bradbury AW, Adam DJ, Bell J, Forbes JF, Fowkes FG, Gillespie I, Ruckley CV, Raab GM. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. *J Vasc Surg*. 2010;51:52S–68S.

65. Dosluoglu HH, Lall P, Harris LM, Dryjski ML. Long-term limb salvage and survival after endovascular and open revascularization for critical limb ischemia after adoption of endovascular-first approach by vascular surgeons. *J Vasc Surg*. 2012;56:361–371.

66. DeRubertis BG, Pierce M, Ryer EJ, Trocciola S, Kent KC, Faries PL. Reduced primary patency rate in diabetic patients after percutaneous intervention results from more frequent presentation with limb-threatening ischemia. *J Vasc Surg*. 2008;47:101–108.

67. Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. *J Vasc Surg*. 2008;47:975–981.

68. Giles KA, Pomposelli FB, Spence TL, Hamdan AD, Blattman SB, Panossian H, Schermerhorn ML. Infrapopliteal angioplasty for critical limb ischemia: relation

of TransAtlantic InterSociety Consensus class to outcome in 176 limbs. *J Vasc Surg*. 2008;48:128–136.

69. O'Brien-Irr MS, Harris LM, Dosluoglu HH, Dryjski ML. Procedural trends in the treatment of peripheral arterial disease by insurer status in New York State. *J Am Coll Surg*. 2012;215:311–321.

70. Stoner MC, Defreitas DJ, Manwaring MM, Carter JJ, Parker FM, Powell CS. Cost per day of patency: understanding the impact of patency and reintervention in a sustainable model of healthcare. *J Vasc Surg*. 2008;48: 1489–1496.

71. Forbes JF, Adam DJ, Bell J, Fowkes FG, Gillespie I, Raab GM, Ruckley CV, Bradbury AW. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: health-related quality of life outcomes, resource utilization, and cost-effectiveness analysis. *J Vasc Surg*. 2010;51:43S–51S.

72. Goodney PP, Holman K, Henke PK, Travis LL, Dimick JB, Stukel TA, Fisher ES, Birkmeyer JD. Regional intensity of vascular care and lower extremity amputation rates. *J Vasc Surg*. 2013;57:1471–1479, 1480.

73. Abu Dabrh AM, Steffen MW, Asi N, Undavalli C, Wang Z, Elamin MB, Conte MS, Murad MH. Bypass surgery versus endovascular interventions in severe or critical limb ischemia. *J Vasc Surg*. 2016;63:244–253.

74. Nolan BW, De Martino RR, Stone DH, Schanzer A, Goodney PP, Walsh DW, Cronenwett JL. Prior failed ipsilateral percutaneous endovascular intervention in patients with critical limb ischemia predicts poor outcome after lower extremity bypass. *J Vasc Surg*. 2011;54:730–735.

75. Jones DW, Schanzer A, Zhao Y, MacKenzie TA, Nolan BW, Conte MS, Goodney PP. Growing impact of restenosis on the surgical treatment of peripheral arterial disease. *J Am Heart Assoc*. 2013;2:e000345 doi: 10.1161/JAHA.113.000345.

76. Schanzer A, Mega J, Meadows J, Samson RH, Bandyk DF, Conte MS. Risk stratification in critical limb ischemia: derivation and validation of a model to predict amputation-free survival using multicenter surgical outcomes data. *J Vasc Surg*. 2008;48:1464–1471.

77. Schanzer A, Goodney PP, Li Y, Eslami M, Cronenwett J, Messina L, Conte MS. Validation of the PIII CLI risk score for the prediction of amputation-free survival in patients undergoing infrainguinal autogenous vein bypass for critical limb ischemia. *J Vasc Surg*. 2009;50:769–775.

78. Schanzer A, Hevelone N, Owens CD, Belkin M, Bandyk DF, Clowes AW, Moneta GL, Conte MS. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. *J Vasc Surg*. 2007;46:1180–1190.

79. Siracuse JJ, Huang ZS, Gill HL, Parrack I, Schneider DB, Connolly PH, Meltzer AJ. Defining risks and predicting adverse events after lower extremity bypass for critical limb ischemia. *Vasc Health Risk Manag*. 2014;10:367–374.

80. Jones WS, Schmit KM, Vemulapalli S, Subherwal S, Patel MR, Hasselblad V, Heidenfelder BL, Chobot MM, Posey R, Wing L, Sanders GD, Dolor RJ. Treatment strategies for patients with peripheral artery disease. Comparative Effectiveness Review No. 118. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC090-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2013. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed December 22, 2015.

81. Mills JL Sr, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, Andros G. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg*. 2014;59:220–234.

82. Zhan LX, Branco BC, Armstrong DG, Mills JL Sr. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. *J Vasc Surg*. 2015;61:939–944.

83. Kent DM, Trikalinos TA. Therapeutic innovations, diminishing returns, and control rate preservation. *JAMA*. 2009;302:2254–2256.

84. Farber A, Rosenfield K, Menard M. The BEST-CLI trial: a multidisciplinary effort to assess which therapy is best for patients with critical limb ischemia. *Tech Vasc Interv Radiol*. 2014;17:221–224.

85. Norgren L, Hiatt WR, Dormandy JA, Hirsch AT, Jaff MR, Diehm C, Baumgartner I, Belch JJ. The next 10 years in the management of peripheral artery disease: perspectives from the 'PAD 2009' Conference. *Eur J Vasc Endovasc Surg*. 2010;40:375–380.

Journal of the American Heart Association

OPEN ACCESS

American Heart Association | American Stroke Association

Critical Limb Ischemia: Current Trends and Future Directions

Martin Teraa, Michael S. Conte, Frans L. Moll and Marianne C. Verhaar

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://jaha.ahajournals.org/content/5/2/e002938