Current review with evolving management strategies in critical limb ischemia

Arun Sharma

Department of Cardiovascular Radiology and Endovascular Interventions, All India Institute of Medical Sciences, New Delhi, India

Correspondence: Dr. Arun Sharma, Department of Cardiovascular Radiology and Endovascular Interventions, All India Institute of Medical Sciences, New Delhi - 110 029, India. E-mail: drarungautam@gmail.com

Abstract

Critical limb ischemia represents the end stage of peripheral artery disease, which is associated with impaired quality of life and considerable morbidity and mortality. Economical impact of the disease is huge with a substantial burden on patients, healthcare providers, and resources. Varied therapeutic strategies have been employed in the management of these patients. These patients usually have complex multilevel occlusive arteriopathy with significant comorbidities, rendering surgical interventions undesirable in many cases. Recent therapeutic advances with evolving endovascular techniques and gene or cell-based therapies have the potential to dramatically change the therapeutic outlook in these patients.

Key words: Critical limb ischemia; peripheral artery disease; revascularization

Introduction

Critical limb ischemia (CLI) represents the most advanced form of peripheral artery disease (PAD) with high rates of cardiovascular events, amputations, and even death.[1] Economical impact of the condition is immense with frequent hospital visits. Varied treatment strategies have been employed in the management of CLI with the primary aim of revascularization whenever feasible, though optimal revascularization strategy is still uncertain due to the lack of sufficient clinical evidence.[2] Medical therapy is highly important for the optimization of cardiovascular risk factors as these factors are responsible for considerable mortality and morbidity. Further angiogenesis promoting therapies, such as gene or cell-based treatments appear promising emerging options in nonrevascularizable CLI.

Access this article online	
Quick Response Code:	Website: www.ijri.org
	DOI: 10.4103/ijri.IJRI_208_19

Definition

Use of CLI term in clinical practice is highly variable with different definitions in use, thus causing variable research reporting in this subset of patients. A uniform strict definition, including hemodynamic assessment is important to improve standardize reporting on CLI. Earlier definitions lack the hemodynamic assessment, as proposed by Fontaine *et al.* for the first time in 1954. As per current consensus definition, CLI is largely defined by a clinical constellation of symptoms including ischemic rest pain, ulcer, or gangrene in the context of objective hemodynamic evidence of manifest arterial insufficiency.[3-5] As CLI represents the most advanced form of PAD, it is usually classified in the higher stages or grades of the Fontaine classification (stage III-IV)

Cite this article as: Sharma A. Current review with evolving management strategies in critical limb ischemia. Indian J Radiol Imaging 2019;29:258-63.

Received: 06-May-2019 **Revision:** 20-Jun-2019
Accepted: 25-Jun-2019 **Published:** 30-Oct-2019

or the Rutherford classification (grades 4–6). The Society for Vascular Surgery has also created a CLI staging scheme recently, which is according to wound extent, ischemia, and degree of concomitant foot infection. This system defines four clinical stages of threatened limb and helps in risk stratification, guiding treatment strategy, and predicting the benefit of revascularization in these patients.[6,7]

Epidemiology

PAD constitutes a common cause of vascular morbidity. It affects nearly 200 million people worldwide and is associated with 3 to 6-fold increased risk of cardiovascular mortality and morbidity as compared to patients without PAD.[8-10] CLI constitutes nearly 1% of the adult population and up to 10% of patients with PAD with an annual estimated incidence of 220–3500 new cases per million population.[2,11-13] Moreover, approximately 5%–10% patients with asymptomatic PAD or intermittent claudication generally progress to CLI in a period of 5 years.[2] CLI is associated with high mortality rates (nearly 16–20%, 50% and 70% at 1, 5, and 10 years, respectively),[14-16] and the prognosis with respect to limb salvage is generally poor with amputation rates as high as 12% and 25% at 6 months and 1 year, respectively.[17,18] Particularly, in no option CLI patients, 6 months amputation rates may range from 10% to 40%. Moreover, higher amputation rates have been shown in CLI patients (12%), 1 year after lower extremity bypass as compared to patients with claudication (1%).[19] Coexistent atherosclerosis in other vascular territories is also commonly seen in these patients; significant coronary artery disease on angiograms in nearly two-third patients with CLI and significant carotid stenosis in approximately a quarter of patients with PAD,[20,21] which is largely responsible for high mortality (13.4%, 19–25%, >60% at 6 months, 1 year and 5 years, respectively) and morbidity in these patients.[17,22,23] There is high likelihood (annual rate 5% –7%) of adverse cardiovascular events (myocardial infarction, stroke, or death) in PAD patients, which is likely to be higher in patients with CLI.

Pathophysiology

CLI is generally caused by diffuse, progressive, multilevel, obstructive atherosclerosis. In minority of cases, CLI can also be secondary to hypercoagulable states, thromboembolism, vasculitis, Burger disease, trauma, cystic adventitial disease, and popliteal entrapment syndrome. The pathophysiology of CLI is a complex process and involves both macro- and micro-vascular changes leading to reduced perfusion to the extremities.[18,24] Angiogenesis, an adaptive response occurs, thereby promoting enlargement of pre-existing collateral vessels to increase the blood flow to the critically ischemic limb. Distal arterioles further adapt to this chronic ischemic process by decreasing wall thickness, wall-to-lumen ratio, cross-sectional area, and with maximal vasodilatation, thus producing a state of vasomotor paralysis, causing an orthostatic-dependent increase in the hydrostatic pressure, thereby producing distal edema. In addition to this, microvascular dysfunction occurs with endothelial damage resulting in inappropriate platelet activation, leukocyte adhesion, and increased free radical production, leading to microthrombi formation and causing impaired tissue oxygen exchange at the capillary level.

Diagnosis

CLI is largely a clinical diagnosis, which must be supported by objective hemodynamic criteria. These patients usually have diminished or absent distal pulses, thin/dry or shiny skin, loss of hair, dependent rubor or elevation pallor, or non-healing ulcer, and increased capillary refill time. Multiple noninvasive tests (including ankle pressure, toe pressure, pulse volume recordings, transcutaneous oxygen pressure, and Doppler evaluation) can be used to establish the diagnosis of CLI, assess foot perfusion, and predict wound healing. Ankle-brachial index (ABI) remains the simplest method, which provides important diagnostic and prognostic information in such patients.[25] An ABI value less than 0.9 is indicative of PAD, while a value less than 0.4 is consistent with CLI.[3] However, ABI assessment is limited in patients with renal failure or diabetes, where it may remain spuriously high or within the normal range, due to impaired vessel compressibility owing to medial calcinosis. In such cases, toe pressure readings may provide an optimal assessment of the distal perfusion.[26] Various imaging modalities (including Doppler, computerized tomography, or magnetic resonance angiography) have been used to assess the complete anatomical extent of the disease; however, digital subtraction angiography is still considered as the gold standard imaging evaluation, often providing a definitive treatment plan in these patients.[27]

Management Options

Multiple treatment strategies [Table 1] have been employed in the management of CLI patients by different specialists involved in patient care, however, definite optimal revascularization remains uncertain. Therapeutic goals of treatment include optimization of coexistent cardiovascular risk factors, ischemic pain relief, ulcer healing, major amputation prevention, quality of life improvement, and patient survival. These aims can be achieved through optimal medical therapy, revascularization (surgical or endovascular), or amputation.

Medical therapy

Coexisting cerebrovascular and coronary artery disease accounts for considerable mortality and morbidity in CLI patients; hence, optimization of risk factors is of prime importance in the management of these patients. Medical therapy is primarily used to optimize these cardiovascular

Table 1: Key points with management options in critical limb ischemia

Classification/Categorization	• Fontaine stage III-IV • Rutherford grades 4-6 • Staging based on wound extent, ischemia, and degree of concomitant foot infection (WIfI) • ABI<0.4
Therapeutic goals	• Optimization of coexistent cardiovascular risk factors • Ischemic pain relief • Ulcer care & infection control • Major amputation prevention • Quality of life improvement and patient survival.
Management options	• Optimal medical therapy - Smoking cessation - Blood pressure control - Strict glycemic control • Revascularization (surgical or endovascular) - Angiosome guidance - Modified vascular access techniques including SAFARI, TAMI or pedal loop • Amputation
Evolving treatment options	• Gene and cell based therapies • Platelet rich plasma • Deep venous arterialization • Stem cell or growth factor eluting stents • Bilayered stents (paclitaxel & growth factor) • Advancements in atherectomy devices and angioplasty balloons (cryoplasty, laser or vibrational angioplasty)

ABI=Ankle-brachial index, SAFARI=Subintimal antegrade flossing using antegrade and retrograde intervention, TAMI=Tibio-pedal arterial minimally invasive retrograde revascularization

risk factors; however, it can also favorably affect limb-related outcomes by achieving pain relief, ulcer care or infection control, and achieving ambulation. Hence, our prime focus should be on the use of optimal medical therapy as it has been shown that optimal medical therapy is not always used. A study evaluating patients requiring infra-inguinal bypass for limb salvage had shown that nearly two-third of patients (aspirin in 50%; thienopyridine in 17%) were taking an antiplatelet drug, whereas only nearly less than half were taking lipid-lowering therapy (46%) or beta-blocker (49%).[28] In another trial, 80% of CLI patients received an antiplatelet agent with only 46% received statin and 77% received beta-blocker.[29] Regardless of the treatment strategy employed for these patients, treating physicians must increase their efforts to place them on appropriate cardio-protective medications.

Smoking cessation, control of hypertension, and hypercholesterolemia with strict glycemic control must be ensured in these patients to achieve optimal cardio-protection. Smoking cessation has been given a high level of recommendation in various guidelines for PAD management as it has been shown to considerably decrease the progression to CLI, amputation, and mortality in these patients.[30] Moreover, active smoking is associated with devastating cardiovascular complications including death. Adequate control of blood pressure (less than 130/80 mmHg) should be maintained in these patients, as 10 mmHg reduction in systolic blood pressure has been shown to be associated with 16% reduction in limb amputation and PAD-related deaths. Angiotensin-converting enzyme inhibitors or β-blocker therapy has been used with encouraging results (ramipril use associated with 27% decrease in the rate of combined cardiovascular events) in such patients.[31]

Hypercholesterolemia has also been shown to be an independent predictor for the development of PAD, and lipid lowering drugs, particularly statins, have been used with a favorable reduction in cardiovascular events, mortality, and limb events following revascularization. Moreover, recent recommendations now stress the use of moderate- to high-intensity statin therapy in these patients.[32] Moreover, patients with symptomatic PAD should also be prescribed antiplatelet monotherapy (aspirin or clopidogrel associated with a reduction in cardiovascular events in nearly a quarter of patients) as dual therapy has shown only a marginal benefit in these patients as compared to the increased risk of bleeding.[33] Use of vasodilators such as iloprost (prostanoids) or naftidrofuryl has also been tried but with variable results.[34] Cilastazol (phosphodiesterase III inhibitor having antiplatelet, vasodilator, and antimitogenic properties) has been shown to favorably increase skin perfusion pressure and wound healing in patients with CLI.[35] Use of oral cilostazol (dosage of 100 mg twice daily), in addition to best medical therapy has resulted in improvement in nearly a quarter of patients with nonreconstructable CLI; however, further studies are required to adequately evaluate its role in these patients.

Revascularization

Revascularization aiming at re-establishing continuous, in-line pulsatile flow to the pedal arch remains the preferred treatment option for CLI patients, which can be achieved by surgery (lower extremity bypass or endarterectomy) or endovascular therapy. Goal of revascularization includes wound healing or treatment of at least one level of obstructive disease in case of tissue loss or ischemic pain, respectively, thereby preserving a functional limb, achieving ambulation, and preventing major limb amputation. The choice of treatment between surgical versus endovascular treatment will largely depend on various patient and procedure-specific factors such as age and co-morbidity, severity of limb ischemia, vascular anatomy/extent of involvement and presence of useable vein graft, and it should be individualized. However, in the recent years, a trend in favor of initial endovascular treatment has been seen. Although there is still a considerable amount of skepticism about the need for angiosome-related revascularization, the concept provides a framework for the interventionalist to plan the procedure. As CLI patients are very sick and have limited options for

limb salvage, modified access techniques such as subintimal antegrade flossing using antegrade and retrograde intervention (SAFARI), tibio-pedal arterial minimally invasive retrograde revascularization (TAMI), or pedal loop techniques may improve chances of recanalization in cases where even conventional methods fail to cross the lesion. Moreover, multiple technical advancements such as atherectomy devices, cryoplasty, drug-eluting balloons, and stents have been made with advanced delivery systems, which make endovascular treatment an attractive option.

However, reintervention rate is higher in the endovascular group to the tune of over 3 interventions for 1 surgical procedure declined, which fades the early benefit of this treatment option.[36-38] The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial, the only randomized controlled trial directly comparing open bypass surgery with balloon angioplasty in CLI patients, has not shown any significant difference in terms of amputation-free survival at 1 and 3 year follow-up.[39] Further, BEST-CLI, BASIL-2, and BASIL-3 trials are still underway, which may provide further direct comparisons between these treatment options. Among endovascular option, different drug-eluting stents were tried in PAD patients. Studies with sirolimus or everolimus drug-eluting stents have not shown any significant difference as compared to PTA or BMS; however, paclitaxel have shown promising results (improved event-free survival with superior primary patency, results being sustained at 2 years follow-up) in femoropopliteal lesions, as in ZILVER PTX trial, which allowed its FDA approval for use in PAD in 2012.[40,41] However, its use in infrapopliteal disease is still limited to focal disease (mean lesion length 26.8 mm) and needs further validation in more common diffuse lesions.[42] Paclitaxel has proved to be a better agent than limus-class drugs, owing to its superior lipophilicity, which allows rapid uptake across cell membranes, thus reducing the risk of systemic absorption. Moreover, it can be applied directly to the metal, which obviates the risk of bio-incompatibilty of delivery polymers.

Amputation

Primary amputation rates have declined to nearly half in the previous decade with the increase in surgical or endovascular revascularization rates. Primary amputation is now reserved to patients with extensive tissue loss or infection, unreconstructable arterial disease, terminal illness, and nonambulatory status with flexion contractures. Efforts should be made to preserve knee joint, as below knee amputation is associated with reduced 30-day mortality (5% versus 16%) and increased long-term survival (74.5% versus 50.6%) as compared to above knee amputation.[43,44]

Gene and Cell-based Therapies

Gene and cell-based therapies are emerging treatment modalities, which showed evidence for favorable outcome in CLI patients, particularly in initial trials. Various gene (fibroblast growth factor, vascular endothelial growth factor, hypoxia inducible factor 1, and hepatocyte growth factor) and cell-based (bone marrow mononuclear cells, mesenchymal stem cells, and endothelial progenitor cells) therapies have been tried, with the majority of studies using intramuscular injection and intra-arterial delivery in minority of the protocols.[45-50] Hepatocyte growth factor and mesenchymal stem cells currently seem most promising, however, needs further validation. Moreover, we should keep in mind that the large and especially randomized placebo-controlled trials failed to replicate these initial promising results, and future larger trials are needed to establish the efficacy of these therapies.

Platelet Rich Plasma

Use of platelet-rich plasma has also been shown beneficial for limb salvage with improvement in ulcer healing rates in CLI patients.[51,52] Concentration and sequestration of platelets within the plasma fraction of autologous blood provide a milieu of various growth factors such as chemokines and cytokines. They may play a major role in initiation and promotion of the process of bone and soft tissue healing by enhancing *in vivo* angiogenesis, improving microcirculation, tissue remodeling, and enhanced wound healing. The notion that platelet-rich plasma could be a source of various essential growth factors, thereby directly benefiting these patients show promise, however, needs further supportive evidence by future studies.

Arterialization of Deep Veins

Deep venous arterialization (DVA) has also been shown to be a safe and feasible novel alternative to prevent major amputation in no-option CLI patients.[53,54] It acts by providing arterialized blood at significant pressure and volumes to the ischemic tissue, thereby enabling wound healing. The LimFlow device (LimFlow SA) is currently the only registered device for total percutaneous DVA, which allows for disruption of the veins with a dedicated valvulotome, in addition to percutaneous creation of an arteriovenous fistula. Although early experience with DVA shows promising results, additional research is necessary for a better understanding of the involved physiologic mechanisms in tissue perfusion, thereby improving clinical outcomes in this subset of patients.

Future Directions

Technical advancements and ongoing research hold promise for further improvements in the management strategies of CLI patients. Combined gene and stem cell therapy may improve outcomes by selectively promoting particular cellular processes to induce a desired biological response. Moreover, it may overcome many limitations

by controlling cell behavior at the intracellular signaling level. Further, ongoing research for the feasibility and efficacy of stem cell or growth factor eluting stents, bilayered stents (paclitaxel on inner layer and growth factor plasmid on outer layer), and advancements in angioplasty balloons (cryoplasty, laser, or vibrational angioplasty) may help in improving the outcome in these patients.

Conclusion

CLI poses considerable effect on the quality of patient life with huge economical impact. Moreover, the management of these patients is quite variable and not yet standardized. Revascularization remains the cornerstone of management; however, optimal revascularization strategy remains elusive. Use of optimal medical therapy should be stressed in all such patients as it is associated with improved outcome with reduction in mortality and morbidity. Recent therapeutic advances with evolving endovascular techniques and gene or cell-based therapies have the potential to dramatically change the therapeutic outlook in these patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5-67.
2. 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 (5 Suppl):69S-75S.
3. Farber A, Eberhardt RT. The current state of critical limb ischemia: A systematic review. JAMA Surg 2016;151:1070-7.
4. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, *et al*. Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg 1997;26:517-38.
5. Patel MR, Conte MS, Cutlip DE, Dib N, Geraghty P, Gray W, *et al*. Evaluation and treatment of patients with lower extremity peripheral artery disease: Consensus definitions from Peripheral Academic Research Consortium (PARC). J Am Coll Cardiol 2015;65:931-41.
6. Mills JL Sr, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, *et al*. Society for Vascular Surgery Lower Extremity Guidelines Committee. 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;59:220-34.e1-2.
7. 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;61:939-44.
8. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, *et al*. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: A systematic review and analysis. Lancet 2013;382:1329-40.
9. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, *et al*. Mortality over a period of 10 years in patients with peripheral arterial-disease. N Engl J Med 1992;326:381-6.
10. Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. Vasc Health Risk Manag 2007;3:229-34.
11. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Eur J Vasc Endovasc Surg 2000;19(Suppl A):Si-xxviii. S1-250.
12. Biancari F. Meta-analysis of the prevalence, incidence and natural history of critical limb ischemia. J Cardiovasc Surg (Torino) 2013;54:663-9.
13. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, *et al*. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg 2014;60:686-95.
14. Nehler MR, Peyton BD. Is revascularization and limb salvage always the treatment for critical limb ischemia? J Cardiovasc Surg 2004;45:177-84.
15. Watelet J, Soury P, Menard JF, Plissonnier D, Peillon C, Lestrat JP, *et al*. Femoropopliteal bypass: *In situ* or reversed vein grafts? Ten-year results of a randomized prospective study. Ann Vasc Surg 1997;11:510-9.
16. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Seely L, Lorenz TJ, *et al*. 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;43:742-50.
17. Bertelè V, Roncaglioni MC, Pangrazzi J, Terzian E, Tognoni EG. Clinical outcome and its predictors in 1560 patients with critical leg ischaemia. Eur J Vasc Endovasc Surg 1999;18:401-10.
18. Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. J Vasc Surg 2010;51:230-41.
19. Goodney PP, Likosky DS, Cronenwett JL. Predicting ambulation status one year after lower extremity bypass. J Vasc Surg 2009;49:1431-9.
20. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF 3rd, Graor RA, *et al*. Coronary artery disease in peripheral vascular patients: A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
21. Cheng SW, Wu LL, Ting AC, Lau H, Wong J. Screening for asymptomatic carotid stenosis in patients with peripheral vascular disease: A prospective study and risk factor analysis. Cardiovasc Surg 1999;7:303-9.
22. Varty K, Nydahl S, Nasim A, Bolia A, Bell PR, London JM. Results of surgery and angioplasty for the treatment of chronic severe lower limb ischaemia. Eur J Vasc Endovasc Surg 1998;16:159-63.
23. Dorros G, Jaff MR, Dorros AM, Mathiak LM, He T. Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: Five-year follow-up. Circulation 2001;104:2057-62.
24. Coats P, Wadsworth R. Marriage of resistance and conduit arteries breeds critical limb ischemia. Am J Physiol Heart Circ Physiol 2005;288:H1044-50.
25. Vogt MT, McKenna M, Wolfson SK, Kuller LH. The relationship between ankle brachial index, other atherosclerotic disease, diabetes, smoking and mortality in older men and women. Atherosclerosis 1993;101:191-202.
26. Williams DT, Harding KG, Price P. An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. Diabetes Care 2005;28:2206-10.
27. Cao P, Eckstein HH, De Rango P, Setacci C, Ricco JB, de Donato G,

et al. Chapter II: Diagnostic methods. Eur J Vasc Endovasc Surg 2011;42(Suppl 2):S13-32.

28. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Namini H, Seely L. Risk factors, medical therapies and perioperative events in limb salvage surgery: Observations from the PREVENT III multicenter trial. J Vasc Surg 2005;42:456-64.
29. Raghunathan A, Rapp JH, Littooy F, Santilli S, Krupski WC, Ward HB, *et al*. Postoperative outcomes for patients undergoing elective revascularization for critical limb ischemia and intermittent claudication: A subanalysis of the Coronary Artery Revascularization Prophylaxis (CARP) trial. J Vasc Surg 2006;43:1175-82.
30. Armstrong EJ, Wu J, Singh GD, Dawson DL, Pevec WC, Amsterdam EA, *et al*. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. J Vasc Surg 2014;60:1565-71.
31. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53.
32. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, *et al*. Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:2020-45.
33. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, *et al*. CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.
34. Smith FB, Bradbury A, Fowkes G. Intravenous naftidrofuryl for critical limb ischaemia. Cochrane Database of Syst Rev 2012:CD002070. doi: 10.1002/14651858.
35. Miyashita Y, Saito S, Miyamoto A, Iida O, Nanto S. Cilostazol increases skin perfusion pressure in severely ischemic limbs. Angiology 2011;62:15-7.
36. Giles KA, Pomposelli FB, Spence TL, Hamdan AD, Blattman SB, Panossian H, *et al*. Infrapopliteal angioplasty for critical limb ischemia: Relation of TransAtlantic InterSociety Consensus class to outcome in 176 limbs. J Vasc Surg 2008;48:128-36.
37. 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;48:1489-96.
38. Forbes JF, Adam DJ, Bell J, Fowkes FG, Gillespie I, Raab GM *et al*. 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.
39. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, *et al*. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): Multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
40. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, *et al*. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: Twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv 2011;4:495-504.
41. Dake MD, Ansel GM, Jaff MR, Ohki T, Saxon RR, Smouse HB, *et al*. Sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal lesions: 2-year follow-up from the Zilver PTX randomized and single-arm clinical studies. J Am Coll Cardiol 2013;61:2417-27.
42. Fusaro M, Cassese S, Ndrepepa G, Tepe G, King L, Ott I, *et al*. Drug-eluting stents for revascularization of infrapopliteal arteries: Updated meta-analysis of randomized trials. JACC Cardiovasc Interv 2013;6:1284-93.
43. Aulivola B, Hile CN, Hamdan AD, Sheahan MG, Veraldi JR, Skillman JJ, *et al*. Major lower extremity amputation: Outcome of a modern series. Arch Surg 2004;139:395-9.
44. Stone PA, Flaherty SK, Aburahma AF, Hass SM, Jackson JM, Hayes JD, *et al*. Factors affecting perioperative mortality and wound-related complications following major lower extremity amputations. Ann Vasc Surg 2006;20:209-16.
45. Ko SH, Bandyk DF. Therapeutic angiogenesis for critical limb ischemia. Semin Vasc Surg 2014;27:23-31.
46. Belch J, Hiatt WR, Baumgartner I, Driver IV, Nikol S, Norgren L, *et al*. Effect of fibroblast growth factor NV1FGF on amputation and death: A randomised placebo-controlled trial of gene therapy in critical limb ischaemia. Lancet 2011;377:1929-37.
47. Powell RJ, Simons M, Mendelsohn FO, Daniel G, Henry TD, Koga M, *et al*. 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.
48. 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;258:922-9.
49. 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;50:775-83.
50. Osipova O, Saaya S, Karpenko A, Zakian S, Aboian E. Cell therapy of critical limb ischemia-problems and prospects. Vasa 2019;10:1-11.
51. Vicenti G, Bizzoca D, Caruso I, Nappi VS, Giancaspro G, Carrozzo M, *et al*. New insights into the treatment of non-healing diabetic foot ulcers. J Biol Regul Homeost Agents 2018;32(6 Suppl. 1):15-21.
52. Kontopodis N, Tavlas E, Papadopoulos G, Pantidis D, Kafetzakis A, Chalkiadakis G, *et al*. Effectiveness of Platelet-Rich Plasma to Enhance Healing of Diabetic Foot Ulcers in Patients With Concomitant Peripheral Arterial Disease and Critical Limb Ischemia. Int J Low Extrem Wounds 2016;15:45-51.
53. Del Giudice C, Van Den Heuvel D, Wille J, Mirault T, Messas E, Ferraresi R, *et al*. Percutaneous deep venous arterialization for severe critical limb ischemia in patients with no option of revascularization: Early experience from two european centers. Cardiovasc Intervent Radiol 2018;41:1474-80.
54. Kum S, Huizing E, Schreve MA, Ünlü Ç, Ferraresi R, Samarakoon LB, *et al*. Percutaneous deep venous arterialization in patients with critical limb ischemia. J Cardiovasc Surg (Torino) 2018;59:665-9.