Limb Salvage and Survival in Chronic Limb-Threatening Ischemia

Subjects: Peripheral Vascular Disease

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Chronic limb-threatening ischemia (CLTI) represents the end-stage form of peripheral arterial disease (PAD) and is associated with a very poor prognosis and high risk of limb loss and mortality. It can be considered very similar to a terminal cancer disease, reflecting a large impact on quality of life and healthcare costs.

chronic limb-threatening ischemia survival limb salvage

1. Introduction

Peripheral arterial disease (PAD) is a global pandemic of growing proportions and increasing healthcare costs around the globe [1]. The Global Burden of Disease study reported that 202 million adults worldwide have PAD, a higher prevalence than ischemic heart disease (154 million), heart failure (64 million), Alzheimer's disease/dementia (44 million), and cancer (43 million) [2]. Alarmingly, the prevalence of PAD will probably grow due to population aging and the growing prevalence of risk factors, in particular diabetes mellitus (DM). Between 2017 and 2045, the prevalence of DM is expected to rise from 451 to 693 million people worldwide (in 2040, 1 in 10 adults will have diabetes), and it is well known that DM increases the risk and severity of PAD [3].

According to the 2019 Global Vascular Guidelines (GVG) from the European Society for Vascular Surgery, advanced PAD is described as chronic limb-threatening ischemia (CLTI) that represents the end-stage form of the disease [4]. This new definition replaced the previous concept of critical limb ischemia (CLI) requiring an objectively documented atherosclerotic PAD in association with ischemic rest pain >2 weeks duration or tissue loss for diagnosis. The GVG recommend using objective hemodynamic tests, such as the ankle-brachial index (ABI) < 0.4, absolute ankle pressure (AP) < 50 mmHg, absolute toe pressure (TP) < 30 mmHg, transcutaneous pressure of oxygen (TcPO2) < 30 mmHg, and flat or minimal pulsatile volume recording (PVR) waveforms to determine the presence and to quantify severity of ischemia in all patients with suspected CLTI (Recommendation 1.1). In addition, the GVG stress the use of a threatened limb classification based on the presence and degree of tissue loss, ischemia, and infection (e.g., WIfI classification) that grades wound extent, degree of ischemia, and severity of infection to guide clinical management (Recommendation 1.2). CLTI definition, being accompanied by objective evidence of significant PAD (e.g., WIfI ischemia grade > 1), excludes purely neuropathic, traumatic, or venous ulcers lacking any ischemic component.

CLTI affects up to 10% of patients with PAD and is associated with significant mortality, pain, amputation rate, and impaired quality of life. Up to 50% of all patients with CLTI are diagnosed with DM, which is associated with lower revascularisation success rates, decreased wound healing, and higher amputation and mortality rates compared with those without diabetes [5].

CLTI generally results from involvement of at least two arterial segments (aorto-iliac, femoro-popliteal, tibio-pedal) or severe tibio-pedal disease alone. The latter is particularly involved in patients with DM, end-stage renal disease (ESRD), or very elderly. CLTI is a strong indication to endovascular, surgical, or hybrid revascularisation, in order to prevent major (above the ankle) amputation with the aim of preserving foot plantar support despite the need for minor (below the ankle) amputations, thus, obtaining limb salvage (LS).

2. CTLI Mortality and Amputation Rate

General and limb prognosis of these frail patients is adverse: they are at continuous risk of a major cardiovascular event, sudden death, and major amputation. When an individual first receives a diagnosis of CLTI, mortality risk is around 20–25% over 1 year, and around 60% over 5 years [6][7]. Reported 5-year all-cause and cardiovascular mortality rates were twice as high (57% and 29%, respectively) compared with patients with intermittent claudication (IC) (31% and 15%, respectively), according to a Dutch national registry study [8].

CLTI can be considered very similar to a terminal cancer disease. Few diseases connote a higher mortality rate. Data collected from American Cancer Statistics Center show that among 22 different types of malignancy, only 6 have a 5-year mortality rate higher than that of CLTI. Yet CLTI is even more deadly than this statistic suggests. Many cancers with high mortality rates are relatively rare, so the overall mortality burden to the population is modest; conversely, the mortality burden associated with some of the most common cancers is blunted due to relatively low mortality rates. Consequently, several deadly cancers, such as melanoma or ovarian cancer, are actually less common and less deadly than CLTI. Because CLTI is both common and deadly, more incident cases die during the 5 years after a CLTI diagnosis than with any type of cancer, except for lung cancer [9].

If left untreated, the overall risk of limb loss in CLTI is estimated at approximately 20–25% at 1 year, reflecting a large impact on quality of life and healthcare costs. More than half of people with a major amputation will be dead in 5 years [10][11].

A meta-analysis of 13 studies with 1527 patients on the natural history of untreated CLTI reported that at a median follow-up of 12 months, both the mortality and the amputation rates were 22%, although there was a marked heterogeneity between the studies [7].

In a study of 574 patients with CLTI who did not undergo revascularisation after 2 years, 31.6% had died, primarily of cardiovascular disease, and 23% required major amputation [12].

A recent study [13] investigated the long-term survival and amputation-free survival at 5 years in a cohort of 150 patients with non-revascularisable or so called “no option” CLTI. Amputation-free survival was 43% five years after inclusion. This outcome was driven by an equal rate of all-cause mortality (35%) and amputation (33%). Amputation occurred predominantly in the first year. Furthermore, 33% of those with amputation subsequently died within the investigated period, with a median interval of 291 days. Meloni et al. reported a 30% amputation rate and 50% mortality rate for no option CLTI diabetic patients at 1 year follow-up in a retrospective cohort study [14].

3. Limb Salvage and Mortality

Major amputation is an established risk factor for death. Perioperative mortality rate after below the knee amputation (BKA) is around 5–10% and rises to 15–20% after above the knee amputation (AKA). Five-year mortality rates of up to 85% have been reported in elderly CLI amputees, and seven-year rates after below and above the knee amputations in a veteran cohort published in 2003 were 72% and 80%, respectively [15][16].

Other studies showed a 3-year death rate of 33.3% after BKA, and 71.4% after AKA. At 5 years, these rates increased to 63.3% for BKA and 85.7% for AKA [17].

Despite the guidelines generally recommend to revascularise CLTI patients, the underlying evidence for such a recommendation is limited. However, if considering the group of patients that undergo some kind of revascularisation in order to prevent major amputation, outcomes are more favourable [18].

A German study on a retrospective real-world cohort [19] comparing the outcomes of CLTI patients with and without revascularisation in a period between 2009 and 2011 showed that revascularisation is associated with significantly better short- and long-term outcomes in term of limb amputation (40.4% vs. 46.5%, respectively) and overall mortality (42.6% vs. 48.2%, respectively).

The Italian CLIMATE registry on 2399 patients treated for CLTI [20] documented an overall mortality of 3.1% at 30 days, and 13.5% at 1 year. Mortality did not statistically differ between genders even if females, who have less comorbidities but are significantly older (over-75), died more than males. Age seems to be a key determinant factor in the outcome of patients treated for CLTI. Age > 75 years, coronary artery disease (CAD), cerebrovascular disease (CVD), and major amputation at the first operation are independent negative prognostic factors for survival at short- and mid-term, as well as haemodialysis treatment and tissue loss for 1-year survival. These findings support the effort to attempt revascularisation in patients with CLTI, avoiding primary major amputation if possible. Approaches to this fragile population should, therefore, be directed towards aggressive risk factor control by using the best medical therapy in the long term, and strategies to decrease the amputation risk by means of timely evidence-based revascularisation in the short term, as pointed out from the GVG.

4. Medical Management Improving Survival in CLTI and Limb Salvage

CLTI is a terminal manifestation of systemic atherosclerosis; therefore, it is often accompanied by clinically significant CAD and CVD, resulting in exceedingly high mortality from stroke and myocardial infarction [21][22][23][24]. The goal of treating patients with CLTI is not only to save a still functional limb, but to reduce major adverse cardiac events (MACE) through aggressive risk factor modification and the best medical therapy. Whereas certain risk factors cannot be modified (such as age and sex), others can (DM, hyperlipidemia, hypertension, diabetes, smoking, and sedentary lifestyle). In the absence of aggressive identification and treatment of risk factors and associated comorbidities, the prognosis of CLTI is usually poor [25][26]. Sub-optimal medical therapy for comorbid conditions has been associated with up to 26% all-cause mortality rates within the first year of CLI diagnosis [4]. Therefore, nowadays, risk factors' aggressive treatment is considered a cornerstone in CLTI management [27][28][29][30][31][32][33].

The GVG strongly recommend the best medical therapy, including the use of moderate- or high-intensity statin, antihypertensive, glycaemic control, and antiplatelet agents, to reduce all-cause and cardiovascular mortality in patients with CLTI, as well as counselling on smoking cessation, healthy diet and weight loss, regular physical exercise, and preventive foot care [4].

Novel oral anticoagulants (NOACs) are assuming an increasing role in reducing MACE and major adverse limb events (MALE) in PAD patients. According to the COMPASS study, a low dose of rivaroxaban (2.5 mg twice a day) plus 100 mg ASA determine a 28% reduction in MACE, a 46% reduction in MALE, and a 31% reduction in the composite endpoint occurrence rates compared to ASA, with no excess of fatal or critical bleedings [34]. The VOYAGER PAD trial demonstrated that dual therapy with low-dose rivaroxaban and aspirin significantly also reduces MACE and MALE occurrence in patients with symptomatic PAD undergoing revascularisation vs. aspirin alone (HR 0.85, 95% CI 0.76–0.96) [35].

References

1. Song, P.; Rudan, D.; Zhu, Y.; Fowkes, F.J.I.; Rahimi, K.; Fowkes, F.G.R.; Rudan, I. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: An updated systematic review and analysis. Lancet Glob. Health 2019, 7, e1020–e1030.
2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017, 390, 1211–1259.
3. Cho, N.H.; Shaw, J.E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.D.; Ohlrogge, A.W.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res. Clin. Pract. 2018, 138, 271–281.

4. Conte, M.S.; Bradbury, A.W.; Kolh, P.; White, J.V.; Dick, F.; Fitridge, R.; Mills, J.L.; Ricco, J.B.; Suresh, K.R.; Murad, M.H.; et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J. Vasc. Surg. 2019, 69, 3S–125S.
5. Mohammedi, K.; Woodward, M.; Hirakawa, Y.; Zoungas, S.; Colagiuri, S.; Hamet, P.; Harrap, S.; Poulter, N.; Matthews, D.R.; Marre, M.; et al. Presentations of major peripheral arterial disease and risk of major outcomes in patients with type 2 diabetes: Results from the ADVANCE-ON study. Cardiovasc. Diabetol. 2016, 15, 129.
6. Mustapha, J.A.; Katzen, B.T.; Neville, R.F.; Lookstein, R.A.; Zeller, T.; Miller, L.E.; Jaff, M.R. Disease burden and clinical outcomes following initial diagnosis of critical limb ischemia in the Medicare population. JACC Cardiovasc. Interv. 2018, 11, 1011–1012.
7. Abu Dabrh, A.M.; Steffen, M.W.; Undavalli, C.; Asi, N.; Wang, Z.; Elamin, M.B.; Conte, M.S.; Murad, M.H. The natural history of untreated severe or critical limb ischemia. J. Vasc. Surg. 2015, 62, 1642–1651.
8. Van Haelst, S.T.W.; Koopman, C.; Den Ruijter, H.M.; Moll, F.L.; Visseren, F.L.; Vaartjes, I.; de Borst, G.J. Cardiovascular and all-cause mortality in patients with intermittent claudication and critical limb ischaemia. Br. J. Surg. 2018, 105, 252–261.
9. Mustapha, J.A.; Katzen, B.T.; Neville, R.F.; Lookstein, R.A.; Zeller, T.; Miller, L.E.; Driver, V.R.; Jaff, M.R. Critical Limb Ischemia: A threat to life and limb. Endovasc. Today 2019, 18, 5.
10. Ward, R.; Dunn, J.; Clavijo, L.; Shavelle, D.; Rowe, V.; Woo, K. Outcomes of critical limb ischemia in an urban, safety net hospital population with high WIfI amputation scores. Ann. Vasc. Surg. 2017, 38, 84–89.
11. Duff, S.; Mafilios, M.S.; Bhounsule, P.; Hasegawa, J.T. The burden of critical limb ischemia: A review of recent literature. Vasc. Health Risk Manag. 2019, 15, 187–208.
12. Marston, W.A.; Davies, S.W.; Armstrong, B.; Farber, M.A.; Mendes, R.C.; Fulton, J.J.; Keagy, B.A. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J. Vasc. Surg. 2006, 44, 108–114.
13. Verwer, M.C.; Wijnand, J.G.J.; Teraa, M.; Verhaar, M.C.; de Borst, G.J. Long Term Survival and Limb Salvage in Patients with Non-Revascularisable Chronic Limb Threatening Ischaemia. Eur. J. Vasc. Endovasc. Surg. 2021, 62, 225–232.
14. Meloni, M.; Izzo, V.; Da Ros, V.; Morosetti, D.; Stefanini, M.; Brocco, E.; Giurato, L.; Gandini, R.; Uccioli, L. Characteristics and Outcome for Persons with Diabetic Foot Ulcer and No-Option Critical Limb Ischemia. J. Clin. Med. 2020, 9, 3745.
15. Klaphake, S.; de Leur, K.; Mulder, P.G.; Ho, G.H.; de Groot, H.G.; Veen, E.J.; Verhagen, H.J.; van der Laan, L. Mortality after major amputation in elderly patients with critical limb ischemia. Clin. Interv. Aging 2017, 12, 1985–1992.

16. Cruz, C.P.; Eidt, J.F.; Capps, C.; Kirtley, L.; Moursi, M.M. Major lower extremity amputations at a Veterans Affairs hospital. Am. J. Surg. 2003, 186, 449–454.
17. Ferraresi, R.; Mauri, G.; Losurdo, F.; Troisi, N.; Brancaccio, D.; Caravaggi, C.; Neri, L. BAD transmission and SAD distribution: A new scenario for critical limb ischemia. J. Cardiovasc. Surg. 2018, 59, 655–664.
18. Almasri, J.; Adusumalli, J.; Asi, N.; Lakis, S.; Alsawas, M.; Prokop, L.J.; Bradbury, A.; Kolh, P.; Conte, M.S.; Murad, M.H. A systematic review and meta-analysis of revascularization outcomes of infrainguinal chronic limb-threatening ischemia. J. Vasc. Surg. 2018, 68, 624–633.
19. Stella, J.; Engelbertz, C.; Gebauer, K.; Hassu, J.; Meyborg, M.; Freisinger, E.; Malyar, N.M. Outcome of patients with chronic limb-threatening ischemia with and without revascularization. Vasa 2020, 49, 121–127.
20. Martelli, E.; Zamboni, M.; Sotgiu, G.; Saderi, L.; Federici, M.; Sangiorgi, G.M.; Puci, M.V.; Martelli, A.R.; Messina, T.; Frigatti, P.; et al. Sex-Related Differences and Factors Associated with Peri-Procedural and 1 Year Mortality in Chronic Limb-Threatening Ischemia Patients from the CLIMATE Italian Registry. J. Pers. Med. 2023, 13, 316.
21. Agnelli, G.; Belch, J.J.; Baumgartner, I.; Giovas, P.; Hoffmann, U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: A systematic review. Atherosclerosis 2020, 293, 94–100.
22. Wong, N.D. Evaluating Multisite Atherosclerosis and its Progression. J. Am. Coll. Cardiol. 2020, 75, 1628–1630.
23. Collet, J.-P.; Cayla, G.; Ennezat, P.-V.; Leclercq, F.; Cuisset, T.; Elhadad, S.; Henry, P.; Belle, L.; Cohen, A.; Silvain, J.; et al. Systematic detection of polyvascular disease combined with aggressive secondary prevention in patients presenting with severe coronary artery disease: The randomized AMERICA Study. Int. J. Cardiol. 2018, 254, 36–42.
24. Stone, K.; Fryer, S.; Faulkner, J.; Meyer, M.L.; Heffernan, K.; Kucharska-Newton, A.; Zieff, G.; Paterson, C.; Matsushita, K.; Hughes, T.M.; et al. Associations of lower-limb atherosclerosis and arteriosclerosis with cardiovascular risk factors and disease in older adults: The Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis 2022, 340, 53–60.
25. Armstrong, E.J.; Wu, J.; Singh, J.D.; Dawson, D.L.; Pevec, W.C.; Amsterdam, E.A.; Laird, J.R. Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease. J. Vasc. Surg. 2014, 60, 1565–1571.
26. Aboyans, V.; Ricco, J.B.; Bartelink, M.L.; Bjorck, M.; Brodmann, M.; Cohnert, T.; Collet, J.P.; Czerny, M.; Carlo, M.D.; Debus, S.; et al. 2017 ESC guidelines on the diagnosis and treatment of Peripheral Arterial Diseases in collaboration with the European Society for Vascular Surgery (ESVS). Eur. Heart J. 2018, 39, 763–821.

27. Sigvant, B.; Kragsterman, B.; Falkenberg, M.; Hasvold, P.; Johansson, S.; Thuresson, M.; Nordanstig, J. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. J. Vasc. Surg. 2016, 64, 1009–1017.e3.
28. Thalmann, I.; Preiss, D.; Schlackow, I.; Gray, A.; Mihaylova, B. Population-wide cohort study of statin use for the secondary cardiovascular disease prevention in Scotland in 2009–2017. Heart 2023, 109, 388–395.
29. Belur, A.D.; Shah, A.J.; Virani, S.S.; Vorla, M.; Kalra, D.K. Role of Lipid-Lowering Therapy in Peripheral Artery Disease. J. Clin. Med. 2021, 11, 4872.
30. Zeitouni, M.; Sabouret, P.; Kerneis, M.; Silvain, J.; Collet, J.-P.; Bruckert, E.; Montalescot, G. 2019 ESC/EAS Guidelines for management of dyslipidaemia: Strengths and limitations. Eur. Heart J.—Cardiovasc. Pharmacother. 2020, 7, 324–333.
31. Creager, M.A.; Hamburg, N.M. Smoking Cessation Improves Outcomes in Patients with Peripheral Artery Disease. JAMA Cardiol. 2022, 7, 15.
32. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur. Heart J. 2018, 39, 3021–3104.
33. Cosentino, F.; Grant, P.J.; Aboyans, V.; Bailey, C.J.; Ceriello, A.; Delgado, V.; Federici, M.; Filippatos, G.; Grobbee, D.E.; Hansen, T.B.; et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur. Heart J. 2020, 41, 255–323.
34. Anand, S.S.; Bosch, J.; Eikelboom, J.W.; Connolly, S.J.; Diaz, R.; Widimsky, P.; Aboyans, V.; Alings, M.; Kakkar, A.K.; Keltai, K.; et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: An international, randomised, double-blind, placebo-controlled trial. Lancet 2018, 391, 219–229.
35. Bonaca, M.P.; Bauersachs, R.M.; Anand, S.S.; Debus, E.S.; Nehler, M.R.; Patel, M.R.; Fanelli, F.; Capell, W.H.; Diao, L.; Jaeger, N.; et al. Rivaroxaban in peripheral artery disease after revascularization. N. Engl. J. Med. 2020, 382, 1994–2004.