

Akhil Gulati, Lawrence Garcia, and Subasit Acharji

## Introduction

Peripheral artery disease (PAD) is often referred to as a continuum of disease of occlusive arterial syndromes that can range from asymptomatic obstructive disease through occlusive disease requiring amputation. This entire spectrum of PAD has prevalence as high as 20% of the general population [1]. This spectrum becomes more progressive and symptomatic as the disease causes an imbalance of distal perfusion pressure to the tissue and metabolic demands within that tissue. On the latter end of this continuum, chronic critical limb ischemia (CLI) has a prevalence that is more difficult to define and is quite variable in the published literature. Unlike asymptomatic PAD or exertional claudication, CLI occurs with inadequate perfusion at rest [2].

Like most of the terminology of peripheral vascular disease, the definitions of CLI have evolved over the years, with first an increasing need to classify the entire continuum of PAD, the need to further classify those undergoing surgical procedures, and then to include more objective measures as well as the clinical presentation. In this chapter, we will discuss the epidemiology of CLI. We will present the historical background of CLI and the risk factors along with its clinical presentations and then after the epidemiology and prevalence of CLI along with its risk stratification and prognostic data before discussing the socioeconomic impact of this disease.

## Definition of Chronic Critical Limb Ischemia

The definition of CLI has evolved over time. It has been classically defined as greater than 2 weeks of extremity rest pain, ulcers, or extremity gangrene, secondary to objectively proven peripheral artery disease. In its most extreme case, CLI can lead to limb loss [1, 2].

Several criteria are often used for objective evidence of CLI, but most commonly involve: (a) ankle-brachial index (ABI) of 0.4 or less, (b) ankle systolic pressure of 50 mmHg or less, (c) toe systolic pressure of 30 mmHg or less, (d) toe-brachial index (TBI) of 0.25 or less, and (e) reduced supine forefoot transcutaneous oxygen pressure (TcPO<sub>2</sub>) less than 30 mmHg [3, 4]. Although not an exact definition, CLI would be seen as corresponding with stages III and IV of Fontaine Classification and categories 4 through 6 of the Rutherford classification system [5, 6] (see Table 2.1).

While the Fontaine and Rutherford classification systems originally were implemented to categorize peripheral arterial disease by symptoms several decades ago, objective criteria were adapted as technology has developed and several consensus documents have then evolved the definition of CLI [7].

The first consensus document was the Second European Meeting Consensus Document on CLI (1991) that used two definitions for CLI based on clinical use and on research use [4] as written below:

1. CLI, in both diabetic and nondiabetic patients, is defined by either of the following two criteria:
  - a. Persistently recurring ischemic rest pain requiring regular adequate analgesia for more than 2 weeks with an ankle systolic pressure  $\leq 50$  mmHg and/or toe systolic pressure  $\leq 30$  mmHg
  - b. Ulceration or gangrene of the foot or toes, with an ankle systolic pressure  $\leq 50$  mmHg or toe systolic pressure  $\leq 30$  mmHg
2. A more precise description of the type and severity of CLI is also necessary for the design and reporting of

A. Gulati, MD • L. Garcia, MD (✉) • S. Acharji, MD  
Section of Interventional Cardiology and Vascular Intervention,  
Vascular Medicine, Department of Cardiovascular Medicine,  
St. Elizabeth's Medical Center, 736 Cambridge St., Boston,  
MA 02135, USA

**Table 2.1** Fontaine's stages and Rutherford categories for lower limb symptom classification

Fontaine's stages		Rutherford categories		
Stage	Clinical presentation	Grade	Category	Clinical presentation
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	I	Mild claudication
IIb	Moderate to severe		2	Moderate claudication
	Claudication		3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
			6	Major tissue loss

clinical trials. In addition to the above definition, the following information is also desirable:

- Arteriography to delineate the anatomy of the large vessel disease throughout the leg and foot
- Toe arterial pressure in all patients, including those who are not diabetic
- A technique for quantifying the local microcirculation in the ischemia area (e.g., capillary microscopy, transcutaneous oxygen pressure [TcPO<sub>2</sub>], or laser Doppler)

There has been some debate on the value of ankle pressures. However these definitions have been generally agreed upon as the threshold to be used.

The next large summary consensus was the Trans-Atlantic Inter-Society Consensus (TASC) Document on Management of Peripheral Arterial Disease (2000) that did continue the method of having a clinical definition, as well as a research definition. It also changed the thresholds for some of the objective criteria [8]:

- Clinical definition of critical limb ischemia (CLI): The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease. The CLI implies chronicity and is to be distinguished from acute limb ischemia.
- Trials and reporting standards definition of CLI: A relatively inclusive entry criterion is favored, the aim being to ensure that the ulceration, gangrene, or rest pain is indeed caused by peripheral arterial disease and that most would be expected to require a major amputation within the next 6 months to a year in the absence of a significant hemodynamic improvement. To achieve this, it is suggested to use absolute pressures of either ankle pressure <50–70 mmHg or toe pressure <30–50 mmHg or reduced supine forefoot TcPO<sub>2</sub> <30–50 mmHg.

Here, there is an emphasis on CLI being defined by symptoms and showing objective-proven arterial occlusive

disease. The thresholds for ankle pressure were raised, possibly to answer some of the critics of the 1991 European Consensus Document. However, the toe pressure and TcPO<sub>2</sub> pressure thresholds were also raised.

The ACC/AHA created practice guidelines in 2005 for management of patients with peripheral artery disease and also addressed the definition of CLI using some of the other consensus statements [9]. It uses the TASC clinical definition as above and points out that most vascular clinicians would define CLI as those patients in whom the untreated natural history would lead to a major limb loss within 6 months [9].

The most recent consensus statement is the TASC Document that was updated (TASC II 2007) that simplified the definition: "The term critical limb ischemia should be used for all patients with chronic ischemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease. The term CLI implies chronicity and is to be distinguished from acute limb ischemia" [3]. It also stresses that ischemic rest pain will most often occur with ankle pressures <50 mmHg and toe pressures <30 mmHg but that in situations where healing is needed (if a venous or traumatic ulcer is not healing well due to poor arterial flow), often ankle pressures less than 70 mmHg and toe pressures less than 50 mmHg are insufficient [3]. There is not complete consensus as to the objective vascular parameters to be used for CLI, but the thresholds we have mentioned are the most commonly used in various clinical practices, as well as for various research articles and publications.

CLI is most often caused by, and associated with, obstructive atherosclerotic arterial disease. While most risk factor modification, research, and focus are on this disease process, it is important to note that since CLI results from the imbalance between supply of nutrients and metabolic demand in distal tissues, there are other causes that can result in CLI. Other causes can include atheroembolic/thromboembolic disease, thrombosis resulting from hypercoagulable states, vasculitides, thromboangiitis obliterans, cystic adventitial disease, Buerger's disease, thoracic outlet syndrome, popliteal entrapment syndrome, trauma, and more [9, 10]. There are also multiple risk factors to CLI as well as contributing factors to the acceleration of the disease process that will be addressed elsewhere.

## Epidemiology of Chronic Critical Limb Ischemia

Peripheral arterial occlusive disease has been well studied over the last several decades with most research dealing with symptomatic disease, including intermittent claudication through the extreme of limb loss. It has been noted that there is a prevalence of 8–10 million Americans who suffer from arterial occlusive disease [3]. While the reported prevalence

of peripheral arterial disease (PAD) may depend on the particular population studied, and the modality used to diagnose it (subjective and objective criteria), if one uses PAD to be defined by an ankle-brachial index of  $<0.90$ , then it may likely be present in up to 4–10 % of patients in the USA and Europe [11–13] and involving a prevalence of an estimated 27 million people in those same areas [14].

There is widespread data about the incidence and prevalence of PAD as an entity; however, there is limited data regarding chronic critical limb ischemia. It is difficult to obtain specific epidemiologic data for CLI for several reasons [7]. First, the identification of CLI is more difficult than identifying some other conditions (like PAD as defined by ABI  $<0.90$ ). As stated above, a general definition that most clinicians use is by attributing rest pain, ulcers, or extremity gangrene to a peripheral arterial occlusive disease, and that lasts longer than 2 weeks. This requires a level of proficiency and diagnostic assessments that are not often readily available in large epidemiological studies [7].

Secondly, as noted, the definition of CLI has evolved over time. There is a heterogeneity of many studies using different definitions and often without the objective parameters to define that CLI has been published. There are often major differences between the various studies that can make the data inconsistent. Lastly, the actual numerical epidemiological data that is usually used and cited is often inferred from other markers, such as the incidence of amputations (which assumes that a quarter of CLI patients undergo this procedure). Data is often presented from assumptions of the natural history of PAD (i.e., perhaps the estimate that 5–10 % of patients with either asymptomatic PAD or claudication will go on to become CLI at 5 years time) [3, 7].

An Italian study by Catalano et al. tried to confront the difficult problem of getting accurate epidemiological data for CLI [15]. The study used three different methods to obtain data. They first created a prospective study on the incidence of CLI in 200 patients who had been suffering from claudication and in 190 controls that showed an incidence of 450 per million people per year for CLI and 112 per million people per year for amputations in those above the age of 45. They also did a 3-month prospective study on CLI hospitalizations in a sample of hospitals in Lombardy, Italy (Northern Italy region), that showed an incidence of 642 per million people per year for CLI and 160 per million people per year in those over the age of 45. Lastly, they also looked at the number of amputations performed in hospitals of two regions (6 years in Lombardy and 2 years in Emilia Romagna) that showed an incidence of 577 per million people per year for CLI and 172 per million people per year for amputations in Lombardy and 530 per million people per year for CLI and 154 per million people per year for amputations in Emilia Romagna. Interestingly, the results revealed an incidence of both CLI and amputation rates that were lower

than expected, with authors suggesting this to be explained by the area of Italy studied being one with a known high rate of “cardiovascular protection” [15].

While epidemiological data may be difficult to obtain, compare, and contrast, much of the data that is available is still fairly useful and reveals the scope of the disease, the natural history of PAD, and the serious effects of CLI and the socioeconomic impact of this disease.

The TASC II guidelines have estimated that the incidence of CLI, as inferred from the natural history of PAD and amputation rates, is approximately 500–1000 per million per year in a European or North American population (150,000 cases per year in the USA) [3]. As noted, some of the large prospective population studies have shown an incidence of 220 new cases per million per year in the general population [15, 16]. The prevalence of CLI is often estimated between 0.5 and 1.2 % in various studies and registries. One particular European cross-sectional study done in Sweden used an age-standardized randomly selected population sample of men and women aged 60–90 years with 5080 subjects included (64 % participation rate) to answer questionnaires on medical history, medication, and symptoms as their ABI was also measured [17]. The study also gave special attention to critical limb ischemia and gender differences. The prevalence of CLI was found to be approximately 1.2 %, with women having a slightly higher prevalence than men (1.5 % vs 0.8 %,  $p < 0.008$ ), although other studies may show the opposite. This study also showed that prevalence of CLI increased as age increased, as one would expect.

In attempting to determine the prevalence of CLI and the risk factors associated with developing CLI, the largest published population study was done in Norway (HUNT 2 Study) between 1995 and 1997 with a questionnaire for the 20,291 participants between the age of 40 and 69 that was specifically aimed at identifying CLI [18]. Questionnaires were sent to all patients over age 20, but the focus was on those 40–69 years of age, and thus the study population consisted of 9640 men and 10,651 women. For the purpose of the study, CLI was defined as having ulcers on toes, feet, or ankles that have failed to heal or persistent pain in the forefoot while in the supine position but with relief of the pain when standing up. The study revealed a prevalence of CLI in this population of 0.24 % (0.26 % for men and 0.24 % for women), with the age-adjusted prevalence of CLI increasing with age as expected. Tobacco use conferred a 2.3 times increased risk of CLI compared to those participants who never smoked, and diabetes mellitus conferred a 4.4 times increased risk of developing CLI compared to the general population. Other risk factors that were independently associated with increased risk of CLI included older age, elevated total cholesterol, elevated serum triglyceride, higher body mass index (BMI), and angina. The prevalence of CLI was found to be 2500 per million inhabitants, similar between

both genders and increasing with age. The study did note, however, that it may be easier and necessary to identify CLI by symptoms and clinical signs (rather than with objective measurements). This does cause drawbacks where one may include patients with non-PAD ulcers or pain in the CLI category. The study may also include some patients with acute limb ischemia (ALI) in the CLI category by the questions that were used in the questionnaire.

Another study was a population-based, prospective cohort study of the comparative value of modern risk stratification techniques for cardiac events and studied 4814 subjects aged 45–75 [19]. As part of this study, PAD was assessed by obtaining ABI and peak ankle artery pressures for all patients, and this data was used (along with patient acknowledging a history of specific PAD or CLI) to determine prevalence. In this study, CLI was considered present if the highest ankle artery pressure measured <70 mmHg. The prevalence of CLI in this population was 0.11 % with a trend toward increased association with age. The study did have some limitations that may have lowered the prevalence by not including some of the more severely ill subjects, not including the subjects that could not get an ABI performed (patients with ulcers or wounds that would already qualify them as CLI subjects) and the overall low response rate that may have been a selection bias against CLI, as well.

The TASC II study noted that 5–10 % of patients with asymptomatic PAD or claudication will progress to CLI within 5 years. Up to 1–3 % of patients with PAD present initially with CLI [3]. This group is often characterized as patients who are older or sedentary and thus have not exerted themselves to get claudication symptoms. Also, these are often patients with sensory neuropathy or patients with other medical issues such as heart failure. Some studies have shown that possibly half of CLI patients in the general population may not have any PAD symptoms even 6 months prior to the onset of clinical CLI [7, 20].

CLI is the initial clinical presentation in only 1–3 % of PAD cases, although arteriographic progression has been documented in up to 60 % of PAD patients after 5 years of follow-up. Other studies have shown that 40–50 % of those affected present with atypical leg pains, 10–35 % with intermittent claudication, and 20–50 % with no symptoms at all [9, 21].

One of the studies that attempted to show the natural history of those with intermittent claudication was the Edinburgh Artery Study in 1988, where 1592 participants between ages 55 and 74 were randomly selected and the presence of PAD was determined by questionnaire on claudication, ABI and a reactive hyperemia test. This cohort was then followed over 5 years for subsequent vascular events. In this cohort, 116 new cases of claudication were identified, and of those 4.1 % underwent vascular surgery/arterial reconstruction, 4.1 %

underwent amputation, and 1.4 % developed leg ulceration at 5 years time [22]. Limitations in this study were the small incidence noted of intermittent claudication in the population and the variable regional practices regarding when to perform amputation.

A much larger and longer study was done over a 15 year period by Aquino et al. who collected data on 1244 men with intermittent claudication with a mean follow-up of 45 months (with some statistically valid data followed for as long as 12 years) [23]. The group collected data on demographics, clinical risk factors, ABI and serially followed ABI, self-reported walking distance, and monitored patients for ischemic rest pain and ischemic ulceration. Results revealed that ABI declined an average of 0.014 per year. The cumulative 10-year risk of development of ischemic ulcers was 23 %, and the 10-year risk of ischemic rest pain was 30 %. Lower ABI and diabetes mellitus were identified as significant predictors of ischemic ulcers, with smoking added as a predictor as well for ischemic rest pain. The study was limited by only following a male population (study done at a Veterans Administration Center), and there was possibly a selection bias (in that it may be likely that sicker patients were the ones referred to the vascular lab). Of note, the study also identified a particularly higher risk of limb event subset of patients who were diabetic with ABI <0.3 [24, 25].

---

### **Risk Factors, Stratification, and Prognosis of Chronic Critical Limb Ischemia**

Chronic critical limb ischemia (CLI) is the result of atherosclerotic peripheral arterial occlusive disease and thus shares many of the same risk factors of atherosclerotic disease in other vascular territories. The risk factors include hypertension, hypercholesterolemia, cigarette smoking, and diabetes mellitus. The latter two are more strongly associated with progressive CLI than others [3]. Diabetic patients develop early onset and more rapidly progressive disease with the involvement of distal vessels. The aorta and iliac arteries are relatively spared when compared to profunda femoris and popliteal and tibial arteries, which may be less amenable to revascularization, thus along with presence of diabetic neuropathy leads to higher rates of amputation compared to nondiabetic. Similarly among smokers, the risk of developing CLI increases directly proportionally to the amount of cigarettes smoked [26].

Transcutaneous oxygen tension (TcPO<sub>2</sub>), determined by blood flow and arterial oxygen tension (PaO<sub>2</sub>), can be a marker of total distal runoff (arterial and arteriolar runoff) or perfusion reserve in forefoot and may predict changes in blood flow to an extremity when flow is severely restricted [27]. Recently a risk stratification tool based on TcPO<sub>2</sub> has been suggested [7]:



- Degree 1: 10 mmHg < forefoot TcPO<sub>2</sub> ≤ 35 mmHg in supine position
- Degree 2: forefoot TcPO<sub>2</sub> ≤ 10 mmHg in supine position but clear improvement (≤ 40 mmHg) in sitting position or under oxygen inhalation
- Degree 3: forefoot TcPO<sub>2</sub> ≤ 10 mmHg in supine position and inadequate or no improvement (< 30–40 mmHg) in sitting position or under oxygen inhalation
- Degree 4: forefoot TcPO<sub>2</sub> ≤ 10 mmHg in supine and in sitting position and/or under oxygen inhalation (very poor prognosis)

While a quarter of ), patients presenting with CLI are alive without clinical CLI and major amputation at one year, 20–25 % of patients will have died, 25–30 % will have had major amputation, and 20 % will still be in CLI state [3].

## Socioeconomic Impact of Chronic Critical Limb Ischemia

Patients with CLI experience a rapid functional decline and 6 min walk performance [28]. The functional impairment affects quality of life and may lead to depressed mood [29].

The financial burden of caring for patients with CLI is sobering. While the yearly cost of clinical care of a patient with CLI was \$43,000 per patient in 1990 [30], the cost of surgical revascularization for CLI was £23,322 sterling in BASIL trial [31]. Although there is an initial cost saving with endovascular revascularization of CLI when compared to surgical option, higher rates of subsequent revascularization offsets the cost advantage later [31, 32]. Ultimately, the yearly cost of managing a patient with CLI undergoing amputation is actually double that of undergoing a limb salvage procedure [30].

## Conclusion

Chronic critical limb ischemia is a vastly important disease process and part of the peripheral arterial occlusive disease spectrum. Much of our data regarding vascular disease covers the entire continuity of PAD as a whole, but there is more limited data regarding the distinct process of CLI. This may often be due to the difficulty and evolution of the CLI definition over the years, including subjective and objective descriptions of the disease. However, there is data that can be used in either population studies as well as inferred data from natural history of PAD and data from both surgical and endovascular studies that extrapolate CLI. Understanding the scope of CLI allows us to not only improve our diagnostic abilities but also our treatment including prevention. Understanding the devastating

effects of the end-stage vascular disease as a social effect, as well as economic effect, will also allow us to further determine cost-effective treatment (medical, endovascular, and surgical) and rehabilitation.

## References

1. Bitar FG, Garcia LA. Critical limb ischemia: an overview of the epidemiologic and clinical implications. *Vasc Dis Manag.* 2010;7:E182–4.
2. Alonso A, McManus DD, Fisher DF. *Peripheral vascular disease.* Sudbury, MA: Jones and Bartlett Publishers; 2011.
3. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;45(Suppl):S5–67.
4. Second European consensus document on chronic critical leg ischemia. *Circulation.* 1991;84 4 Suppl:1–26.
5. Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders. *Helv Chir Acta.* 1954;21:499–533. German.
6. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg.* 1997;26:517–38.
7. Becker F, Robert-Ebadi H, Ricco JB, et al. Chapter I: definitions, epidemiology, clinical presentation and prognosis. *Eur J Vasc Endovasc Surg.* 2011;45 Suppl 2:S4–12.
8. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg.* 2000;31:S1–296.
9. Hirsch AT, Haskal ZJ, Hertzner 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 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association 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): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113(11):e463–654.
10. DeBakey ME, Crawford ES, Garrett E, et al. Occlusive disease of the lower extremities in patients 16 to 37 years of age. *Ann Surg.* 1964;159:873–90.
11. Criqui MH, Fronek A, Barrett-Conner E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation.* 1985;71(3):510–5.
12. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the national Health and Nutrition Examination Survey, 1999–2000. *Circulation.* 2004;110:738–43.
13. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA.* 2001;286:1317–24.
14. Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA.* 2006;295:547–53.

15. Catalano M. Epidemiology of critical limb ischaemia: north Italian data. *Eur J Med*. 1993;2:11–4.
16. C S. Critical limb ischemia. New developments and perspectives. Turin: Edizioni Minerva Medica; 2010.
17. Sigvant B, Wiberg-Hedman K, Bergqvist D, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg*. 2007;45:1185–91.
18. Jensen SA, Vatten LJ, Myhre HO. The prevalence of chronic critical lower limb ischemia in a population of 20,000 subjects 40–69 years of age. *Eur J Vasc Endovasc Surg*. 2006;32:60–5.
19. Kroger K, Stang A, Kondratieva J, et al., Heinz Nixdorf RECALL Study Group. Prevalence of peripheral arterial disease—results of the Heinz Nixdorf Recall Study. *Eur J Epidemiol*. 2006; 21:279–85.
20. Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. *J Vasc Surg*. 2010;51:230–41.
21. Ouriel K. Peripheral arterial disease. *Lancet*. 2001;358:1257–64.
22. Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol*. 1996;25:1172–81.
23. Aquino R, Johnnides C, Makaroun M, Whittle JC, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. *J Vasc Surg*. 2001;34:962–70.
24. Jelnes R, Gaardsting O, Hougaard Jensen K, et al. Fate in intermittent claudication: outcome and risk factors. *Br Med J*. 1986;293: 1137–40.
25. Naschitz JE, Ambrosio DA, Chang JB. Intermittent claudication: predictors and outcomes. *Angiology*. 1988;39:16–22.
26. Rajagopalan S, Grossman PM. Management of chronic critical limb ischemia. *Cardiol Clin*. 2002;20:535–45.
27. Moosa HH, Makaroun MS, Peitzman AB, et al. TcPO<sub>2</sub> values in limb ischemia: effects of blood flow and arterial oxygen tension. *J Surg Res*. 1986;40(5):482–7.
28. McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *JAMA*. 2004;292(4):453–61.
29. Arseven A, Guralnik JM, O'Brien E, et al. Peripheral arterial disease and depressed mood in older men and women. *Vasc Med*. 2001;6(4):229–34.
30. Singh S, Evans L, Datta D, et al. The costs of managing lower limb-threatening ischaemia. *Eur J Vasc Endovasc Surg*. 1996; 12(3):359–62.
31. Adam DJ, Beard JD, Cleveland T, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. *Lancet*. 2005;366(9501):1925–34.
32. Stoner MC, Defreitas DJ, Manwaring MM, et al. Cost per day of patency: understanding the impact of patency and reintervention in a sustainable model of healthcare. *J Vasc Surg*. 2008;48(6):1489–96.

<http://www.springer.com/978-3-319-31989-6>

Critical Limb Ischemia

Acute and Chronic

Dieter, R.; Dieter, III, R.A.; Dieter, III, R.A.; Nanjundappa,  
A. (Eds.)

2017, XXII, 671 p. 555 illus., 430 illus. in color.,

Hardcover

ISBN: 978-3-319-31989-6