The Costs of Critical Limb Ischemia

Patient prognoses and the economic impact of CLI on vascular practices and the national health care system.

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Symptomatic peripheral arterial disease (PAD) is caused by an imbalance between the supply of nutrients to the extremity and the metabolic demand for these substances at a tissue level. This balance is typically lost in atherosclerotic PAD when an arterial stenosis impedes adequate blood flow to the needs of the skeletal muscle. Unlike individuals with exertional claudication, patients with critical limb ischemia (CLI) have inadequate perfusion at rest.[1,2]

CLI is defined as extremity pain at rest or as impending tissue loss that is caused by a severe or chronic compromise of blood flow, including ulcers or gangrene attributable to PAD. In its worst instances, CLI leads to limb loss. Symptoms of CLI persist for longer than 2 weeks, implying chronicity and distinguishing it from acute limb ischemia.[1,2] The diagnosis of CLI should be confirmed by ankle-brachial index (ABI), toe systolic pressure, or transcutaneous oxygen tension. Ischemic rest pain most commonly occurs below an ankle pressure of 50 mm Hg or a toe pressure less than 30 mm Hg.[1,3] Patients with CLI would correspond to stages III and IV of the Fontaine classification and categories 4 through 6 (grades II and III) of the Rutherford classification (Table 1).

EPIDEMIOLOGY AND RISK FACTORS

Although the reported prevalence of PAD depends on the population studied and the diagnostic modality used to assess for its presence, PAD, as defined by an ABI < 0.90 in either leg, is likely present between 4% to 10% of patients in the United States (US) and Europe,[4-7] involving an estimated 27 million people in these geographic areas.[8] For example, although PAD was present in 0.9% of participants aged 40 to 49 in the National Health and Nutrition Evaluation Survey (NHANES),[7] the reported prevalence of PAD was as high as 29% of patients in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, inclusive of patients older than 70 years, or 50 to 69 years plus diabetes or active smoking.[6]

CLI is the initial clinical presentation in only 1% to 2% of PAD cases; 40% to 50% of those affected with PAD

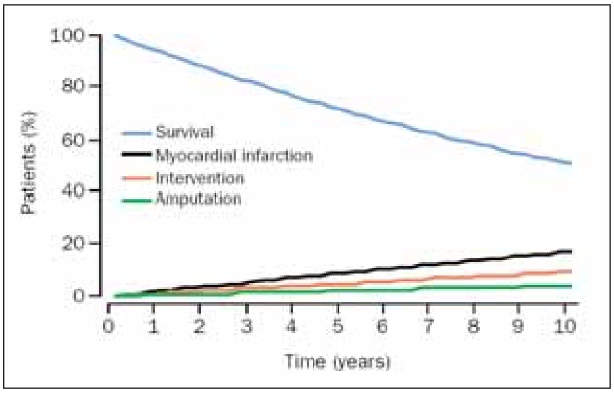

Figure 1. Survival, myocardial infarction, surgical or percutaneous revascularization, and major amputation over a 10-year follow-up in patients presenting initially with intermittent claudication. Reprinted from The Lancet, 358, Ouriel K, Peripheral arterial disease, 1257-1264, 2001, with permission from Elsevier.[9]

begin with atypical leg pain, 10% to 35% with intermittent claudication, and 20% to 50% with no symptoms. Although arteriographic progression has been documented in up to 60% of PAD patients after 5 years of follow-up, only a further 1% to 2% of PAD cases will result in CLI and eventual amputation (Figure 1).[9-11]

The prognosis is not benign after the onset of CLI. At 1 year after the development of CLI, it is estimated that up to 25% of patients have resolved, 20% have ongoing CLI, 30% have had an amputation, and 25% have died.[1]

It is well known that traditional cardiovascular risk factors appear to play a similar role in the development of PAD. In general, PAD is more frequent in males, smokers, increases with age, in patients of black race and in patients with diabetes and hypertension. The most important clinical predictors for CLI progression are ongoing tobacco abuse and diabetes. Collectively, studies suggest that approximately 80% of patients with PAD are current or former smokers.[12,13] Smoking cessation, however, may only modestly decrease the risk of progression. For example, the Edinburgh Artery Study found that the relative risk of claudication decreased from 3.7 to 3 in patients who discontinued smoking for less than 5 years. Although it is unknown if the risk ever returns to baseline with smoking cessation,[14] what is known is that PAD deterioration does occur in patients with claudication who continue to smoke.[10] Smoking and diabetes are also implicated in the risk for amputation. Smoking is associated with a limb amputation rate of 11% in patients with claudication, and diabetes is associated with a 21% risk of amputation as compared with 3% in nondiabetic patients.[9,10]

CLINICAL PRESENTATION

Although CLI is usually caused by atherosclerotic PAD, it can also be caused by atheroemboli, thromboemboli, vasculitis, hypercoagulable states, thromboangiitis obliterans, cystic adventitial disease, popliteal entrapment, or trauma. In addition, any factor that contributes to reduced blood flow to the microvasculature may exacerbate CLI (eg, low cardiac output, diabetes, vasospasm). Furthermore, increases in the demand for blood supply may also exacerbate CLI (eg, infection, skin breakdown, trauma).[2]

Patients with CLI usually present with limb pain at rest, may have trophic skin changes, or tissue loss. The discomfort is often worse when lying supine and may lessen when the limb is kept in the dependent position.[2,15] Table 2 displays the most characteristic clinical features of CLI.

The initial evaluation of patients with CLI should have four primary objectives: (1) confirmation of the diagnosis, (2) localization of the lesion, (3) assessment of the requirements for successful revascularization, and (4) assessment of the endovascular or operative risk.

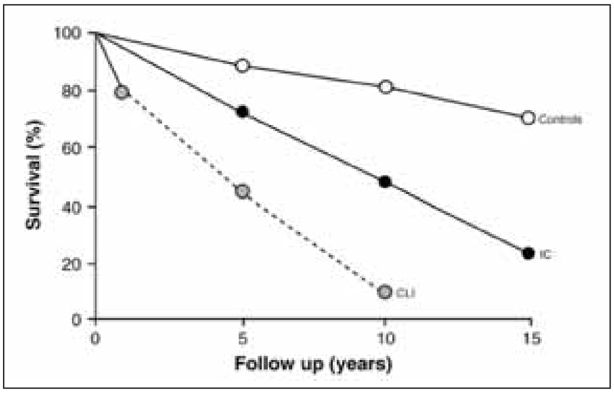

Figure 2. Survival of patients with peripheral arterial disease. IC, intermittent claudication; CLI, critical limb ischemia. Reprinted from Eur J Vasc Endovasc Surg, 33, Norgren L et al, Inter-society consensus for the management of peripheral arterial disease (TASC II), S1-S75, 2007, with permission from Elsevier.[1]

In order to achieve these objectives, several tests have been devised to confirm the diagnosis of threatening ischemia, assess foot perfusion and predict wound healing (Table 2). For example, an ABI > 1.3 is a predictor of major amputation. Transcutaneous oxygen pressure monitoring (an assessment of skin microcirculation) has been shown to predict limb survival. These parameters can help determine whether patients who are not candidates for revascularization are better served by undergoing amputation rather than aggressive local therapy.[16] Further imaging tests (eg, ultrasound, computed tomography, magnetic resonance, conventional angiography) should certainly be performed to fully evaluate the patient and determine candidacy for revascularization.

Remarkably, a recent study showed that only 35% of patients undergoing limb amputation in the US had an ABI documented, and only 16% of amputees underwent peripheral angiography.[17] In any case, CLI patients should be regarded as having a high risk for cardiovascular morbidity and mortality, a factor that should be taken into account when considering revascularization or amputation strategies.

THE FATE OF THE LIMB AND THE FATE OF THE PATIENT

In general, a peculiarity of PAD is that claudication symptoms are relatively benign with respect to the legs, and usually the risk of limb loss is largely overshadowed by the risk of morbid cardiovascular

TABLE 1. CLASSIFICATION OF PAD: FONTAINE'S STAGES AND RUTHERFORD'S CATEGORIES				
Fontaine		**Rutherford**		
Stage	**Clinical Presentation**	**Grade**	**Category**	**Clinical Presentation**
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate 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

events.[9] We mentioned, however, that patients with CLI have much worse survival outcomes when compared to patients with claudication (Figure 2). One-year CLI outcomes could approximate the following one-fourth rule: one-fourth of patients would have resolution of their CLI, one-fourth would have ongoing CLI, one-fourth would require amputation, and one-fourth would be dead.[1] Commonly accepted indications for amputation include the following:

- Necrosis of the weight-bearing portions of the foot (if patient is ambulatory)
- Uncorrectable flexion contracture
- Paresis of the extremity
- Refractory ischemic rest pain
- Sepsis
- Very limited life expectancy due to comorbid conditions

Amputations, however, not only have devastating psychological and quality-of-life effects on patients but also have a tremendous negative impact on their survival. It is estimated that the perioperative mortality could be 5% to 10% for below-the-knee amputations and 15% to 20% for above-the-knee amputations.[3] Perioperative morbidity can be as high as 20% to 30%.[17] Furthermore, the 1-year mortality rate in CLI patients requiring amputation can be as high as 45%.[9]

A second amputation is required in 30% of cases, and full mobility is achieved in only 50% of patients who have below-knee amputation and 25% of those having above-knee amputation.[3]

It is estimated that between 220,000 and 240,000 major and minor lower extremity amputations are performed for CLI in the US and Europe annually.[17] Despite advances in medical and interventional therapies, the amputation rate has in fact increased from 19 per 100,000 to 30 per 100,000 person/year over the past 2 decades, mainly driven by an increase in diabetes and aging of the patient population. In patients older than 85 years of age, a primary amputation rate of 140 per 100,000 persons/year has been reported.[17]

Successful rehabilitation is achieved in less than two-thirds and one-half of patients after below-knee and above-knee amputations, respectively. Fewer than 50% of amputees ever achieve full mobility.[17]

TREATMENT STRATEGIES FOR CLI

Medical therapy for CLI patients can be summarized in pain relief, local ulcer care and pressure relief, treatment of infection, and aggressive modification of atherosclerotic risk factors.[16] These therapies will be discussed elsewhere in this edition of *Endovascular Today*.

ECONOMIC IMPACT OF AMPUTATION FOR CLI

Amputations are also associated with significant expenses that are very difficult to assess in cost-effectiveness analyses (eg, home health aides, construction and adaptations at the patients' homes, influence on family and productivity economics, long-term health care costs, etc.) for our patients.

A recent cost-effectiveness analysis of US Medicare patients revealed that 67% of patients with CLI underwent primary amputation as a first-line treatment, with 23% of patients undergoing surgical and 10% percutaneous revascularization. Remarkably, about 80% of wound complications, strokes, and myocardial infarctions occurred in the primary amputation patients in that study.[17] These findings raise the suspicion that patients with CLI are not being adequately treated, and that amputation appears to be overutilized despite being associated with worse patient outcomes.

Two surgical revascularization series showed significant improvements in the prognosis of CLI patients when compared to limb amputation. In the first, patient survival was associated with an absolute 34% increase in 5-year survival in patients undergoing surgical revascularization for limb salvage.[18] In the second,

TABLE 2. FEATURES OF CLI
Physical Examination
• Dry skin, thickened nails, loss of hair, loss of subcutaneous fat or muscle atrophy
• Coolness to palpation
• Decreased or absent pulses
• Elevation pallor or dependent rubor
• Nonhealing wound or ulcer, especially over bony prominences, distally, and on the plantar surface of the foot
Noninvasive Vascular Laboratory
• Ankle-brachial index ≤ 0.4
• Ankle systolic pressure ≤ 50 mm Hg
• Toe systolic pressure ≤ 30 mm Hg
Measures of Skin Microcirculation
• Capillary density ≤ 20 mm^2
• Absent reactive hyperemia on capillary microscopy
• Transcutaneous oxygen tension < 10 mm Hg
Adapted from Slovut DP, Sullivan TM. Vasc Med. 2008;13:281-291.[16]

primary amputation was shown to be three times more costly than surgical revascularization in both diabetic and nondiabetic patients.[19]

In terms of percutaneous therapies, three recent cost-effectiveness reports show cost reductions of approximately 30% to 50% in terms of procedure cost and cost-per-leg-year saved.[20-22] For example, the use of laser in these interventions appears to further improve the cost-effectiveness of percutaneous revascularization when compared to surgery or amputation.[17]

CONCLUSION

CLI is a condition characterized by the inability to provide blood supply necessary to fulfill the metabolic demands of the extremities at rest. It may lead to limb loss by means of amputation, and it is also associated with significant cardiovascular and perioperative morbidity and mortality. It appears that CLI is markedly under-recognized, and an alarming number of patients do not undergo basic vascular evaluation prior to amputation or limb loss. It is important to recognize that there is no evidence that primary amputation is an overall cost-effective treatment strategy for CLI. Furthermore, recent data suggest that percutaneous intervention could be more cost-effective than surgical revascularization and amputation in patients with CLI. ■

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