Global burden

In 2010, estimates suggested that >200 million people worldwide were living with peripheral arterial disease (PAD). This figure represented a 23.5% increase since 2000, an elevation that is believed to be largely attributable to aging populations and the growing prevalence of risk factors, in particular diabetes mellitus (DM). These figures are thought to almost certainly underestimate the true burden of disease because they are largely based on community-based studies that define PAD on the basis of reduced ankle-brachial index (ABI).

PAD represents a local manifestation of a lethal systemic disease – atherosclerosis – and portends a 2-6-fold increase in both cardiovascular and cerebrovascular events. The diagnosis is also associated with an annual mortality rate of 4-6%. In addition to causing lifestyle-limiting claudication symptoms, uncontrolled disease can progress to critical limb ischemia (CLI). Within the spectrum of PAD, CLI represents the end stage and the diagnosis portends a high rate of limb loss along with patient mortality. Leg amputation due to atherosclerotic PAD gives rise to an acute mortality rate of approximately 30% and a 5-year survival rate of less than 30%.

Epidemiology

The annual incidence of CLI has been estimated at 220-3,500 per 1,000,000 people – its prevalence is approximately 1% of the adult population – and up to 10% of patients with PAD may have CLI. While symptomatic PAD patients will progress to CLI, asymptomatic patients can also progress to CLI. Between 5% and 10% of patients with asymptomatic PAD or intermittent claudication will progress to CLI over a 5-year period. Given the aging of the population in general, the global increase in metabolic syndrome, and the ongoing effect of diabetes and smoking, the prevalence of both PAD and CLI is predicted to increase.

Smoking, diabetes, advanced age, and chronic renal dysfunction have been characterized as independent factors associated with progression to CLI. Men are more likely to suffer from PAD than women. Men have been reported to have a higher prevalence of PAD in high-income countries, whereas women seem to have a higher prevalence of PAD in low- and middle-income countries (LMICs). As life expectancy increases, the burden of PAD seems likely to rise in LMICs.

In a meta-analysis from the United States, the prevalence of PAD in men ranged from 6.5% (aged 60-69 years) to 11.6% (aged 70-79 years) to 29.4% (>80 years). There were similar age-related increases in PAD prevalence in women (5.3%, 11.5%, and 24.7% in these age categories, respectively). Given that the life expectancy of women still exceeds that of men, the overall burden of PAD (total number of individuals affected) is likely to be greater in women than in men. The epidemiology of
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PAD is likely to be similar in other developed countries, such as the United Kingdom, and regions, such as the European Union. However, as these populations become more multicultural, differences in disease burden among communities within these nations seem likely to become apparent, further complicating the epidemiology of the condition.

Data on the epidemiology of PAD and in particular of CLI in other parts of the world are even more limited. In one Japanese community study of people over 40 years old, the prevalence of ABI <0.9 was very low (1.4%). In a population-based cohort of 4,055 Chinese men and women older than 60 years, the prevalence of PAD (ABI <0.9) was 2.9% and 2.8%, respectively. Another population-based cohort of 1,871 individuals younger than 65 years in two countries from Central Africa showed that the overall prevalence of PAD was 14.8%.

There is a considerable body of evidence showing that PAD is more common among black individuals than among whites. There is also evidence that Asians and Hispanics have a lower prevalence of PAD than whites. It is not clear whether these differences have a genetic basis or simply reflect differential exposure to traditional risk factors. However, disease risk profiles appear to change as populations migrate, a phenomenon that suggests the environment is more important than genetic makeup. Another explanation may be that ABI is intrinsically lower in black individuals, resulting in a falsely high prevalence of PAD.

There are far more international data on the epidemiology of intermittent claudication (IC) than of CLI. The annual incidence of IC in 60-year-old men has been shown to range from 0.2% in Iceland to 1.0% in Israel. A study using data from a large, insured U.S. population estimated the annual incidence of PAD, defined by the presence of a diagnosis or procedure insurance claim, to be 2.4% in a cohort of adults over 40 years old. Studies reporting on the epidemiology of PAD based on ABI rather than on the presence of symptomatic disease have suggested that the prevalence of asymptomatic PAD may be similar in men and women, although IC appears to be more prevalent in men. Differences in presentation between men and women with IC may influence the accuracy of prevalence estimates.

Risk factors for PAD/CLI

Modifiable risk factors for PAD have been comprehensively studied in high-income countries (HICs) and include smoking, DM, hypertension, hypercholesterolemia, and air pollution. A global study suggested that although these risk factors may be equally applicable to LMICs, for most, the strength of the association was greater in HICs. This outcome may be because HIC studies often include a larger number of older patients and because the exposure time tends to be shorter in LMICs.

Smoking is inarguably a significant risk factor in the development and progression of PAD. Notably, whereas smoking rates are falling in most HICs, this is not the case in LMICs. DM is also strongly associated with the development of PAD, and risk increases with the duration of DM in affected individuals. Patients with DM are widely recognized to be at markedly higher risk of amputation. The rapidly increasing worldwide prevalence of type 2 DM is concerning and likely to have a significant impact on the future incidence and prevalence of PAD and CLI as well as their morbid end points.

Hypertension is associated with the development of PAD as well as dyslipidemia responsible for the development and progression of atherosclerosis. Whereas elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) are widely accepted as risk factors for PAD, reduced high-density lipoprotein cholesterol (HDL-C) levels also appear to be associated with increased mortality in PAD patients. A ratio of the two may also be a useful predictor of PAD. Whereas hypertriglyceridemia appears to be atherogenic, its role in the development and progression of PAD remains incompletely defined.

Chronic kidney disease (CKD), particularly end-stage renal disease (ESRD), is a strong risk factor for PAD and limb loss, especially in association with DM. Affected patients frequently have heavily calcified arteries and a distal pattern of arterial disease.
Finally, people of lower socioeconomic status and educational attainment tend to have a higher prevalence of IC and probably also of CLI, although the association is not always strong and can often be explained in part by their increased exposure to other risk factors, such as smoking.\textsuperscript{15,18,30}

**Incidence and prevalence of CLI**

As already noted, high-quality data on the epidemiology of CLI are lacking, especially from LMICs, with many estimates being extrapolated from the incidence and prevalence of IC, amputation, and DM. Unfortunately, such estimates can be highly misleading for a number of reasons. First, IC does not progress to CLI in a predictable manner. Second, CLI probably represents <10\% of all PAD patients, and those undergoing amputation for CLI are at very high risk of premature death (and so more likely to be absent from population-based studies). Third, the clinical and hemodynamic data required to reliably diagnose CLI are difficult to obtain in large populations.

For many years, the annual incidence of what has typically been termed CLI was estimated at 500 to 1,000 new cases per million individuals in Western countries.\textsuperscript{31} Unfortunately, there are no reliable contemporary epidemiologic data that take into account recent changes in lifestyle (such as reduced smoking rates), identification and medical management of cardiovascular risk factors, prevalence of obesity and diabetes, and overall increasing life expectancy around the world. In 2013, a meta-analysis involving six studies and close to 83,000 patients showed the overall prevalence of severe chronic limb ischemia (defined by Fontaine stage, ankle pressure [AP] <70 mmHg, and ABI <0.60) to be 0.74\% (95\% confidence interval [CI], 0.26-1.46), with marked heterogeneity among studies (prevalence, 0.11-1.59\%).\textsuperscript{32}

**Clinical presentation**

The term “critical limb ischemia” (CLI) is outdated and fails to encompass the full spectrum of patients who are evaluated and treated for limb-threatening ischemia in modern practice. Instead, the new term CLTI has been proposed to include a broader and more heterogeneous group of patients with varying degrees of ischemia that can often delay wound healing and increase amputation risk. Two large guidelines have recently addressed this issue.\textsuperscript{33,34} A diagnosis of CLTI requires objectively documented atherosclerotic PAD in association with ischemic rest pain or tissue loss (ulceration or gangrene).

Ischemic rest pain is typically described as affecting the forefoot and is often made worse with recumbency while being relieved by dependency. It should be present for >2 weeks and be associated with one or more abnormal hemodynamic parameters. These parameters include an ABI <0.4 (using higher of the dorsalis pedis [DP] and posterior tibial [PT] arteries), absolute highest AP <50 mmHg, absolute toe pressure [TP] <30 mmHg, transcutaneous oxygen pressure (TcPO$_2$) <30 mmHg, and flat or minimally pulsatile pulse volume recording (PVR) waveforms (equivalent to Wound, Ischemia, foot Infection [WIFI] ischemia grade 3). Pressure measurements should be correlated with Doppler arterial waveforms, keeping in mind that AP and ABI are frequently falsely elevated because of medial calcinosis, especially in people with DM and ESRD. For this reason, a combination of tests may be needed. In patients with DM or ESRD, toe waveforms and systolic pressures are preferred. One study demonstrated that AP alone failed to identify 42\% of patients with CLTI. TP and TcPO$_2$ measurements were more accurate than AP and were also more predictive of 1-year amputation risk (TP <30 mmHg or TcPO$_2$ <10 mmHg).\textsuperscript{33}

Tissue loss related to CLTI includes gangrene of any part of the foot or nonhealing ulceration present for at least 2 weeks. It should be accompanied by objective evidence of significant PAD (e.g., WIFI ischemia grade $\geq$1). This definition excludes purely neuropathic, traumatic, or venous ulcers lacking any ischemic component. However, the WIFI scheme recognizes that a wide range of ischemic deficits may be limb threatening when it coexists
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with varying degrees of wound complexity and superimposed infection. CLTI is present if either ischemic rest pain or tissue loss with appropriate hemodynamics is present.

The WIfI classification is intuitive and has been made user-friendly by the availability of free online application software provided by the Society for Vascular Surgery (SVS) [SVS Interactive Practice Guidelines; https://itunes.apple.com/app/id1014644425]. Data accrued in nearly 3,000 patients to date have suggested that the four WIfI clinical stages of limb threat correlate with the risk of major limb amputation and time to wound healing. It has also been suggested that novel WIfI composite and mean scores may also predict other clinically significant events. The WIfI system appears to contain the key limb status elements needed to gauge the severity of limb threat at presentation.

References


Background

In the United States, data from recent literature have estimated an annual incidence of critical limb ischemia (CLI), in an overall peripheral artery disease (PAD) population, ranging from 0.26% to 0.48% and a prevalence of 1.28%. It has also been estimated that 5% to 10% of patients aged ≥50 years and suffering from PAD will eventually develop CLI within five years. First defined in 1982 by an expert consensus panel as a “patient cohort with a threatened limb [...] due to severe peripheral arterial disease,” CLI is characterized by rest/night pain and tissue loss (ulceration, gangrene) and associated with a high risk of major amputation, cardiovascular events, and death with a mortality rate of 20% within 6 months after the diagnosis and 50% at 5 years. The ideal outcome of revascularization in patients with CLI is complete relief from ischemic symptoms, healing of trophic disorders and ulcers, avoidance of amputation, improvement of limb function and quality of life, and, in the mid-term, a prolonged survival.

Clinical examination in addition to one or more instrumental tests are fundamental for CLI diagnosis. Correct management requires the identification of cardiovascular risk factors and an accurate evaluation of the aspect of the limb/foot. Features such as coolness, dry skin, muscle atrophy, hair loss, and dystrophic toenails are frequently observed in patients with PAD. Peripheral pulses (femoral, popliteal, dorsalis pedis, and posterior tibial artery) also have to be well examined even if their presence cannot exclude completely a potential condition of ischemia. In patients with critical limb ischemia, a careful diagnosis requires modern non-invasive vascular diagnostic techniques to provide adequate information for a medical or surgical approach. When required, further information will come from the use of more accurate imaging techniques, such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA), and selective use of lower extremity angiographic techniques.

Diagnostic methods

The objectives of modern non-invasive testing are: to confirm the presence of the disease, to provide reproducible physiological data concerning disease severity, to document the location and hemodynamic importance of vascular lesions, to define the correct strategy in case intervention is needed, or to reduce unnecessary invasive procedures in patients with adequate blood flow and not an ischemic foot ulcer.

Below is a brief summary of the main non-invasive (first-level examinations) and invasive (second level examination) testing.

Non-invasive examinations include:
1) ankle-brachial index (ABI);
2) toe-brachial index (TBI);
3) transcutaneous oxygen pressure (TcPO₂);
4) duplex ultrasonography (DUS).
Invasive examinations include:
5) CTA;
6) MRA;
7) digital subtraction angiography (DSA).

1) ABI
ABI is the first diagnostic step after clinical examination. First described by Winsor in 1950, this index is recommended as the first-line non-invasive hemodynamic test in all patients with suspected CLI. It can be considered as a prognostic marker for cardiovascular events and functional impairment. This index provides indirect information on arterial disease, but it cannot localize the anatomical level of arterial obstruction. The ABI represents the ratio of ankle to brachial systolic pressure and is recommended to be calculated by dividing the higher systolic pressure of the dorsalis pedis and tibialis posterior vessels at the ankle with the higher of the systolic pressures measured in the brachial artery in both arms. The normal range of ABI is quoted as 0.91-1.31, and an ABI ≤0.90 has 75% sensitivity and 86% specificity to diagnose lower extremity artery disease.

Sensitivity and specificity of ABI are lower in patients with diabetes mellitus (DM) or end-stage chronic renal disease (ESRD), ranging from 65% and 85% respectively, because of medial arterial calcification. In a recent study analyzing patients undergoing both ABI and angiography measurements, Chung et al. showed that the most significant factor affecting the validity of ABI was DM. Nevertheless, the American Diabetes Association recommends screening for ABI in all diabetic patients aged >50 years, as well as in younger insulin-dependent patients with other vascular risk, with the aim to reduce cardiovascular events. Although the ABI is a valid cardiovascular prognostic instrument, the test has known limitations and it should be associated with DUS.

2) TBI
The prevalence of DM and ESRD in CLI patients may preclude an accurate assessment of ABI, due to arterial stiffness. In this particular setting, toe systolic blood pressures are often more accurate in quantifying vascular disease because the digital vessels are usually spared from calcification. Toe systolic pressure can be expressed as a ratio of the toe pressure to the highest pressure recorded in either arm to obtain the TBI. The toe pressure is normally approximately 30 mmHg less than the ankle pressure and TBI should be >0.75. Values <0.7 are considered abnormal and TBI <0.25 is consistent with severe CLI.

3) TcPO$_2$
TcPO$_2$ is a non-invasive method evaluating the metabolic state of lower limbs with CLI and diabetic feet. This parameter is usually used to identify the chance of healing in diabetic patients with foot ulceration. It is not widely applicable and the overall accuracy may be limited because of the presence of inflammatory lesions, ulceration, or tissue loss.

4) DUS
DUS is a non-invasive, sensitive, and specific examination that allows clinicians to obtain several pieces of data about peripheral flow, even if the quality of this information is related to the operator’s experience and skills and the patient’s compliance and collaboration. It is the least expensive instrumental tool and the only modality that does not require contrast or radiation exposure, as required for CTA, MRA, and DSA. Davies et al. reported a sensitivity and specificity of 100% for duplex ultrasound arterial mapping (DUAM). DUS can provide information on the vessel wall, plaque morphology and echolucency, and luminal and turbulent flow, which can be difficult to assess by other imaging modalities. DUS is also important to address vein quality for bypass substitutes, and it is the first choice for routine follow-up after revascularization.

5) CTA
With the advantages in accuracy and acquisition times, CTA is nowadays characterized by high-resolution and contrast-enhanced images that allow a precise “roadmap” of the vascularization, essential for determining interventional
strategies (localization and severity of a lesion, upstream/downstream status). Beyond general limitations (radiation, nephrotoxicity, and allergies), the pitfalls are severe calcifications (impeding the appreciation of stenosis, mostly in distal arteries) and the lack of functional and hemodynamic data.

6) MRA
The current American College of Cardiology Foundation/American Heart Association Task Force (ACC/AHA) Task Force on Practice Guidelines give a strong recommendation for MRA to diagnose anatomical location and the presence of significant stenosis in patients with lower extremity PAD. In a meta-analysis, MRA also showed improved specificity and sensitivity over CTA and DUS. It provides multiple advantages compared with CTA: patients are not exposed to ionizing radiation and the risk of contrast-induced nephropathy (CIN) is minimized when gadolinium is used in recommended doses. However, it tends to overestimate the degree of stenosis. Indeed, it cannot visualize arterial calcifications but only residual lumen vessel, even in a high-grade stenosis lesion. This factor underestimates the difficulty of surgical and endovascular revascularization. Claustrophobia and the presence of metallic implants (such as pacemakers) or foreign bodies may preclude the examination or produce artefacts.

7) DSA
DSA is still considered the gold standard for diagnosis of PAD, especially for CLI patients. This technique should minimize the amount of iodinated contrast material and the dose of ionizing radiation used while maximizing imaging of the distal vasculature. Nevertheless, with the improvement of imaging techniques, DSA is less commonly performed today as a diagnostic exam by vascular surgeons given its invasive character and risk of complications. Many vascular specialists perform DSA as a diagnostic and therapeutic procedure at the same time with the aim to complete a vascular map of a CLI patient and better visualize below the knee vessels.

Prognosis
The TransAtlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) recommends revascularization as the optimal treatment for patients with CLI, but the type of revascularization remains unclear. The BASIL trial compared the outcomes of amputation-free survival and overall survival after angioplasty vs. surgery. Physician-centered outcomes, such as graft patency, limb salvage, and survival, were similar between surgery and endovascular arms at short-term follow-up, but there was a significant advantage in these outcomes at 2 years in the surgical arm.

The ACC/AHA Task Force on Practice Guidelines concluded that in patients with CLI and a life expectancy of >2 years, bypass surgery is a “reasonable” initial treatment. For those who do not have an autogenous vein conduit available, balloon angioplasty is recommended as a first approach. Nonetheless, about 20% of patients with CLI will undergo amputations and 25% will die after 1 year. The risk of amputation, unacceptably high, is strongly influenced by disease severity, the presence of comorbid conditions, and limb infection. Previous studies by Baser and Spreen have suggested that the probability of amputation is at least 50% higher in CLI patients with DM versus those without this comorbidity. Overall, it seems that major adverse events seen in patients with CLI did not notably differ between endovascular and open bypass. In fact, perioperative mortality (1-7%) rates were similar across treatment types and lesion locations. Major adverse cardiovascular event (1-7%) and major amputation (0-7%) rates were likewise similar between endovascular interventions and vein bypass surgery. Early amputation rates for non-autogenous bypass grafting are higher than for great saphenous vein bypass.

Torbjörnsson et al. conducted a study on patients with CLI who had undergone revascularization; the authors focused on risk factors related to amputation. They found, using Cox regression analysis, eight factors associated with shorter limb salvage: older age, cardiac disease, DM, stroke, renal impairment,