Critical limb ischemia is a manifestation of peripheral arterial disease that severely restricts limb perfusion resulting in a mismatch between metabolic tissue demands and oxygen delivery. By definition, CLI is associated with the clinical constellation of chronic ischemic rest pain or ulceration in conjunction with hemodynamic evidence of reduced tissue perfusion (abnormal ankle pressure or great toe pressures or transcutaneous oxygen pressure) (3,4). It is noteworthy, although not surprising, that many physicians are unfamiliar with the concept of CLI, since medical training programs place little emphasis on the diagnosis and treatment of vascular disease. For example, neither Harrison’s, nor Cecil’s textbooks of medicine have a single index entry for CLI (5,6). A title search for CLI in articles published in the Journal reveals a single citation (7). Based on CLI’s literary representation, one might assume that CLI is of little importance in the day-to-day practice of cardiologists or primary care physicians.

Critical limb ischemia is a silent plague whose enormity is underappreciated even by those who routinely treat it. Few realize that the number of CLI cases exceeds the number of new colorectal or breast cancer cases in the U.S. (3,8). The estimated incidence of new CLI cases in Western countries is between 500 to 1,000/million population/year, which translates into 150,000 to 300,000 cases annually in the U.S. The first year mortality and morbidity of CLI exceeds most malignancies with a death rate of 25% and amputation rate of 30% (3). Within 3 years, 60% of CLI patients will have died (3). It is surprising that despite modern medical management (or the absence thereof), amputations for vascular disease continue to increase (9).

So why should cardiologists worry about CLI? The reason is that most of these patients die from unrecognized and undertreated cardiovascular causes (3). This is not unexpected since CLI and coronary artery disease, carotid, and renal vascular diseases share similar risk factors and pathophysiology. Yet for some inexplicable reason, most physicians are indifferent when it comes to aggressively treating risk factors in patients with vascular disease. For instance, in the contemporary BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial (a randomized trial of percutaneous transluminal angioplasty vs. bypass surgery for CLI), only one-third of the patients received lipid-lowering agents and barely 50% were on any antplatelets (10).

With these issues in mind, I read the study of Guzman et al. (1) with anticipation. The authors measured TAC from knee to ankle using the well-established Agatston CAC scoring algorithm. The TAC scores were calculated for normal control subjects, patients with claudication, and CLI. The latter 2 groups were culled from their vascular surgery clinic. Receiver-operating characteristic analysis yielded a TAC cutoff value ≥400 that resulted in a sensitivity of 94%, specificity of 47%, and negative predictive value of 98% for amputations. Multivariate analysis demonstrated that TAC >400 was the strongest predictor of amputation when compared with either ankle-brachial index or traditional coronary risk factors. Furthermore, no patients with TAC <400 underwent amputation, whereas 1 of 5 with TAC >400 were amputated. The authors conclude that TAC by multidetector computed tomography “may be a useful measure to stratify patients into risk categories and guide therapy aimed at limb preservation” (1).

Despite 20 years of investigation, the clinical utility of CAC remains controversial (11,12). Most studies of CAC either address risk stratification in the asymptomatic patient or triage of the symptomatic patient (i.e., chest pain) who might benefit from coronary angiography. A recent study in asymptomatic subjects has convincingly demonstrated that the higher the CAC score the more strongly it was an independent predictor of all-cause mortality (13). Unfortunately, few studies of CAC are directly analogous to the present one. However, if we extrapolate and consider claudication to be equivalent to stable angina, CLI (rest pain or ulceration) to be equivalent to unstable angina/myocardial infarction, and death comparable to amputation, then this study can reconcile the results
that show that the rate of amputation may be a function of the number and extent of diseased tibial vessels.

As the authors note, there is no reliable test for predicting the risk of amputation in CLI. The question then becomes whether TAC can be used to fill this void. Although the data convincingly demonstrate the relationship between a TAC ≥400 and amputation, the interpretation is less persuasive regarding its clinical utility. In this study, the mere presence of CLI conferred a 1 in 3 risk of major amputation, whereas a TAC cutoff of ≥400 predicted amputation in 1 in 2 patients. However, it is not apparent that this additional knowledge would translate into a clinically meaningful dividend because the converse is also true: one-half of the patients with TAC >400 did not undergo amputations. Since the relationship between TAC >400 and amputation was not linear, does this method help us assess the relative risk for an individual patient? Clearly, until proven otherwise, all patients with CLI should be considered to be at risk for amputation regardless of the TAC score. Despite this limitation, TAC may prove to be a useful tool for future investigations. The impressive negative predictive value of TAC, especially among claudicants, may permit identification of those patients at low risk for subsequent amputation, because virtually no patients were amputated when the TAC was ≤400. Additionally, serial measurement of TAC may prove to be a robust epidemiologic tool when investigating the natural history of claudication and CLI.

As demonstrated by this study, a 33% major 1-year amputation rate in the 21st millennium is distressing. The delayed medical awareness and subsequent poor clinical outcomes clearly underscore the need for a reappraisal of our educational, diagnostic, and therapeutic approach to CLI. The most effective first step is to have patients at risk for CLI screened for CLI. The question then becomes whether TAC can be used to fill this void. Although the data convincingly demonstrate the relationship between a TAC ≥400 and amputation, the interpretation is less persuasive regarding its clinical utility. In this study, the mere presence of CLI conferred a 1 in 3 risk of major amputation, whereas a TAC cutoff of ≥400 predicted amputation in 1 in 2 patients. However, it is not apparent that this additional knowledge would translate into a clinically meaningful dividend because the converse is also true: one-half of the patients with TAC >400 did not undergo amputations. Since the relationship between TAC >400 and amputation was not linear, does this method help us assess the relative risk for an individual patient? Clearly, until proven otherwise, all patients with CLI should be considered to be at risk for amputation regardless of the TAC score. Despite this limitation, TAC may prove to be a useful tool for future investigations. The impressive negative predictive value of TAC, especially among claudicants, may permit identification of those patients at low risk for subsequent amputation, because virtually no patients were amputated when the TAC was ≤400. Additionally, serial measurement of TAC may prove to be a robust epidemiologic tool when investigating the natural history of claudication and CLI.

As demonstrated by this study, a 33% major 1-year amputation rate in the 21st millennium is distressing. The delayed medical awareness and subsequent poor clinical outcomes clearly underscore the need for a reappraisal of our educational, diagnostic, and therapeutic approach to CLI. The most effective first step is to have patients at risk (those with coronary risk factors) remove their shoes and socks once a year when they come to the office. As Yogi Berra said, “you can observe a lot by watching” (14). Additionally, the traditional, surgically driven “conservative” algorithms for treating CLI have been successful in conserving neither the limb nor the patient. Emerging evidence suggests that CLI should be approached in the same manner as patients with unstable coronary syndrome (i.e., early angiographic evaluation and aggressive endovascular intervention). Recently, a number of smaller studies have suggested that this approach may yield limb salvage rates in excess of 90% (15–17). Furthermore, emerging data suggest that aggressive modification with lipid lowering and antiplatelet agents yields significant clinical dividends (18,19).

Albert Einstein noted that “not everything that counts can be counted, and not everything that can be counted counts” (20). Is TAC worth counting? It is far too early to tell. However, as with all compelling studies, this one raises more questions than it answers and illuminates an area of clinical confusion and frustration. I am encouraged by the authors’ fresh approach and eagerly look forward to further application of their methodology.

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