Chronic critical limb ischemia (CLI) is the leading cause of nontraumatic major amputations on a worldwide basis. CLI is one of the most severe manifestations of obstructive peripheral arterial disease. Patients presenting with CLI often have comorbid conditions associated with high mortality rates. Its definition is typically clinical as patients presenting with true ischemic rest pain, nonhealing ischemic ulcers, or gangrene. It is much more prevalent in patients with diabetes and the elderly. Critical limb ischemia is emerging as a critical issue in world health as people are living longer and diabetes is epidemic. Great strides have been made in the interventional and surgical therapy of CLI with reported limb salvage rates of >90%. Despite these reports there remains great debate about how these patients should be treated. Many patients are still referred straight to major amputation without having vascular consultation or noninvasive imaging. Arguments about whether there should be an “intervention first” vs “direct surgical revascularization first” approach persist.

Major amputation is associated with significant mortality and morbidity risk as well as substantially increased medical cost as compared with limb salvage. Amputation at an inappropriate level may lead to need for additional amputations or may unduly impact morbidity if too aggressive.

In the past few years there have been many advancements in the definition, diagnosis, and treatment of CLI. In this editorial I will highlight those that I have regarded as monumental.

DEFINITION

We cannot achieve ideal therapeutic consensus unless we are comparing treatment strategies in patients with truly matched disease. Rest pain is not equivalent to advanced gangrene with concomitant infection, yet historical studies include both as CLI. Mills created the Wound, Ischemia, and foot Infection (WIIfI) system of wound assessment to help stratify these patients more precisely. This classification should be incorporated into clinical studies to allow better outcome evaluation with different treatment strategies. This could lead to a more scientific treatment decision process. True ischemic rest pain must be clearly distinguished from neuropathic pain.

Another concept that is becoming more widely accepted is the “angiosome” concept in helping to guide therapies in CLI. Angiosomes are 3-dimensional blocks of tissue supplied with blood predominately by certain arteries. In CLI collateral arterial perfusion may be inadequate, therefore direct perfusion of the angiosome-related vessel by surgery or intervention may be paramount.
DIAGNOSTIC ASSESSMENT

A basic clinical history and thorough physical exam with baseline clinical laboratories is crucial in all patients presenting with CLI. The clinician needs to globally assess these patients first, then concentrate on the legs.

Use of noninvasive diagnostics such as ABI and vascular ultrasound are well-established. Measurements of skin perfusion pressure (SPP) and transcutaneous $O_2$ (TCOM) are being used more widely to more precisely assess adequacy of tissue perfusion and likelihood of treatment success or need for additional therapy.

Great strides have been made in computerized tomographic angiography (CTA), magnetic resonance angiography (MRA), and diagnostic angiography in evaluating anatomy and guiding therapy. The greatest limitation of CTA and diagnostic angiography in the past was the necessity for iodinated contrast, which brought inherent risks of contrast-induced nephropathy (CIN) and allergic response. Dystrophic calcification often precludes accurate assessment by CTA and MRA. More widespread acceptance and utilization of CO$_2$ (related to more user friendly and sterile devices) as a contrast agent as described by Caridi et al would allow more thorough angiographic assessment utilizing small catheters with no risk of allergic response or CIN.$^{11}$

CO$_2$ angiography and external duplex arterial ultrasound are being used more commonly as imaging modalities during interventional therapies. These modalities have expanded diagnostic and revascularization treatment options in CLI patients.

ACCESS

Access is a crucial part of any interventional procedure. Access affects risk of bleeding, ability to reach a lesion, ability to cross a lesion, the size of device that can be delivered, and the risk of vascular complications. Access complications can adversely affect outcomes. There has been more widespread use of radial artery access in subclavian, mesenteric, and renal artery interventions to lessen the risk of bleeding complications, but currently available devices do not allow interventionists to treat most cases of CLI via this approach. More widespread use of pedal$^{12,13}$ and even digital artery access$^{14}$ is resulting in successful intervention when crossing can’t be achieved in an antegrade manner. Pedal access is associated with less bleeding and may allow earlier ambulation. The “pedal loop” technique as described by Graziano et al allows treatment of patients with below-the-ankle disease.$^{15}$ In this technique, a guidewire is passed either from the dorsal to plantar arch or vice versa, then the entire segment is treated with percutaneous transluminal angioplasty to establish outflow.

INTERVENTIONAL TREATMENTS

CLI may be caused by multilevel disease or may be the result of only infrapopliteal (IP) disease. Usually the IP disease is diffuse and long total occlusions common. Better guidewires, dedicated crossing tools, and re-entry tools are emerging as useful interventional tools to cross lesions.

The YUKON, DESTINY, and ACHILLES trials (utilizing “olimus” drugs on balloon-expandable stent platforms) have all shown encouraging patency results in short proximal IP lesions, but no major improvement in limb salvage.$^{16-18}$ Several single-center trials had shown patency benefit (of IP vessels) with drug-eluting balloons$^{19}$ (DEB) in long segment IP disease, but the premature cessation of the IN.PACT DEEP DEB trial secondary to safety and lack of efficacy have dampened initial clinical enthusiasm. Ongoing IP drug-eluting balloon clinical trials may provide additional answers.$^{20}$

Use of both drug-eluting balloons above the knee and
drug-eluting stents (DES) above the knee has shown patency benefit\textsuperscript{21-23} and is likely to be helpful in CLI patients with multilevel disease. Drug-eluting stents such as Zilver PTX (Cook Medical) and drug-eluting balloons such as Lutonix (Bard) have received FDA approval for above-the-knee applications and are currently being utilized by clinicians.

Atherectomy has had two clinical trials suggesting benefit. The randomized controlled EXCITE trial\textsuperscript{24} utilizing laser atherectomy to treat diffuse SFA in-stent restenosis showed a safety and efficacy benefit in the therapy of diffuse SFA in-stent restenosis and occlusion vs percutaneous transliminal angioplasty. The DEFINITIVE LE\textsuperscript{25} trial utilizing TurboHawk (Covidien) is the largest atherectomy registry to date. It showed similar outcomes in diabetic and nondiabetic patients and demonstrated excellent safety and efficacy profile in a wide spectrum of atherosclerotic peripheral artery disease.

**SUMMARY**

Most patients presenting with CLI have options other than major amputation as first-line approach. Angiography and intervention can be safely attempted in the overwhelming majority of patients with less risk and cost than direct amputation. The use of ultrasound guidance and CO\textsubscript{2} angiographic imaging allow evaluation and therapy even in patients with profound renal dysfunction and severe iodinated contrast allergy. Even patients with no obvious outflow vessels can have successful intervention with techniques such as “pedal loop” which create outflow. It is imperative that interventional therapy not preclude further surgical options and that surgical options not preclude subsequent interventional therapy which may be required later as this is progressive disease. Restoration of arterial blood supply is crucial, but is only part of required therapy. A more standardized approach to treating patients with CLI is needed. Successful therapy requires better prevention and earlier diagnosis, restoration of blood flow, wound healing (multifactorial), medical therapy including antiplatelet therapies and lipid-lowering drugs, mechanical unloading, lifestyle modifications, and long-term preventive therapies. If we are to achieve a more standardized approach we need randomized clinical trials, more precise definitions including arterial disease patterns, concomitant infection, and degree of tissue damage. We need continued training to ensure that assessed outcomes are indicative of treatment effectiveness and not tainted by operator inexperience. We need better understanding of what percentage of patients are surgical candidates as estimates vary widely. We need to assess cost of therapies, long-term effectiveness, morbidity, and rates of limb salvage. We need better screening, prevention, and technology breakthroughs to improve overall outcomes. We must follow these patients closely as there is a high associated cardiovascular mortality risk with dramatically shortened life expectancy.

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