JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 68, NO. 18, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER http://dx.doi.org/10.1016/j.jacc.2016.04.071

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Critical Limb Ischemia

An Expert Statement

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ABSTRACT

Critical limb ischemia (CLI), the most advanced form of peripheral artery disease, is associated with significant morbidity, mortality, and health care resource utilization. It is also associated with physical, as well as psychosocial, consequences such as amputation and depression. Importantly, after a major amputation, patients are at heightened risk of amputation on the contralateral leg. However, despite the technological advances to manage CLI with minimally invasive technologies, this condition often remains untreated, with significant disparities in revascularization and amputation rates according to race, socioeconomic status, and geographic region. Care remains disparate across medical specialties in this rapidly evolving field. Many challenges persist, including appropriate reimbursement for treating complex patients with difficult anatomy. This paper provides a comprehensive summary that includes diagnostic assessment and analysis, endovascular versus open surgical treatment, regenerative and adjunctive therapies, and other important aspects of CLI. (J Am Coll Cardiol 2016;68:2002–15) © 2016 by the American College of Cardiology Foundation.

Clinically, critical limb ischemia (CLI) is defined as ischemic rest pain, tissue loss, or gangrene in the presence of peripheral artery disease (PAD) and hypoperfusion of the lower extremity (1). Approximately 1% to 3% of patients with PAD may present with CLI; however, with increasing life expectancy and the prevalence of diabetes, obesity, and sedentary lifestyles, these estimates are likely to increase (2,3). CLI is associated with significant mortality, morbidity, and increased utilization of health care resources (4–7). These patients are restricted in physical function and may experience

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Manuscript received April 5, 2016; accepted April 17, 2016.

depression (8). Despite the heightened morbidity and mortality, and extensive evidence for revascularization, a significant portion of patients undergoing major amputation do not have a vascular evaluation in the year before their amputation (9), and many patients with CLI experience prolonged wait times before any intervention (10). Furthermore, there are also significant geographic, racial, and socioeconomic disparities in revascularization and amputation rates among patients with CLI (11–15).

CLASSIFICATION

The Rutherford categorization has classically defined CLI as rest pain (class IV), tissue loss (class V), and/or gangrene (class VI) (16). Alternatively, the Fontaine classification labels rest pain as class III and tissue loss or gangrene as class IV (17). Neither of these classifications incorporates wound size, perfusion assessment, or infection (18). Recently, the Society for Vascular Surgery Lower Extremity Guidelines Committee has developed the Threatened Limb Classification System: risk stratification based on wound, ischemia, foot infection (WIfI). This system recognizes the multifactorial nature of the threatened limb by accounting for wound size and location, concomitant infection, and the degree of ischemia. The WIfI classification is intended to provide a more meaningful analysis of outcomes in these high-risk patients. A number of other wound classification systems are available, including the perfusion, extent/size, depth/tissue loss, infection, sensation system (19), the University of Texas system (20), and variants of the sepsis, arteriopathy, denervation (21), and St. Elian (22) systems. Most of these classification schemes lack perfusion assessment and were originally designed to classify tissue loss, not gangrene. Although the WIfI classification is a step forward, the hemodynamic cutpoints are likely inaccurate in light of recent publications highlighting the limitation of the ankle-brachial index (ABI) and toe pressure in accurately diagnosing CLI (23,24). Continued research on a personalized classification system would provide a basis for development of an optimal revascularization strategy in clinical practice (25).

PATHOPHYSIOLOGY

Despite the high prevalence of untreated PAD, only a small proportion of these patients present with CLI. Rest pain is typically associated with multilevel disease, including both inflow (iliac, common femoral, or superficial femoral arteries) and outflow (tibial arteries) disease. However, ischemic pain is potentially relieved after revascularization of inflow disease alone (26,27). Patients with tissue loss and gangrene typically require a more complete revascularization by re-establishing direct flow to the wound.

The etiology of ulcer formation is frequently multifactorial and may relate to pressure, trauma, venous insufficiency, congestive heart failure, or poor hygiene (28). Patients with diabetes frequently develop neuropathy with motor and sensory changes of the foot, leading to poor biomechanics, limited joint mobility, and bony deformity (Charcot's foot) (29). These changes can result in ulcer formation. Therefore, the etiology of the ulcer should be identified and addressed to facilitate healing and minimize recurrence.

Once the etiology of the ulcers has been identified, the presence of arterial insufficiency needs to be assessed. Under normal intact conditions, minimal skin perfusion is necessary to maintain adequate nutrition. However, an increased level of blood supply is usually required when skin ulcers are present to successfully complete the healing process (30). Inadequate blood supply can lead to cell death, endothelial dysfunction, inflammation, and an inability to provide proper local immunologic response to infection. Autonomic dysregulation, altered blood viscosity, and decreased erythrocyte fluidity occur (29,31). This vicious cycle is further perpetuated by local edema and other factors, such as diabetes and smoking.

CLI TEAM

CLI is a complex disease process that requires a multidisciplinary team approach. This approach fosters a broader understanding of the disease with a more comprehensive use of medical, endovascular, and surgical options, and it favors collaboration over competition (**Figure 1**). Physicians possess varying degrees of skills and experience, but the goal of the team approach is to provide advanced therapies specifically for wound care and revascularization. A team approach also includes wound nurses, home health, and other resources to enhance care. When advanced therapies are not available, referral to a center of excellence may then be appropriate. However, public reporting for lower extremity vascular procedures are not currently available, nor are there any guidelines to define operator or institutional experience related to CLI.

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

AFS = amputation-free survival

BMS = bare-metal stent

CLI = critical limb ischemia

CMS = Centers for Medicare & Medicaid Services

CTA = computed tomography angiography

DCB = drug-coated balloon

DES = drug-eluting stent

MALE = major adverse limb events

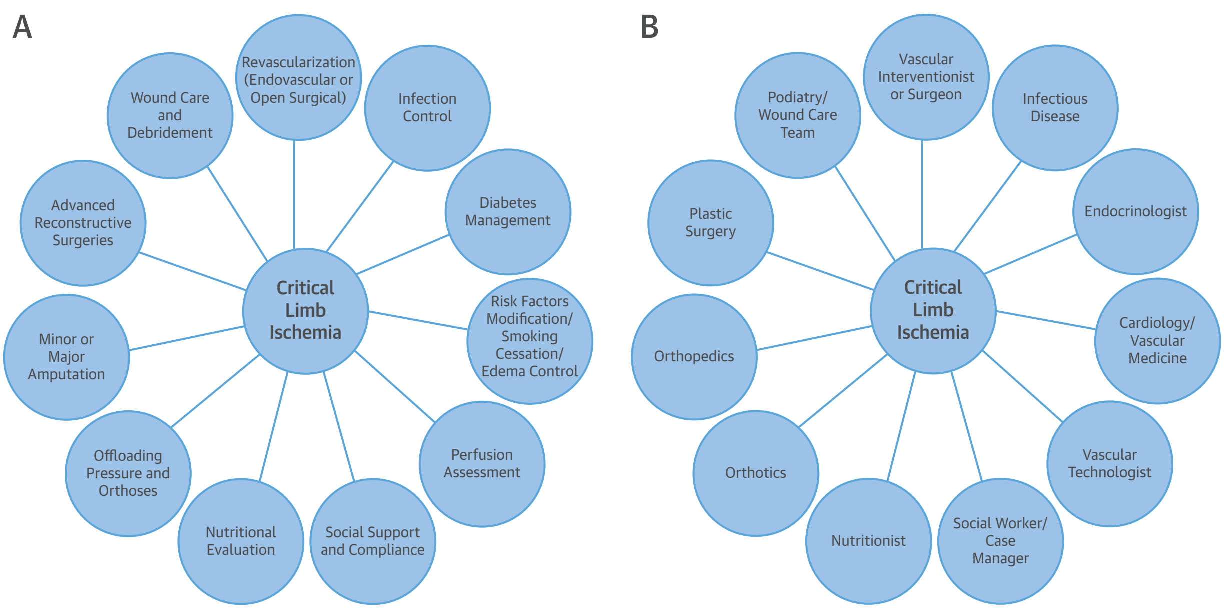
MRA = magnetic resonance angiography

PAD = peripheral artery disease

RCT = randomized controlled trial

WIfI = risk stratification based on wound, ischemia, and foot infection

FIGURE 1 Potential Components and Required Specialists for the Diagnosis and Treatment of Critical Limb Ischemia



(A) Potential components of critical limb ischemia diagnosis, management, and follow-up, and **(B)** the multidisciplinary team of experts that may be required to address these factors.

DIAGNOSIS

Hemodynamic measurements, such as ABI, ankle pressure, and toe pressure, support the clinical diagnosis of CLI. Other measurements to assess skin perfusion include transcutaneous oxygen saturation, skin perfusion pressure, and infrared oximetry. Hemodynamic assessment in CLI remains a challenge (Table 1). The ABI is reported as the higher of the posterior or anterior tibial arteries compared with the higher brachial pressure, regardless of wound location. It can be falsely elevated in patients with medial calcinosis of the tibial arteries and only provides perfusion assessment to the ankle. Approximately 30% of patients with CLI have a near-normal or normal ABI (>0.90) (24,32,33). Toe pressure may have better correlation with infrageniculate arterial patency and Rutherford class because the digital arteries are often compressible. Because none of the hemodynamic tools described in Table 1 are 100% sensitive and specific, inadequate wound healing despite appropriate care should prompt further investigation.

Anatomic assessment by using duplex ultrasound, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) are routinely used in clinical practice to detect PAD and to identify the location and degree of arterial obstruction in the lower extremities (34,35). In most centers, Doppler ultrasound is readily available; however, in patients who are obese, this test can be technically difficult and rarely provides a full assessment of tibial and/or pedal artery patency due to calcific shadowing (36). Formal training of technologists in the performance of tibial artery duplex ultrasonography is critical to improving the diagnostic accuracy.

CTA has been evaluated in patients with PAD and can provide valuable information about aortoiliac and femoropopliteal disease (37). Its utility is reduced in smaller, heavily calcified tibial and pedal arteries (38). CTA requires exposure to ionizing radiation and iodinated contrast medium. MRA does not require radiation but is technically more labor-intensive and, on rare occasions, can also be affected by calcific shadowing, specifically in the tibial arteries (39). Furthermore, many patients with CLI have underlying chronic kidney disease, which may limit contrast-enhanced MRA due to concerns about nephrogenic systemic fibrosis. The choice of Doppler ultrasound, CTA, or MRA will likely depend on local expertise, availability, and cost, and their use should be tailored to each individual patient's needs.

A number of other cutting-edge technologies, including contrast-enhanced magnetic resonance imaging (40,41), indocyanine green angiography (42),

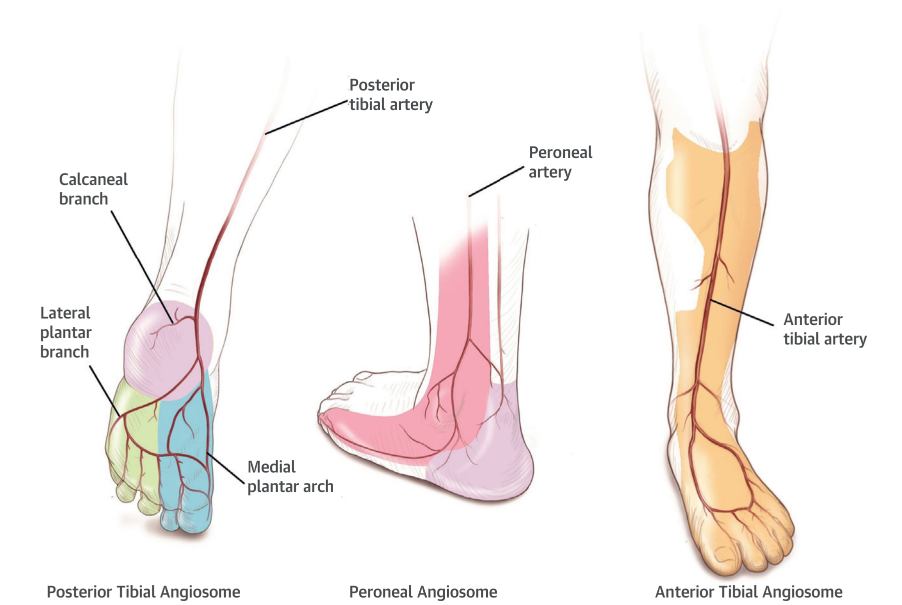
TABLE 1 Overview of the Diagnostic Tools Available in CLI

	Indications/Advantages	Disadvantages
ABI or ankle pressure	■ Helps establish a diagnosis and a baseline perfusion ■ Can be used to monitor efficacy of revascularization ■ Generally easy to perform	■ Can be falsely elevated in noncompressible vessels (advanced age, diabetes, and kidney disease) ■ Does not localize disease ■ May be normal or near-normal with isolated infrapopliteal disease
Toe-brachial index or toe pressure	■ Useful in noncompressible vessels in which ABI can be nondiagnostic ■ Generally easy to perform	■ Does not localize disease
Leg segmental pressure	■ Helps indirectly localize disease ■ Can be used to monitor efficacy of revascularization ■ Generally easy to perform	■ Can be falsely nondiagnostic in noncompressible vessels
Plethysmography/pulse volume recording	■ Can help establish a diagnosis ■ Can be used to monitor efficacy of revascularization ■ Useful in noncompressible vessels ■ May indirectly localize disease	■ Might be abnormal in low cardiac stroke volume ■ Not reliable in inflow disease ■ Not angiosome-specific
Continuous-wave Doppler ultrasound	■ Useful in noncompressible vessels ■ Generally easy to perform	■ Limited sensitivity for proximal disease ■ Limited in infrapopliteal disease ■ Limited in localizing the disease ■ Limited by patient's body habitus
Duplex ultrasound	■ Accurate visual assessment of disease and its location ■ Hemodynamic assessment of degree of stenosis ■ Used for routine surveillance after bypass ■ Readily available	■ Highly dependent on operator skills ■ Limited in evaluation of iliac vessels (due to bowel gas and/or obesity) and distal small vessels, especially if heavily calcified ■ Not well established to assess long-term patency of angioplasty
CTA	■ Provides visual assessment of the disease (stenosis/plaque) and allows the walls of large vessels to be evaluated ■ May help interventional planning ■ Three-dimensional imaging ■ Provide better resolution than MRA	■ Iodinated contrast (nephrotoxic) and radiation exposures ■ Lack of adequate evaluation in the presence of dense calcification or metallic stents ■ Not very useful for infrapopliteal and pedal arch assessment
MRA	■ Provides visual assessment of the disease (stenosis/plaque) and allows evaluation of the walls of small and large vessels ■ Helps interventional planning ■ Three-dimensional imaging ■ Unlike CTA, no radiation or iodinated contrast medium exposure ■ Unlike CTA and duplex ultrasound, calcifications do not cause artifacts	■ Gadolinium exposure; contraindicated if GFR <30 ml/min/1.73 m^2 ■ Contraindicated in the presence of metallic materials that are not compatible with MRA ■ Limited evaluation in the presence of certain stents; fair evaluation with alloy ones ■ Might be limited in the assessment of below-the-knee vessels due to venous artifact. However, time-resolved MRA addresses this limitation ■ Might require sedation if claustrophobia or agitation exists
Digital-subtraction angiography	■ Gold standard ■ Real-time temporal information augments hemodynamic assessment	■ Invasive with risks ■ Radiation and contrast medium exposure ■ Two-dimensional imaging
$TcPO_2$	■ Assesses microcirculation (regional perfusion) and helps confirm the diagnosis of CLI ■ Can predict wound healing ■ May be useful for monitoring efficacy of revascularization	■ Limited accuracy in the presence of edema, skin thickness, or infection. ■ Can be falsely normal ■ Requires skin heating to ≥40°C ■ Time-consuming
SPP	■ Assesses microcirculation, severity of ischemia, and wound healing potential ■ Can be useful in monitoring efficacy of revascularization ■ Can be measured in shorter time compared with $TcPO_2$	■ Might be insensitive to mild degrees of ischemia ■ Probe size and shape may affect measurements ■ Can be painful
Indocyanine green	■ May help assess microcirculation ■ Limited available data for CLI	■ Invasive ■ Not safe in patients with kidney disease ■ Time-consuming

ABI = ankle-brachial index; CLI = critical limb ischemia; CTA = computed tomography angiography; GFR = glomerular filtration rate; MRA = magnetic resonance angiography; SPP = skin perfusion pressure; $TcPO_2$ = transcutaneous oxygen pressure.

single-photon emission computed tomography imaging (43), and vascular optical tomographic imaging (44), are currently under investigation but may have limited availability. The ideal perfusion assessment technology for detection of limb ischemia and wound healing should be easy to use, reliably reproducible, provide capillary and angiosome perfusion assessment, and be cost-effective.

FIGURE 2 Six Angiosomes of the Below-the-Knee Lower Extremity



The below-the-knee skin and tissue are supplied by 3 main arteries and 6 angiosomes. The anterior tibial artery supplies the anterior shin and dorsum of the foot, the posterior tibial artery supplies the medial heel and the medial and lateral plantar angiosomes, and the peroneal artery supplies the lateral aspect of the heel and the lateral border of the foot.

THE ANGIOSOME CONCEPT

In 1987, Taylor and Palmer (45) described the angiosome concept by delineating the human body into 3-dimensional blocks of tissue fed by specific arterial and venous sources, named angiosomes. Angiosomes are connected by collateral vessels or choke vessels that are able to supply indirect flow to a vascular territory in the absence of direct flow. The infrapopliteal territory is supplied by 3 main arteries: the anterior tibial, posterior tibial, and the peroneal. Collectively, these 3 vessels supply 6 angiosomes (Figure 2). A meta-analysis found a 60% relative risk reduction of major amputation with an angiosome-direct revascularization compared with an angiosome-indirect revascularization, regardless of mode of revascularization (46). This approach, when feasible, may also allow faster healing by providing direct flow to the ulcer (25).

MEDICAL THERAPY

Although revascularization is the primary therapy for CLI, medical therapy serves as an essential therapeutic adjunct. The primary goal of medical therapy is to prevent myocardial infarction, stroke, and death, but it further helps to accelerate wound healing, prevent amputation, and improve quality of life. Because all patients with CLI by definition have PAD, aggressive risk factor modification is an important first step. This approach should include complete smoking cessation, high-dose statin, antiplatelet, and antihypertensive therapy to reduce major adverse cardiovascular events (27,47,48). Despite the high rates of associated morbidity and mortality, patients with CLI continue to be undertreated with guideline-recommended therapies (49). The role of medical therapy to improve limb outcomes, quality of life, and patency and to reduce reintervention and recurrent CLI is less clear (50). Retrospective studies have shown a reduction in repeat revascularization and amputation rates among patients with CLI who were treated with guideline-recommended therapies (51). Cilostazol has also been shown to significantly reduce restenosis rates in patients undergoing lower extremity endovascular therapy, but this approach has not gained widespread acceptance in the current societal guidelines (52).

REVASCULARIZATION

Revascularization is the cornerstone of therapy for CLI and has a Class I recommendation by all professional guidelines (27,53). Without revascularization,

TABLE 2 RCTs Comparing Open Surgical With Endovascular Revascularization for CLI

	BASIL (65)	BASIL II	BEST-CLI (117)
Population	■ Rutherford classes IV, V, and VI due to infrainguinal disease	■ Rutherford classes IV, V, and VI due to infrainguinal disease	■ Rutherford classes IV, V, and VI due to infrainguinal disease
No. of patients	■ 452 patients	■ Aims to recruit 600 patients	■ Aims for 2,100 patients
Follow-up	■ Mean of 3.1 yrs	■ Aims for a mean over 3 yrs	■ From 2 to 4.2 yrs
Design	■ Bypass surgery or balloon angioplasty	■ Saphenous vein bypass or any endovascular procedure	■ Saphenous vein bypass vs. endovascular procedure, also smaller subset with PTFE
Primary endpoints	■ Time to major (above the ankle) limb amputation or death from any cause	■ Time to major (above the ankle) limb amputation or death from any cause	■ MALE (amputation above the ankle or major reintervention) or death from any cause
Results	■ No significant difference in short- or long-term between 2 approaches	■ Not yet available	■ Not yet available
Possible limitations	■ Selection bias with significant exclusions ■ Angioplasty only ■ Possibly underpowered ■ Hemodynamic parameters not included ■ Synthetic bypass included ■ One-third of the patients were not included on antiplatelet agents and two-thirds were not on statin therapy ■ Level of operator experience unknown	■ Hemodynamic parameters not included ■ Heterogeneity of endovascular options ■ Operator experience unknown	■ Broad heterogeneity of allowed endovascular revascularization options; defining the "best treatment" is left to each interventionist's discretion ■ Operator experience ■ No core laboratory adjudication for angiographic data

BEST-CLI = Best Endovascular Versus Best Surgical Therapy in Patients With Critical Limb Ischemia; BASIL = Bypass Versus Angioplasty in Severe Ischemia of the Leg; CLI = critical limb ischemia; MALE = major adverse limb events; PTFE = polytetrafluoroethylene; RCTs = randomized controlled trials.

up to 40% of patients with CLI will require lower limb amputation by 1 year (9). Furthermore, after an index amputation, a significant number of patients will require contralateral amputation (5.7% and 11.5% at 1 and 5 years, respectively), have recurrent ulcers on the ipsilateral leg, or die (9,54). Every attempt should be made to offer the most efficacious, timely, safe, and cost-effective form of revascularization to patients with CLI (11).

Revascularization options for patients with CLI include endovascular, surgical, or the combination of both (hybrid procedure). One randomized controlled trial (RCT), BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg), compared surgery versus balloon angioplasty among 452 patients with CLI (6). After 5 years of follow-up, both therapies had similar rates of amputation-free survival and mortality. Most recently, a review by the Agency for Healthcare Research and Quality that included the BASIL trial, in addition to 19 other observational studies, found no differences in all-cause mortality, amputation, and amputation-free survival between the 2 revascularization strategies (55). Data from the Nationwide Inpatient Sample have demonstrated a marked rise in endovascular revascularization in the last decade, which has been temporally associated with reduced rates of major amputation (56). However, the rates of CLI admissions have remained constant, despite advances in medical therapy (57). Indeed, in >650,000 patients, endovascular therapy for CLI was associated with lower mortality, lower health care costs, and shorter hospital length of stay. Given the morbidity and mortality associated with surgical revascularization, and the significant technological advances in endovascular intervention for CLI, some practitioners have adopted an "endovascular first" approach (58).

Uncertainty remains about the specific role of open surgery versus endovascular therapy. This therapeutic equipoise serves as the basis for the BEST-CLI (Best Endovascular versus Surgical Therapy in Patients With Critical Limb Ischemia) study, a prospective, multicenter, randomized trial comparing "best endovascular" versus "best surgical" options for treating CLI (Table 2). Despite the increasing nationwide numbers of endovascular interventions for CLI, we advocate a personalized approach in selecting the best revascularization option (59,60). Important patient-level data should be considered, such as age, comorbidities, life expectancy, kidney function, risk associated with anesthesia, and compliance. Furthermore, anatomic factors (e.g., availability of venous conduit, distal target, runoff, calcification, previous procedures) should be noted. These discussions should occur in a multidisciplinary setting that includes all stakeholders so that no patient should undergo a major amputation without consideration of all treatment alternatives.

TABLE 3 Primary Patency Rates for Various Open Surgical Revascularization Modalities*

	Graft Type	Primary Patency Rate (%) 1 Year	2 Years	3 Years	4 Years	5 Years
Above the knee femoropopliteal grafts	Saphenous vein bypass (69)	83	80	78	77	77
	PTFE (71)	74	60	56	53	50
Below the knee femoropopliteal grafts	Saphenous vein bypass (71)	83	78	75	72	67
	PTFE (64,70)	88	81	54	54	-
Femoral-infrapopliteal grafts	Saphenous vein bypass (67)	89	86	83	80	74
	PTFE (68)	45	35	31	25	18

*Data were obtained from multiple sources; primary patency is therefore an approximation.
PTFE = polytetrafluoroethylene.

Both surgery and endovascular intervention have experienced significant advances. A single reversed or in situ saphenous vein bypass remains the gold standard for surgical revascularization, when available (27,53). Alternative conduits include spliced arm and leg veins, and prosthetic polytetrafluoroethylene with or without heparin bonding. Because a significant majority of technical issues with prosthetic bypass grafts seem to occur at the distal anastomosis, a number of alternative approaches (e.g., vein patches) have been described (61,62). However, no single modification has shown superiority in large-scale studies (63). In general, femoral grafts to the above-knee popliteal target have the highest patency rates, and patency falls when the distal target is the below-knee popliteal or tibial artery (**Table 3**) (63-71).

Endovascular therapy has also evolved with better techniques and technologies (72). It is important to note that many of the devices were approved for use in patients with claudication, and not CLI, because of trial design to limit patients with poorer outcomes (73). Despite this limitation, the current data suggest that bare-metal stents (BMS) have an advantage over balloon angioplasty in intermediate and long superficial femoral artery lesions, and self-expanding drug eluting-stents (DES) have demonstrated superior 2-year patency over balloon angioplasty with provisional stenting ($p < 0.01$) (74). Drug-coated balloons (DCBs) have also demonstrated superior patency compared with angioplasty in femoral-popliteal arteries (75-77). The DCB patency benefit compared with angioplasty alone has been sustained at 2 and 5 years (75,78). These devices offer the promise of improved patency with a reduced need for stents in the superficial femoral artery, but, as of yet, no head-to-head randomized comparison between DCB and DES have been performed (73), and cost-effectiveness has yet to be clarified. However, 1 retrospective, propensity score-based comparison of DCB versus DES in TransAtlantic InterSociety Consensus Classification System C and D lesions found no difference in patency between the 2 devices at 1 year (79).

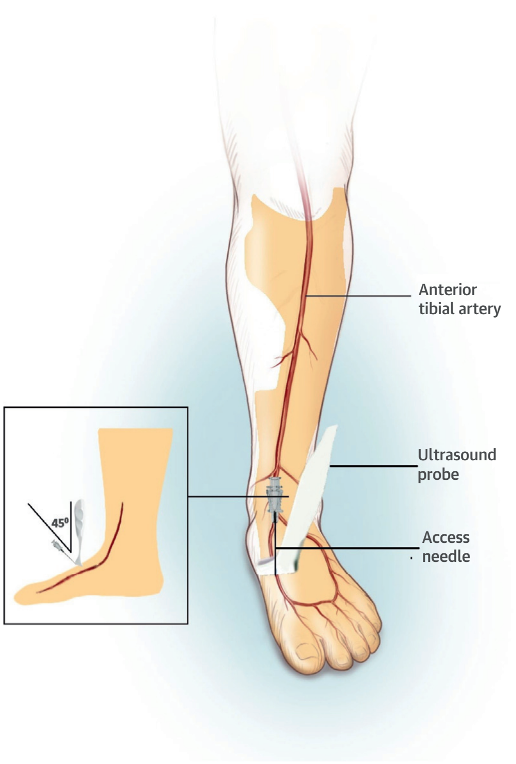
DES, BMS, and DCBs for infrapopliteal arteries have also been evaluated in RCTs for patients with claudication and CLI. Four randomized trials have been completed, with 3 comparing DES versus either BMS or angioplasty alone, and 1 trial comparing DES versus DCBs for infrapopliteal disease. Collectively, these trials provide convincing evidence favoring infrapopliteal DES over angioplasty or BMS for: 1) higher patency; 2) reduced reinterventions; 3) reduced amputation; and 4) improved event-free survival (80-83). However, these results are not limited to patients with CLI, as most trials have included patients with severe claudication (84).

DCBs were studied to address the cost and safety concerns surrounding long stented segments below the knee. Although earlier data with the DEBATE-BTK (Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation) trial showed lower restenosis at 1 year with DCBs compared with angioplasty (74% vs. 27%; $p < 0.001$) (85), the much larger randomized IN.PACT DEEP (Randomized AmPhirion DEEP DEB vs Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia) trial failed to show this benefit (86). In fact, the DCB arm had a trend toward higher amputation rates compared with angioplasty alone. The ongoing Lutonix DCB Versus Standard Balloon Angioplasty for Treatment of Below-The-Knee (BTK) Arteries (NCT01870401) trial is currently recruiting patients with CLI and infrapopliteal disease.

Drug-eluting self-expandable stents and drug-eluting bioabsorbable scaffolds for infrapopliteal disease have been studied in small trials and have shown encouraging results (87). However, as of September 2016, neither of these technologies is approved for infrapopliteal use in the United States.

A number of other endovascular modalities to either enhance crossing (chronic total occlusion devices, re-entry) or to debulk lesions, including atherectomy, cutting/scoring balloon angioplasty, and covered and interwoven stents, have been used to treat patients with CLI (88). Cutting balloons and rotational atherectomy may be helpful in lesions that are resistant to dilation, but there is no comparative evidence in de novo lesions suggesting that the more expensive devices (i.e., atherectomy devices, cryoplasty, laser angioplasty) should be preferred over conventional therapy (88-92). However, in an RCT of 250 patients undergoing laser atherectomy plus angioplasty versus angioplasty for in-stent restenosis or occlusion, laser

FIGURE 3 Ultrasound-Guided Retrograde Pedal Access



Ultrasound-guided pedal access using a hockey-stick probe. Pedal access can be obtained by using a 4-cm micropuncture needle at a 45° angle from the probe. The vessel of interest, ultrasound probe, and needle should be all parallel so that the needle can be seen under direct ultrasound visualization.

atherectomy yielded a significant reduction in target lesion revascularization at 6 months (93).

The endovascular field has also experienced many technical advances. Of these, retrograde tibiopedal access has gained significant momentum worldwide (94,95). This approach improves lesion traversal rates (**Figure 3**) (95). Data from the BASIL trial showed that >20% of patients had a failed attempt at crossing chronic total occlusions (6). Similarly, 1 of the most experienced centers in the world reported a 20% antegrade failure rate (94). The retrograde approach can potentially lower costs by reducing the need for chronic total occlusion devices, decrease lesion crossing time, favor intraluminal crossing, and improve procedure success rates. We found that allowing approximately 10 min for the antegrade approach, followed by retrograde pedal or tibial access in complex chronic total occlusion devices in patients with CLI, improved our success rate from 61% to 93% (96). Pedal access can be and is frequently obtained with ultrasound guidance, although many operators also prefer the fluoroscopic approach. Tibial access can lead to bleeding with resultant compartment syndrome; meticulous attention to hemostasis at the tibial access site can minimize this risk. In general, the operator should minimize sheath size and manipulation of these vessels to reduce spasm, trauma, and occlusion.

REGENERATIVE AND ADJUNCTIVE THERAPIES

A number of regenerative therapies, including angiogenic recombinant proteins, gene therapy, cell-based therapies (including stem or progenitor cells), and chemokines have been tested in patients with PAD and nonrevascularizable CLI (97). However, angiogenic recombinant proteins have not been tested in RCTs in patients with CLI. Granulocyte-macrophage colony-stimulating factor was tested in patients with PAD in an RCT and failed to improve objective performance endpoints (98). A meta-analysis of gene-based therapies failed to show a difference in amputation-free survival (AFS), major adverse limb events (MALE), or time to amputation (97). Many of these trials have been criticized for including Rutherford class VI and nonrevascularizable patients at the end stage of the disease process. Given the limitations and controversy surrounding recombinant protein- and gene-based therapies, bone marrow-derived cell-based therapies have emerged as an alternative to treating patients with CLI. A recent meta-analysis of 12 RCTs found no statistically significant difference for AFS; however, other endpoints, such as ABI, transcutaneous oxygen saturation, and pain-free walking distance, were improved among those treated with cell-based therapies compared with those receiving placebo (99). A number of challenges for regenerative therapies remain, including proper patient selection, appropriate endpoints, source and quality of cells, route of delivery, and number of injections, including frequency (100).

Three other standalone or adjunctive therapies that are currently available to treat CLI and hasten wound healing include hyperbaric oxygen therapy, intermittent pneumatic compression (arterial flow pump), and spinal cord stimulators. Hyperbaric oxygen therapy is widely used without independently adjudicated data to support its use. A recent meta-analysis of all published data on hyperbaric oxygen for treatment of diabetic foot ulcers (as of August 2013) found 7 trials, comprising a total of 376 patients (101). These included a heterogeneous patient population with both ischemic and nonischemic wounds.

All trials had major limitations, including lack of data on wound type, size, adequacy of revascularization, and wound-healing rates. In general, patients with diabetic ischemic ulcers had increased wound healing at 1 year, but AFS remained the same. Patients with nonischemic diabetic ulcers had no clinical benefit. At the present time, hyperbaric oxygen therapy may be used selectively in patients with ischemic ulcers to improve the wound healing rate. Future larger studies may help identify patients who would benefit from this therapy as an adjunct to revascularization.

Intermittent pneumatic compression (arterial flow pump) and spinal cord stimulators have mainly been evaluated in patients with CLI without a revascularization option (97). Intermittent pneumatic compression has been shown to increase collateral and skin blood flow in patients with PAD and CLI (102–104) and to increase claudication distance by 200% and resting ABI by 17% (105). Intermittent pneumatic compression has also been shown to reduce amputation rates, but studies are limited to single-center retrospective evaluations (106). At present, intermittent pneumatic compression for wound healing and relief of rest pain is not reimbursed by the Centers for Medicare & Medicaid Services (CMS) or most third-party payers. Although additional randomized data are necessary, some investigators have found intermittent pneumatic compression therapy to be useful in patients with severe small vessel disease, such as those with diabetes and end-stage renal disease, and those with anatomy that cannot be revascularized. Spinal cord stimulation requires a subcutaneously implanted neurostimulator to activate the lower thoracic spinal cord with an electrode placed in the epidural space. Spinal cord stimulation has been shown to increase skin capillary perfusion in patients with CLI (107). A recent meta-analysis of 5 RCTs found a significant reduction in amputation with spinal cord stimulators; however, this therapy was not associated with lower mortality or faster ulcer healing (97).

FOLLOW-UP AND WOUND CARE

Offloading, infection and edema control, debridement, perfusion assessment, and evaluation of patency are some of the components of follow-up and wound care in CLI. Wound debridement is a critical step in healing (108). This goal can be achieved with a variety of strategies, including enzymatic, autolytic, mechanical, or surgical approaches. However, aggressive surgical/sharp debridement should be avoided in patients without revascularization. Frequent visits in the early stages of wound healing are required to address the concerns mentions in the preceding text; however, once the ulcer heals, the patient should be scheduled for the fitting of proper orthotics and seen 1 to 2 times per year for full examination and foot inspection. In general, wound health and the progression of healing are the most sensitive and specific indicators of adequate perfusion. Failed or slow healing may also be an indication of other confounding features, such as infection, uncontrolled edema, or noncompliance with off-loading.

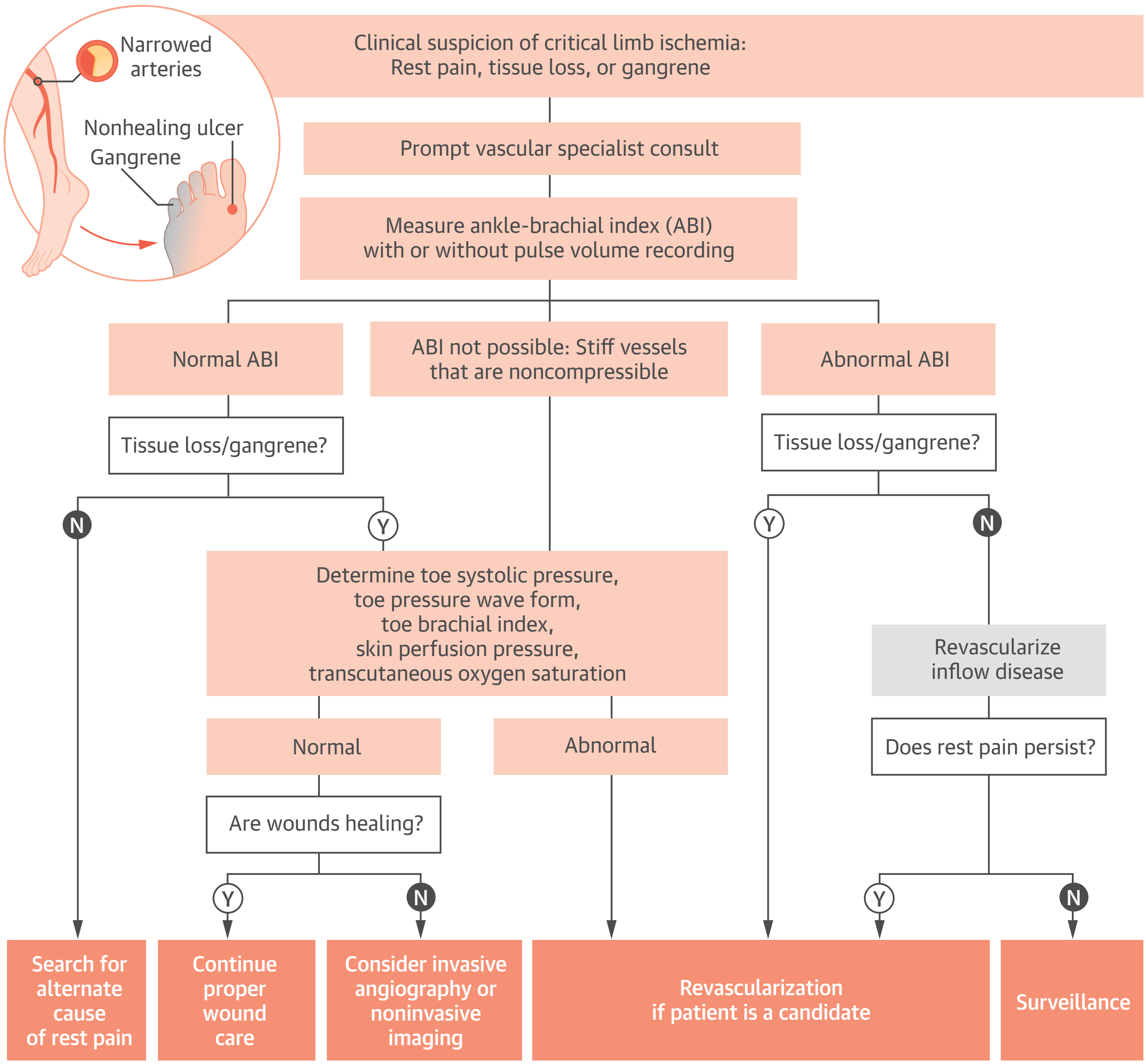
More general guidelines and appropriate use for duplex ultrasound and hemodynamic assessment have also been published (109). Ultimately, in the presence of an unhealed wound and no other identifiable cause, a lower extremity angiogram should be performed.

Mixed venous and arterial ulcers represent a significant treatment challenge. Most venous ulcers should at least have an ABI and toe pressure assessment to ensure adequate perfusion. If there is any evidence of arterial insufficiency, these patients should be considered for prompt revascularization. Adequate revascularization will also allow more intense edema control with leg elevation and other forms of compression wrapping or stockings. Most patients can tolerate high-pressure wrapping after full revascularization. In patients with pain upon leg elevation, severe arterial inflow disease should be entertained and tested with pulse volume recording with exercise or noninvasive imaging. Without improving arterial blood flow and controlling limb edema, these ulcers rarely heal.

APPROPRIATE ENDPOINTS FOR CLI

The early focus in clinical practice and trials has been on AFS and mortality. For example, in the BASIL trial, the primary endpoint was intention-to-treat AFS (6). Although important, AFS fails to capture other endpoints that are important to the patient, health care, and society. Importantly, lack of major amputation in the setting of persistently unhealed wounds fails to capture recurrent hospitalization for infection, pain control, reintervention, and impaired quality of life (25). Because of these limitations, MALE (which encompasses above-ankle amputation of the index limb), major reintervention (defined as new bypass graft, jump or interposition graft revision), thrombectomy, or thrombolysis has been introduced (110). It is our belief that a renewed focus on wound healing, rates of wound healing, and time to wound healing and ambulation may be a step forward for this field beyond AFS, MALE, and MALE plus perioperative death within 30 days (111,112).

CENTRAL ILLUSTRATION Management Algorithm for Patients With Suspected Critical Limb Ischemia



Shishehbor, M.H. et al. J Am Coll Cardiol. 2016;68(18):2002-15.

Algorithm for the diagnosis and management of critical limb ischemia.

DISPARITIES

In the American College of Surgeons National Surgical Quality Improvement Program, black subjects comprised 29% of major amputation procedures, but only 12% and 10% underwent open and endovascular revascularization, respectively (12). Indeed, black race has repeatedly been shown to be associated with higher rates of amputations but with the lowest rates of revascularization (12-14). Furthermore, black subjects, compared with white subjects, are even less likely to undergo simple testing (ABI) before major amputation (113). Similarly, there are major geographic disparities, with significantly higher rates of amputations in the east and south-central regions of the United States, despite multiple adjustments for comorbidities and clustering within the U.S. Census (14). Advances in telemedicine and virtual medicine may provide cost-effective ways to close the disparity gap in patients with CLI (114). Furthermore, we must identify quality metrics that keep all parties accountable for overutilization, as well as for underutilization of proven therapies, such as revascularization to prevent amputation and improve survival (115). Collaboration from multiple medical specialty societies and CMS will be needed to achieve this goal.

AFFORDABLE HEALTH CARE AND THE BUNDLED PAYMENTS FOR CARE IMPROVEMENT INITIATIVE

The Patient Protection and Affordable Care Act is designed to reduce wasteful Medicare spending and improve quality at the lowest cost, thus providing value-based health care. As part of this plan, the value-based purchasing program pays hospitals on the basis of their performance for certain quality measures. However, these quality measures have yet to be defined for CLI. Unfortunately, unlike heart failure and transcatheter aortic valve replacement, assessment of functional status for CLI is not mandated, reported, or reimbursed. Furthermore, although major amputation is captured by most administrative and research databases, few data are available regarding other important quality metrics, such as time to wound healing or ambulation.

Another important initiative by the CMS is the Bundled Payments for Care Improvement Initiative that will likely affect patients with CLI more than those with many other chronic conditions. Under this program, hospitals will share the risk of the procedure and future complications and readmissions from it for a bundled payment by CMS or other third-party payer. Unfortunately, patients with CLI have many comorbidities, are typically high risk for surgery or endovascular revascularization, require multiple treatment devices, and pose significant risk for readmission and wound complications. A more appropriate reimbursement algorithm should take all of these complexities into account and should encourage treating such patients. If not conducted appropriately, such initiatives may discourage physicians and institutions from performing high-risk and complex procedures in patients with CLI, similar to what was observed in New York after public reporting of coronary artery bypass surgery (116).

CONCLUSIONS

There is renewed excitement among physicians, industry, government, and institutions in engaging the most advanced form of PAD (i.e., CLI). Despite these efforts, many patients undergo an amputation without even a vascular assessment. Many ongoing initiatives, including the National Institutes of Health-sponsored BEST-CLI and the European BASIL II and BASIL III trials, will provide much-needed guidance regarding appropriate treatment and follow-up for patients with CLI and help to address unanswered questions related to defining high-quality, cost-effective outcomes for this condition. At the present time, all patients who are candidates for revascularization and who present with rest pain, tissue loss, or gangrene should undergo hemodynamic assessment followed by revascularization (**Central Illustration**). If local wound care or revascularization expertise is not available, or is unable to address the underlying vascular disease, patients should then be referred to specialized centers.

ACKNOWLEDGMENTS The authors thank Kathryn Brock for her editorial assistance and Dr. Tarek Hammad for assistance with tables and figures.

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KEY WORDS amputation, endovascular, open bypass, peripheral artery disease