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Critical limb ischemia

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Opinion statement

Critical limb ischemia (CLI), defined as chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease, is the most advanced form of peripheral arterial disease. Traditionally, open surgical bypass was the only effective treatment strategy for limb revascularization in this patient population. However, during the past decade, the introduction and evolution of endovascular procedures have significantly increased treatment options. In a certain subset of patients for whom either surgical or endovascular revascularization may not be appropriate, primary amputation remains a third treatment option. Definitive high-level evidence on which to base treatment decisions, with an emphasis on clinical and cost effectiveness, is still lacking. Treatment decisions in CLI are individualized, based on life expectancy, functional status, anatomy of the arterial occlusive disease, and surgical risk. For patients with aortoiliac disease, endovascular therapy has become first-line therapy for all but the most severe patterns of occlusion, and aortofemoral bypass surgery is a highly effective and durable treatment for the latter group. For infrainguinal disease, the available data suggest that surgical bypass with vein is the preferred therapy for CLI patients likely to survive 2 years or more, and for those with long segment occlusions or severe infrapopliteal disease who have an acceptable surgical risk. Endovascular therapy may be preferred in patients with reduced life expectancy, those who lack usable vein for bypass or who are at elevated risk for operation, and those with less severe arterial occlusions. Patients with unreconstructable disease, extensive necrosis involving weight-bearing areas, nonambulatory status, or other severe comorbidities may be considered for primary amputation or palliative measures.

Introduction

Lower-extremity peripheral arterial disease (PAD) is estimated to affect between 8 million and 10 million Americans [1,2]. This prevalence is expected to increase, not only in the United States, but across the world as the population ages, cigarette smoking persists, and the epidemic of diabetes mellitus and obesity grows [2]. Critical limb ischemia (CLI), the most advanced form of PAD, is associated with a high risk

of cardiovascular events, including major limb loss, myocardial infarction, stroke, and death [1,3–5]. The likelihood of death has been reported to be as high as 20% within 6 months of CLI diagnosis and surpasses 50% at 5 years post diagnosis [6,7]. These high mortality rates exceed those seen in any other pattern of occlusive disease, including patients with symptomatic coronary artery disease [8, 9], and reflect the severe systemic effects associated with a diagnosis of CLI.

To date, no pharmacologic or biologic therapy has demonstrated efficacy in reversing the circulatory impairment seen in patients with CLI. Therefore, if successful revascularization is not feasible, impaired quality of life, limb loss, and death have been the norm rather than the exception [10•].

The economic impact of this growing burden of PAD is being experienced acutely in the United States and many other nations. A study analyzing Medicare data for 2001 found that $4.37 billion was spent on PAD-related treatment [2]. In total, PAD-related treatment accounted for approximately 13% of all Medicare Part A and B expenditures for the PAD-treated cohort, and 2.3% of all Medicare Part A and B annual spending.

The widespread adoption of endovascular procedures by multiple disciplines has significantly increased treatment options [6, 11]. This change in treatment paradigm has been driven by technological advances, as well as by the desire of patients and physicians to reduce procedural risk, albeit with potential tradeoffs of inferior durability and greater cost [6]. Between 1996 and 2006, the number of endovascular lower-extremity interventions in the Medicare population reportedly increased by 230%, whereas the number of bypass procedures decreased by 42% [12].

Despite the enormity of the patient population at risk and the multiple treatment options available, rigorous high-level evidence to support informed clinical decision making in patients with CLI has been lacking. There are few high-quality prospective studies and even fewer randomized controlled clinical trials. In this review, we attempt to summarize the existing evidence guiding therapeutic decision making in CLI.

Treatment

Diet and lifestyle

- No clinical trials have been conducted, or are ongoing, that specifically address the role of diet modifications/supplements in the progression of CLI.
- Lipid abnormalities, including elevated total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein cholesterol, and hypertriglyceridemia, are strongly associated with lower-extremity PAD. As a result, low-cholesterol diets have been recommended for patients with CLI [13].
- Cigarette smoking is a strong predictor of lower-extremity PAD, with a large number of epidemiologic studies establishing an increased incidence of PAD in smokers compared with nonsmokers. Furthermore, the severity of PAD tends to increase in a dose-dependent manner with the number of cigarettes smoked [14]. Interventions directed at smoking cessation, or decreased usage, are critical [11,13].

Pharmacologic treatment

- To date, no pharmacologic therapy has demonstrated efficacy in reversing the arterial occlusive lesions, or the resulting impaired perfusion, seen in patients with CLI. The Circulase trial (Mitsubishi Pharma Corp, Tokyo, Japan), published in 2006, randomly assigned

379 CLI patients with no revascularization option to receive lipo-ecraprost (parenteral prostaglandin) or placebo. The study treatment was found to confer no benefit (or harm) on the primary study end point, death or amputation above the ankle at 180 days [15].

- Various reports have demonstrated that cardioprotective medications such as statins, β-blockers, angiotensin-converting enzyme inhibitors, and antiplatelet agents are associated with a decreased cardiovascular event rate in patients with PAD [16–21]. However, these studies have been conducted in heterogeneous populations, not specifically in patients with CLI. In a retrospective analysis of 1404 CLI patients who had undergone surgical revascularization, statins were demonstrated to confer a significant survival advantage at 1 year (hazard ratio [HR] for mortality, 0.71; $P=0.03$) [22]. However, optimum dosing and therapeutic targets (eg, LDL cholesterol, C-reactive protein levels) for statin therapy in PAD patients are uncertain, and more clinical trials are needed to determine whether statins have direct beneficial effects in the peripheral circulation (limb). In general, current recommendations for the use of cardioprotective medications in CLI follow published general PAD guidelines [13,19].

Interventional procedures

- Various endoluminal catheter-based devices have been developed for patients with CLI. These evolving technologies include balloon angioplasty, CryoPlasty therapy (Boston Scientific, Natick, MA), stent/stent-graft placement, laser atherectomy, and mechanical atherectomy. Beyond single-center case series demonstrating feasibility and technical success, a paucity of high-level data precludes critical evaluation of these technologies. These results often are difficult to interpret because of differences in patient selection, use of multiple therapeutic modalities, and variable end points with variable study durations. A summary of several of the larger, recent series reporting outcomes of endovascular treatment for patients with CLI is presented in Table 1.

- The Transatlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II), published in 2006, was developed by an international working group charged with reviewing the literature and putting forth recommendations for the diagnosis and treatment of PAD [11]. All recommendations were assigned a grade based on the level of available evidence to support that recommendation. The working group recommended endovascular therapy as the first-line treatment method for patients with TASC A and B lesions. Of note, this recommendation received a grade C for evidence, which was defined as "…evidence obtained from expert committee reports or opinions….no applicable studies of good quality"[11].

- The BASIL (Bypass Versus Angioplasty in Severe Ischaemia of the Leg) trial, sponsored by the UK National Institute of Health Research Health Technology Assessment program, is the only randomized controlled trial (RCT) comparing open surgical bypass with

Table 1. Recent studies reporting outcomes in patients undergoing endovascular therapy for treatment of critical limb ischemia

Study	Patients, *n*	Study type	Outcome measure(s)	Event rate, %
Laird et al., 2006 [62]	155	Multicenter series	Amputation-free survival (6 mo)	82
Bosiers et al., 2007 [63]	51	Multicenter series	Amputation-free survival (1 y)	79
DeRubertis et al., 2008 [64]	184	Single-center series	Limb salvage (1 y)	88.3
			Primary patency (1 y)	54±5
			Primary patency (2 y)	43±7
Giles et al., 2008 [65]	176	Single-center series	Freedom from restenosis, reintervention, or amputation (1 y)	39
			Freedom from restenosis, reintervention, or amputation (2 y)	35
			Primary patency (1 y)	53
			Primary patency (2 y)	51
			Limb salvage (3 y)	84
			Survival (1 y)	81
			Survival (3 y)	54
Romiti et al., 2008 [66]	–	Meta-analysis	Primary patency (1 y)	58.1±4.6
			Primary patency (3 y)	48.6±8.0
			Secondary patency (1 y)	68.2±5.9
			Secondary patency (3 y)	62.9±11.0
			Limb salvage (1 y)	86.0±2.7
			Limb salvage (3 y)	82.4±3.4
			Survival (1 y)	87.0±2.1
			Survival (3 y)	68.4±5.5

endovascular therapy in patients with severe limb ischemia (SLI) due to infrainguinal disease; therefore, it is worth considering in detail [6]. The term *SLI* was used to "admit patients with chronic, potentially limb threatening, ischemia but who did not necessarily have ankle pressures less than 50 mmHg and thus did not strictly fulfill the requirements of the term CLI" [6]. It also is important to note that patients were eligible for BASIL if they were deemed suitable for either angioplasty or bypass and if they met the investigators' criterion of "grey area of clinical equipoise."

- The BASIL trial began enrollment in 1999 and randomly assigned 452 patients from 27 centers across Scotland and England. In 2005, the BASIL trialists reported an analysis of outcomes out to 2 years—demonstrating no difference in overall survival or amputation-free survival by intention-to-treat analysis between surgical bypass and endovascular therapy, with surgery being more expensive in the short term [6]. However, post hoc analysis demonstrated that beyond 2 years, patients initially assigned to open bypass surgery had a significantly improved amputation-free survival (adjusted HR, 0.37; 95% CI, 0.17–0.77; *P*=0.008) and reduced all-cause mortality (adjusted HR, 0.34; 95% CI, 0.17–0.71; *P*=0.004) relative to angioplasty [6]. This finding of the BASIL trial was considered significant enough to warrant funding of an extension study, the results of which were

reported recently [23,24,25●,26,27●]. For the overall follow-up period (mean follow-up, 3.1 years; range, 1–5.7 years), there was no significant difference in overall survival or amputation-free survival by intention-to-treat analysis. However, for patients surviving to 2 years post procedure (70% of the study cohort), initial randomization to open bypass was associated with significantly improved overall survival (mean gain of 7.3 months; P=0.02) and a trend toward increased amputation-free survival (mean gain of 5.9 months; P=0.06). The investigators also published the trial outcomes using an as-treated analysis [25●], an approach that accounts for early treatment cross-overs but, importantly, sacrifices the power of randomization. In this analysis, they found that among patients assigned to open surgery, those who received prosthetic grafts (25% of the surgical group) experienced reduced amputation-free survival compared with those who received vein grafts (P=0.003). They also observed that patients who underwent bypass surgery after an initial failed angioplasty experienced significantly worse amputation-free survival than those who underwent bypass as the initial therapy (P=0.006), suggesting a real potential downside to failed angioplasty in SLI.

- The primary recommendations from the BASIL trial perhaps are best summarized by the authors in the following statement:

  – "….SLI patients predicted to live more than 2 years, and with a useable vein, should usually have bypass surgery first. This is because the long term results of saphenous vein bypass surgery are good, the rate of balloon angioplasty failure is high, and the results of bypass surgery after failed balloon angioplasty are significantly worse than for bypass surgery. However, patients expected to live less than 2 years, and those without a useable vein, should usually have balloon angioplasty first as they will not survive to reap the longer term benefits of surgery and the results of prosthetic bypass surgery are poor" [25●].

- There are several important limitations and controversies surrounding the application of the BASIL trial to current practice [28], yet this study stands as a seminal RCT in the field of advanced limb ischemia and a basis for the design of future trials.

Endovascular treatment of CLI

Standard procedure(s)	Percutaneous angioplasty with or without adjunctive atherectomy (mechanical or laser) and with or without adjunctive stenting.
Contraindications	Relative: low estimated glomerular filtration rate, anatomically unfavorable disease (common femoral artery lesion, extensive calcification, long segment occlusions, severe popliteal and/or infrapopliteal disease).
Complications	Thrombosis, embolization, blue toe syndrome, amputation, loss of surgical target for bypass, access site complications (hemorrhage, pseudoaneurysm, arteriovenous fistula), contrast nephropathy, and renal failure.

Special points	Techniques for endovascular treatment in the aortoiliac segment have become more standardized and durability more consistent for TASC A to TASC C disease (absence of a long segment occlusion for a complete description of TASC criteria, please see Norgren et al. [10●]). Adequate treatment of the common and profunda femoris arteries is of primary importance in CLI and may require a hybrid or fully open approach (eg, femoral endarterectomy). The role of covered stents in the aortoiliac segment is poorly defined. For infrainguinal therapy, treatments and results are more heterogeneous. Several devices are available for different lesion anatomies and technical circumstances (eg, best approach for complete total occlusions), but little evidence is available to support one over the other. The benefit of routine use of nitinol stents in the superficial femoral artery is still under debate [29]. No RCT data are available demonstrating a benefit for the use of stents in popliteal or distal vessels, or for the use of drug-eluting stents in lower-extremity vessels.
Cost/cost-effectiveness	Several cost-effectiveness analyses have been performed comparing endovascular therapy with open surgery in patients with CLI [24, 30]. Stoner et al. [30] analyzed 381 femoropopliteal revascularization procedures (open bypass, n=183; endovascular, n=198) performed for claudication and CLI. In the subset of patients with CLI, they reported an initial cost saving with endovascular therapy ($7176 vs $13,277; $P<0.001$). However, during the 1-year study period, the patients who were treated with endovascular therapy went on to require reinterventions, so this cost saving ultimately was lost at 1 year. Similarly, in the cost-effectiveness study that accompanied the BASIL trial, no significant difference was seen, as the survival, hospital costs, and health-related quality-of-life differences were minimal between the surgical and endovascular study arms [24].

Surgery

- Open surgical bypass using autogenous vein traditionally has been the gold-standard revascularization technique for patients with CLI due to infrainguinal disease. However, this paradigm is evolving as new endovascular technologies are being developed, used, and tested.

- Aortofemoral bypass using prosthetic conduit is a standard surgical approach for extensive (eg, TASC D) aortoiliac disease or in the setting of failed prior endovascular therapy. Expected operative mortality is approximately 3% and durability is excellent (85%–90% patency at 5 years and beyond).

- As noted earlier, adequate treatment of disease in the common and deep femoral arteries (eg, endarterectomy and/or patch angioplasty) at the time of either inflow or outflow reconstruction is of primary importance for the long-term fate of the limb in CLI patients.

- Two RCTs examining novel CLI treatments (gene therapy [31] and prostaglandin therapy [15]), a multicenter prospectively maintained vascular registry [32], and one RCT comparing balloon angioplasty with surgical bypass in patients with CLI (BASIL) [6] have provided a wealth of high-quality outcomes data pertaining to vein bypass surgery in patients with CLI. Several authors have used the information contained in these surgical CLI datasets to further our understanding of risk stratification and outcome prediction [22,33–39,40●],

quality of life [41], disparities in care [42], reintervention rates and the associated outcomes [43], and resource utilization [41].

- Both BASIL [6] and PREVENT III (PIII) [31] challenge the nihilistic paradigms about mortality rates in patients with CLI: 85% of PIII patients survived beyond 1 year, and 70% of BASIL patients survived longer than 2 years. These data suggest that CLI patients may be done a tremendous disservice if the selection of their therapies is founded on the concept that all CLI patients carry a substantial mortality risk that warrants a short-term approach.

- A recent meta-analysis in patients with CLI undergoing infrainguinal bypass demonstrated 5-year primary patency, secondary patency, and limb salvage rates of 63%, 71%, and 78%, respectively [44]. Recently, a working group under the auspices of the Society for Vascular Surgery used pooled data from the PIII, BASIL, and Circulase studies to develop expected outcomes for vein bypass surgery as the relevant standard for comparing new devices. This group endorsed a set of three safety and six efficacy objective performance goals for CLI based on the pooled data from these surgical controls [40•]. These outcomes are summarized in Table 2.

- Given the relative high-risk nature of the CLI patient population, as well as the variety of available treatment options, the ability to use

Table 2. Suggested end point definitions for revascularization in critical limb ischemia and expected event rates for open bypass surgery[a]

End point	Definition	Event rate, % (95% CI)
Safety outcomes (30 d)		
MACE	Myocardial infarction, stroke, or death (any cause)	6.2 (4.7–8.1)
MALE	Above-ankle amputation of the index limb or *major* reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)	6.1 (4.6–7.9)
Amputation	Above-ankle amputation of the index limb	1.9 (1.1–3.1)
Efficacy outcomes (1 y)[b]		
Perioperative death or MALE	Perioperative death (30 d) or any MALE	76.9 (74.0–79.9)
Amputation-free survival	Above-ankle amputation of the index limb or death (any cause)	76.5 (73.7–79.5)
Reintervention, amputation, or stenosis	Any reintervention, above-ankle amputation of the index limb, or stenosis	46.5 (42.3–51.2)
Reintervention or amputation	Any reintervention or above-ankle amputation of the index limb	61.3 (58.0–64.9)
Limb salvage	Freedom from above-ankle amputation	88.9 (86.7–91.1)
Survival	Freedom from death (any cause)	85.7 (83.3–88.1)

[a]Reported by the Society for Vascular Surgery Working Group for the development of objective performance goals for evaluating catheter-based treatment [40]•. Data are pooled from prospective trials of vein bypass surgery in critical limb ischemia. Additional data are available at http://www.criticallimb.org/.
[b]All rates are freedom from event.
MACE major adverse cardiovascular events, *MALE* major adverse limb events

preprocedure variables to predict a given outcome has become increasingly important. Several recent advances have been made in an attempt to improve individual patient risk prediction at the time of initial patient evaluation. The PIII CLI risk score is an easy-to-use risk stratification model developed to predict amputation-free survival in CLI patients undergoing open infrainguinal surgical bypass [45]. This prediction tool was derived from the cohort of patients who underwent autogenous vein bypass for CLI in the context of the PIII randomized trial [46]. The PIII CLI risk score was then validated both internally, using the trial cohort, and externally, using a multicenter retrospective cohort of patients (total $n = 3286$). In this study, the PIII CLI risk score was found to be a highly reliable and simple tool for stratifying CLI patients selected to undergo bypass surgery into low-, medium-, and high-risk categories. At the time of a patient's initial presentation, five easily obtainable binary variables may be used to provide patients and providers with a valid estimate of the likelihood of amputation-free survival at 1 year after surgical revascularization. These variables are dialysis dependency, tissue loss, advanced age, advanced coronary artery disease, and low hematocrit. Numerous key publications have identified predictors of specific outcomes in case series of patients with CLI (Table 3). When looked at comprehensively, it becomes clear that patency and limb salvage outcomes are, for the most part, linked to characteristics of the bypass graft (ie, type of conduit) and the specific patient anatomy (ie, adequacy of runoff score). In contrast, mortality and functional outcomes appear to be more influenced by systemic comorbidities, preoperative medications, and physiologic characteristics.

Surgical treatment of CLI

Standard procedure(s)	Lower-extremity bypass grafting with or without femoral endarterectomy, with or without adjunctive inflow (aortoiliac) treatment. The preferred graft conduit for infrainguinal bypass is autogenous saphenous vein followed by other autogenous venous conduits. Prosthetic or other nonautogenous conduits should be considered significantly inferior secondary choices for infrainguinal bypass in the CLI patient.
Contraindications	Unacceptable surgical risk (eg, multiple comorbidities, advanced age), advanced tissue loss on weight-bearing surface, nonambulatory status, no identifiable target vessel with runoff to ankle/foot. Relative contraindications: lack of adequate-quality autogenous vein conduit for infrageniculate bypass, poor-quality target vessel, extensive infection or necrosis compromising graft or vessel coverage.
Special points	The inflow artery must have uncompromised hemodynamics, and arterial outflow should be continuous to the ankle and foot. Vein graft origin (saphenous vein is superior to all other venous conduits for infrainguinal reconstruction), graft diameter, and graft length all are key variables influencing short-term and long-term patency [39]. Reversed, nonreversed, or in situ vein configurations all are effective, and the choice is dictated primarily by surgeon preference and anatomic circumstances.
Cost/cost-effectiveness	See "Cost/cost-effectiveness" under "Endovascular treatment of CLI."

Table 3. Recent studies identifying independent predictors for select outcomes in patients with critical limb ischemia

Study	Patients, *n*	Study type	Inclusion criterion	Primary outcome measure	Significant predictors
Robinson et al., 2009 [67]	1646	Single-center series	Bypass surgery for CLI or claudication	Patency	High-risk conduit, CLI, smoking, age ≥65 y, African American, female
Schanzer et al., 2007 [39]	1404	Multicenter RCT	Bypass surgery for CLI	Patency	Graft diameter, graft length, non–single segment GSV, popliteal artery origin
Bradbury et al., 2010 [23]	452	Multicenter RCT	Bypass surgery and angioplasty for SLI	Death	Age, MI, stroke, tissue loss, ankle pressure, number of detectable ankle pressures, creatinine, smoking, BMI, Bollinger score, diabetes
Goodney et al., 2010 [37]	2036	Multicenter registry	Bypass surgery for CLI or claudication	Death	CHF, diabetes, CLI, absence of single-segment GSV, age >80 y, dialysis, emergent procedure
Schanzer et al., 2008 [22]	1404	Multicenter RCT	Bypass surgery for CLI	Death	Statin therapy, age ≥75 y, CAD, CKD stage 4/5, tissue loss
Owens et al., 2007 [68]	456	Single-center series	Bypass surgery for CLI or claudication	Death	Age, CKD stage 4/5
Schanzer et al., 2009 [36]	1166	Multicenter registry	Bypass surgery for CLI	Amputation-free survival	Age ≥75 y, dialysis, tissue loss, anemia, advanced CAD
Schanzer et al., 2008 [45]	1404	Multicenter RCT	Bypass surgery for CLI	Amputation-free survival	Age ≥75 y, dialysis, tissue loss, anemia, advanced CAD
Biancari et al., 2007 [69]	3925	Multicenter registry	Bypass surgery for CLI	Amputation-free survival	Diabetes, CAD, foot gangrene, urgent operation
Goodney et al., 2009 [34, 35]	2036	Multicenter registry	Bypass surgery for CLI or claudication	Amputation or loss of secondary patency	Age 40–49 y, nonambulatory preoperatively, dialysis, diabetes, CLI, composite vein grafts, tarsal bypass target, nursing home preoperatively
Rossi et al., 2003 [70]	468	Single-center series	Bypass surgery for CLI or claudication or aneurysm	Amputation	Gender, nonautologous conduit, redo bypass
Toursarkissian et al., 2002 [71]	124	Single-center series	Bypass surgery for CLI or claudication	Amputation	Angiographic score, foot score, diabetes
Alback et al., 1998 [72]	132	Single-center series	Bypass surgery for CLI or claudication	Amputation	"Ad hoc" grading system of outflow arteries

Table 3. *(continued)*

Study	Patients, *n*	Study type	Inclusion criterion	Primary outcome measure	Significant predictors
Simons et al., 2010 [73]	1457	Multicenter registry	Bypass surgery for CLI	Clinical failure (persistent symptoms and/or amputation) despite bypass patency	Dialysis, preoperative ambulation with assistance, history of CABG or PCI
Goodney et al., 2009 [34]	1400	Multicenter registry	Bypass surgery for CLI or claudication	Ambulatory failure	Nonambulatory preoperatively, CLI, age ≥70 y, postoperative MI, postoperative amputation
Taylor et al., 2006 [74]	1000	Single-center series	Bypass surgery for CLI	Ambulatory deterioration/ failure	Female, diabetes, renal insufficiency, dementia, homebound preoperatively, postoperative amputation
Nguyen et al., 2006 [41]	1404	Multicenter RCT	Bypass surgery for CLI	Decreased improvement in quality of life	Diabetes, postoperative graft-related event
Taylor et al., 2006 [74]	1000	Single-center series	Bypass surgery for CLI	Non-independent living	Age ≥70 y, ulceration, previous stroke, dementia, nonambulatory, postoperative amputation

BMI body mass index, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease; *CHF* congestive heart failure, *CKD* chronic kidney disease, *CLI* critical limb ischemia, *GSV* great saphenous vein, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *RCT* randomized controlled trial, *SLI* severe limb ischemia

Other treatments

- Although hyperbaric therapy commonly is used for nonhealing wounds, its efficacy has not yet been established in patients with CLI. It may be of limited utility in patients in whom revascularization is not technically feasible or for those who have failed all previous revascularization attempts.
- Spinal cord stimulation has been proposed as an alternative to primary amputation in CLI patients with ischemic rest pain who are not amenable to revascularization. This technique requires the implantation of a subcutaneous pulse generator that stimulates electrodes at the L3-L4 level. Although this technique has not enjoyed widespread use, a recent meta-analysis did demonstrate significant pain reduction and an 11% reduced amputation rate compared with medical therapy alone [47]. The role for this therapy presently is unclear.
- Intermittent pneumatic compression in patients with CLI is another proposed therapy for augmenting distal arterial oxygen delivery in

those who are not amenable to revascularization. Preliminary investigations have demonstrated increased muscular, collateral, and skin blood flow in patients receiving compression therapy [48]. Furthermore, a small study comparing CLI patients receiving compression therapy ($n=24$) with those receiving optimal medical management ($n=24$) did demonstrate that compression therapy was associated with improved wound healing, limb salvage, and transcutaneous oximetry [49]. Larger studies are needed to determine a role for intermittent pneumatic compression in CLI.

Emerging therapies

- New revascularization strategies for CLI patients not amenable to either endovascular or surgical revascularization are being explored. Based on an increased mechanistic understanding of angiogenesis and arteriogenesis, novel therapeutic approaches including molecular, genetic, and cell-based treatments have entered the clinical trial phase [50].

- In the PIII study, published in 2006, 1404 CLI patients undergoing bypass surgery were randomly assigned to receive edifoligide (a DNA molecule that inhibits cell cycle gene expression and was hypothesized to reduce neointimal hyperplasia) or placebo. The study treatment was found to confer no benefit or harm on either the primary study end point of time to index graft reintervention or major amputation or the secondary end points of all-cause graft failure, significant graft stenosis, amputation/reintervention-free survival, and nontechnical primary graft patency [31].

- Several gene therapy RCTs using hepatocyte growth factor [51], fibroblast growth factor [52], and vascular endothelial growth factor [53–55] have been carried out in an attempt to activate the angiogenesis pathway. Preliminary data from these studies suggest limited gains. In one study, the authors demonstrated improvement in their primary study end point (improvement in the angiographic indices 3 months after vascular endothelial growth factor gene transfer) [54]. In a phase 2 double-blind RCT, intramuscular injection of hepatocyte growth factor plasmid in 104 CLI patients demonstrated safety, and transcutaneous oxygen levels increased at 6 months in the high-dose group [51]. Nikol et al. [52] reported a European phase 1/2 RCT examining a plasmid-based fibroblast growth factor gene delivery approach in 125 CLI patients; there was no significant difference in the primary end point (ulcer healing), but amputation-free survival was improved. Larger RCTs are required in the field, but significant challenges in study design, recruitment, and costs have slowed progress in this area.

- Cell therapy is a regenerative medical approach for CLI aimed at enhancing angiogenesis. Cell therapy trials to date have included relatively few patients compared with gene therapy trials. Nonetheless, the preliminary findings are encouraging. Autologous cells of various sources (eg, peripheral blood, bone marrow, adipose tissue)

and cell type (endothelial progenitors, mesenchymal stem cells, peripheral blood mononuclear cells) have been used in phase 1/2 investigations in CLI. Bone marrow mononuclear cells injected into the gastrocnemius [56] and intra-arterial infusion of circulating blood-derived progenitor cells [57] both have been associated with improvements in prespecified primary end points. There are several ongoing studies in this area.

• Drug-eluting balloons and stents have undergone limited evaluation in the lower-extremity circulation to date. Recent reports of superficial femoral artery angioplasty using a paclitaxel-coated balloon have shown encouraging results [58–60], and further trials are planned in the CLI population. Drug-eluting stents are being evaluated in the femoral and infrapopliteal arteries. No data are available yet on the utility of these technologies for CLI.

• Bioresorbable stents offer the potential to prevent recoil post angioplasty, improve remodeling, and eliminate the long-term inflammatory response to the implant. This technology is in an early stage. An initial trial of a bioresorbable stent for infrapopliteal disease in CLI patients failed to show any significant benefit [61].

Disclosure

No potential conflicts of interest relevant to this article were reported.

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