CLI TRIAL UPDATE

Where Do We Stand on Data Collection?

An overview of the current evidence and perspectives on what data are still needed.

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Critical limb ischemia (CLI) is defined as chronic ischemic rest pain, tissue loss, or gangrene in the presence of peripheral artery disease (PAD). Only up to 3% of patients with PAD have CLI, but the incidence is increasing due to the growth of the frail and aging vascular patient population. Moreover, CLI is the most advanced stage of PAD and is associated with a high risk of major amputation, disability, and death.[1] Treatment of CLI is aimed at wound healing, improvement in quality of life, prevention of major amputation, and prolonged survival. To achieve this, most patients will ultimately require a revascularization procedure. However, CLI is a complex disease process and patients require multidisciplinary care. Other than revascularization, CLI patients should aggressively seek modification of cardiovascular risk factors, pain control, wound care, and prevention or treatment of infection.[2]

In these complex patients, there is a need for risk stratification tools. Both the Rutherford and Fontaine classifications do not recognize the multifactorial nature of the threatened lower extremity. The Society for Vascular Surgery's Lower Extremity Guidelines Committee introduced a tool to assess the threatened lower extremity called the Wound, Ischemia, and foot Infection (WIfI) classification system.[3] Using this classification system, it is possible to better predict the 1-year lower extremity amputation risk and identify which CLI patients will most likely benefit from revascularization.[4]

CLI is typically associated with multilevel disease. Patients with ischemic rest pain may benefit from proximal revascularization alone, but those with tissue loss and gangrene require more extensive revascularization of all affected arterial segments to reestablish direct flow toward the wound.[5] Current treatment strategies for CLI propose open or endovascular revascularization with runoff distal to the ankle but not specifically targeted to the location of the ischemia.

ANGIOSOME CONCEPT

An angiosome is a three-dimensional unit of tissue fed by a source artery. There are six recognizable angiosomes related to the foot and ankle. Angiosomes are connected by collaterals or choke vessels, but severe atherosclerosis and diabetes can affect this compensatory mechanism.[6] Although originally introduced by Taylor and Palmer to provide an anatomic basis for planning reconstructive surgery, the angiosome concept is widely embraced by endovascular specialists in their treatment paradigm.[7]

There is still no consensus on whether direct revascularization of the affected angiosome in CLI patients results in better outcome compared with indirect revascularization. High-quality evidence from randomized controlled trials (RCTs) is not available. Based on a systemic review and meta-analysis of almost 4,000 patients from predominantly retrospective studies, there is a strong indication that direct revascularization of the affected angiosome significantly improves wound healing and the major amputation rate after endovascular treatment of patients with CLI. However, in the presence of collaterals, outcomes after indirect revascularization were similar to those after direct revascularization. Therefore, patients without collaterals may benefit even more from direct revascularization as a primary treatment strategy.[8]

BYPASS SURGERY

Bypass surgery has been the gold standard for many years and is associated with excellent long-term patency rates but also significant morbidity. Due to the increase in the frail and aging vascular population and the rapid development of endovascular techniques and improved skills, experienced centers advocate an "endovascular-first" approach.[9,10] This minimally invasive treatment option comes with less morbidity, but the long-term patency rates are still limited. The BASIL trial showed similar outcomes after bypass surgery and balloon

angioplasty in terms of amputation-free survival and overall survival in patients with CLI.[11] However, for those who survived for at least 2 years after randomization, bypass surgery was associated with a significant increase in overall survival and a trend toward amputation-free survival.[12] In other words, CLI patients have to survive for at least 2 years to benefit from the more invasive bypass surgery treatment option.

The BASIL trial is currently the only available RCT comparing surgical and endovascular revascularization in patients with CLI and has been criticized for the very low use of stents (nine cases) and the immediate technical failure rate of 20%. However, the results of two large ongoing RCTs are awaited. The BASIL-2 trial is an RCT that is comparing a vein bypass–first with a best endovascular treatment–first revascularization strategy in 600 patients with severe limb ischemia due to infrapopliteal disease.[13] The BEST-CLI trial is a prospective, multidisciplinary, randomized trial enrolling 2,100 patients with CLI who are candidates for both surgical and endovascular revascularization.[14] Both trials have a pragmatic design, leaving the choice of a specific procedural strategy within the assigned revascularization approach to the individual treating investigator. The results of both trials will provide high-quality evidence for a personalized approach in selecting the optimal revascularization strategy in this population of vulnerable patients.

ENDOVASCULAR THERAPY

Drug-Coated Balloons

In recent years, several new technologies have been introduced to improve patency rates after endovascular treatment of PAD. Probably the most promising recent technical development in the endovascular treatment of PAD is the use of drug-eluting devices. Multiple high-quality RCTs and meta-analyses have shown less binary restenosis and less clinically driven target lesion revascularization (CD-TLR) after treatment with drug-coated balloons (DCBs) in the femoropopliteal artery.[15,16]

In contrast to treatment of the femoropopliteal arteries, the efficacy of DCBs in the infrapopliteal arteries has not yet been established. Two early single-center RCTs showed promising results using the In.Pact Amphirion DCB (Medtronic) for the treatment of infrapopliteal lesions. The DEBELLUM trial showed reduced CD-TLR and late lumen loss (LLL) after 6 months in the DCB group.[17] In the DEBATE-BTK trial, DCB treatment resulted in reduced 1-year rates of restenosis, TLR, and target vessel occlusion.[18] However, the IN.PACT DEEP trial randomized 358 CLI patients 2:1 to In.Pact Amphirion DCB or percutaneous transluminal angioplasty (PTA) and did not show any difference in CD-TLR or LLL after 12 months. The primary safety endpoint was met, but a trend toward an increased major amputation rate in the DCB group was observed.[19] Similarly, in the BIOLUX P-II RCT, which randomized patients to either the Passeo-18 Lux DCB (Biotronik, Inc.) or PTA, both primary safety and performance endpoints were similar at 6 months.[20] A meta-analysis of five RCTs showed favorable angiographic outcomes after DCB use at 1-year follow-up, but no differences were observed with regard to clinical outcomes.[21] Enrollment of 442 patients in the Lutonix BTK trial is completed and results are anticipated.

Drug-Eluting Stents

The Zilver PTX trial evaluated the long-term safety and efficacy of endovascular treatment of the femoropopliteal artery with the Zilver PTX drug-eluting stent (DES; Cook Medical). Treatment with primary and provisional DES use resulted in improvements in patency, TLR, and clinical outcomes compared with PTA or bare-metal stents (BMSs). These results were sustained through 5 years.[22] A head-to-head comparison of endovascular treatment of the femoropopliteal artery with DCB versus DES in the REAL PTX trial showed no significant difference in primary patency or freedom from TLR after 36 months.[23] Further data from head-to-head comparisons of DCBs versus DESs in real-world cohorts of CLI patients, such as the DRASTICO, SWEDEPAD, BASIL-3, EMINENT, and FOREST trials, are eagerly awaited.[24,25]

A recent meta-analysis by Katsanos et al reported an increased long-term mortality rate following treatment with paclitaxel-eluting balloons and stents in the femoropopliteal arteries.[26] Due to this concerning safety signal, the SWEDEPAD, BASIL-3, and FOREST trials have currently paused the recruitment of patients. Likewise, in the BASIL-2 trial, the use of paclitaxel-eluting balloons and stents has been paused.

Similar to the femoropopliteal artery, DES treatment of the tibial arteries is an effective treatment. The ACHILLES, YUKON, and DESTINY trials randomized patients to treatment with either a sirolimus/everolimus-eluting stent or PTA or BMS.[27-29] They all showed improved primary patency rates after DES treatment at 1 year. In the IDEAS trial, the results following DES use were compared with those of DCB use. The authors concluded that DES use results in lower immediate postprocedure stenosis and a reduced vessel restenosis rate at 6 months.[30] It can be concluded from several meta-analyses that treatment with a DES results in improved angiographic outcomes compared to PTA or BMS in focal disease of the infrapopliteal arteries. The impact on clinical endpoints remains

largely unknown.[31-33] The PADI trial, which randomized patients to treatment with either DES or PTA with bailout BMS, recently reported long-term clinical outcomes. The authors concluded that DES treatment of infrapopliteal lesions significantly improved event-free and amputation-free survival after 5 years.[34]

Due to the limited length of the DESs used in the infrapopliteal arteries, which were originally developed for the coronary arteries, they have only proven to be effective in preventing restenosis in focal lesions. It is unknown whether this technology is as effective for longer infrapopliteal lesions. The impact of long-term complications of balloon-expandable stents, such as stent fracture and stent thrombosis, is also largely unknown. In prospective single-arm series, treatment of infrapopliteal arteries with bioresorbable vascular scaffolds and self-expanding DESs have shown promising results.[35,36]

Covered Stents

The Viabahn endoprosthesis (Gore & Associates) is a polytetrafluoroethylene-covered self-expanding stent graft that has been evaluated in two RCTs as an endovascular alternative for femoropopliteal bypass surgery. In patients with long superficial femoral artery (SFA) lesions (> 25 cm), it has shown similar patency rates at 4-year follow-up when compared to prosthetic suprageniculate femoropopliteal artery bypass surgery.[37] In more recently published data from Reijnen et al, treatment with a heparin-bonded endoluminal bypass was associated with less morbidity, faster recovery, and improvement in quality of life at 1 year. Due to the low enrollment rate, this study was terminated after reaching the sample size for the quality-of-life endpoint.[38]

In the VIASTAR trial, treatment of the SFA with the heparin-bonded Viabahn endoprosthesis was compared with use of a BMS. At 2 years, a significantly improved patency rate was observed in patients treated with the heparin-bonded covered stent. However, the improved patency rate had no impact on clinical outcomes or TLR.[39]

High-quality data regarding treatment of infrapopliteal arteries using covered stents are not available.

Atherectomy

Successful endovascular treatment of calcified lesions is still a major challenge. In general, debulking calcified atherosclerotic plaque using atherectomy may result in a more uniform angioplasty result at lower pressures. Consequently, less recoil and dissection may occur, resulting in a decrease of bailout stenting. Debulking atherectomy may also result in disruption of the calcium barrier, optimizing drug delivery and transfer into the arterial wall. To leave nothing behind and obtain long-term patency, atherectomy is used in combination with a DCB for the treatment of complex lesions. Several methods of atherectomy are available, including rotational, directional, excimer laser, and orbital atherectomy. Due to the risk of distal embolization, atherectomy is frequently used in combination with distal filter protection.

The COMPLIANCE 360° trial was a pilot trial showing improved lesion compliance and a decrease of adjunctive stenting using orbital atherectomy in the treatment of calcified femoropopliteal disease.[40] In the EXCITE trial, treatment with excimer laser atherectomy followed by PTA demonstrated superior procedural success, decreased 30-day major events rates, and increased freedom from TLR at 6 months.[41] However, claudicants were predominantly enrolled in this trial. DEFINITIVE LE is a prospective, multicenter, single-arm trial that has enrolled 800 patients treated with directional atherectomy. Subgroup analysis showed promising results in 145 patients following treatment of infrapopliteal artery lesions. In CLI patients, the 1-year primary patency rate was 78% and freedom from major amputation was 93.8%.[42]

OPTIONS FOR CLI PATIENTS UNSUITABLE FOR REVASCULARIZATION

Multiple regenerative and adjunctive therapies have been evaluated in CLI patients without revascularization options. Up to now, angiogenic gene therapy and autologous cell–based therapies in CLI patients have not resulted in an improvement in clinical outcomes.[43,44] The ongoing PACE trial is a phase 3, placebo-controlled RCT evaluating the effect of placenta-derived mesenchymal cell therapy in 246 patients with Rutherford category 5 CLI who are unsuitable for revascularization.[45] In a recent meta-analysis, intermittent pneumatic compression and spinal cord stimulation resulted in a significantly reduced risk of amputation, but the quality of evidence was considered low.[46] According to the DAMO$_2$CLES trial, the addition of hyperbaric oxygen therapy to standard wound care does not improve complete wound healing or limb salvage in patients with ischemic diabetic foot ulcers.[47] A recent meta-analysis showed small beneficial effects of prostanoids for rest pain relief and ulcer healing, but no effect was found on the incidence of amputations.[48] High-quality data assessing the effect of lumbar sympathectomy in CLI patients are not available.

In "no-option" patients, percutaneous deep vein arterialization is being investigated. The PROMISE I trial is a single-arm, multicenter pilot study investigating the feasi-

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bility and effectiveness of the LimFlow stent graft system (LimFlow SA). Promising short-term results in 10 patients have been published. Technical success was 100% and amputation-free survival was 100% at 6 months. Trial enrollment has since been expanded to 35 patients and midterm follow-up (24 months) is expected.[49]

FUTURE PERSPECTIVES

Translation of RCT results into real-world clinical practice can be challenging. Due to strict inclusion and exclusion criteria, high-risk patients and the most advanced lesions are often excluded. In the future, there will always be a demand for independent, large, multicenter, head-to-head trials comparing innovative technologies. A long-term follow-up period will be mandatory to evaluate possible safety issues. Due to the complexity of the CLI patient, who frequently has multilevel disease, trial designs comparing treatment strategies instead of comparing only a single technology in a single vascular segment, including patient-reported outcomes, will become more important. Wound healing, ambulation, and quality of life will be important clinical endpoints in addition to amputation and mortality rates.

Along with RCTs, data from large, prospective, observational studies evaluating the long-term results of treatment strategies, such as the OLIVE registry and the LIBERTY study, will result in risk scores and prediction models to provide guidance for tailor-made revascularization therapy of CLI patients in real-world clinical practice.[50,51] ■

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