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GUIDELINES

PERIPHERAL ARTERIAL DISEASE

Lower extremity arterial disease perspective: IUA consensus document on "LEAD management" Part 2

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Lower limb arterial disease (LEAD) is associated with significant morbidity, including a high percentage of amputation and adverse cardiovascular outcomes. That makes prevention and treatment of LEAD of utmost importance. Several risk factors have been identified in the pathophysiology of LEAD. Modifiable and non-modifiable risk factors for atherosclerosis have been implicated in the development and progression of the disease[1] and they participate in the pathogenesis of LEAD. Non-modifiable risk factors like male gender, age greater than 50 years and family history of vascular disease[2] (Figure 1) need to be carefully considered to assess the level of risk and trigger a faster management of modifiable risk factors. Cigarette smoking and uncontrolled diabetes represent the leading cause in the development and progression of LEAD.

In the first part of consensus on the management of LEAD[3] general principles on the pathogenesis and treatment were discussed. In this second part of the IUA consensus document we discuss the upgrade in the therapy, completing some parts, and in general in the management of the patients with LEAD.

While limb problems themselves are devastating, LEAD is typically a precursor of obstructive atherosclerotic disease elsewhere, which includes the cerebral along with coronary arteries.[4] Indeed, people with LEAD have an elevated incidence of ischemic stroke and myocardial infarction (MI), while also participating in cardiovascular mortality.[5] Furthermore, individuals with coronary artery disease (CAD) together with LEAD have a substantially greater risk of cardiovascular death than CAD alone. Most importantly, LEAD is a considerable burden for patients when it comes to quality of life while participating in financial well-being.

A multitude of options exist for the treatment of LEAD. LEAD management may be categorized into conservative measures aimed at vascular protection[4-7] and surgical interventions either open or endovascular surgery. Vascular prevention includes on one hand measures targeting control of cardiovascular risk factors that represent two groups: lifestyle modification as smoking cessation, regular exercise, diet, weight reduction and medical therapies for the control lipids, hypertension and diabetes. Further, vascular control includes antithrombotic treatment aimed to prevent thromboembolic complications.

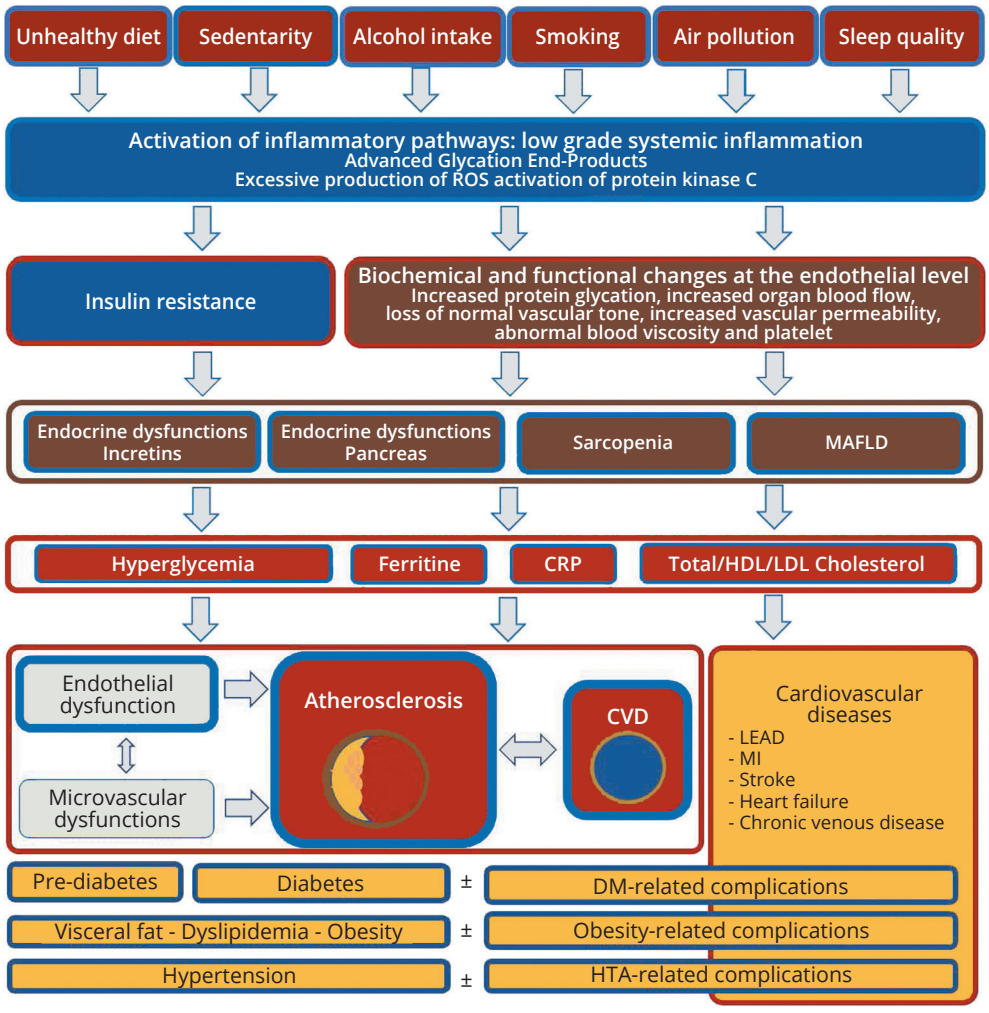

Figure 1.—Modifiable cardiovascular risk factors and their implication on atherogenesis and LEAD development.

The aim of this narrative review is to define the role of individual risk factors and to discuss options of conservative treatment of LEAD.

Modification of risk factors

Smoking

Smoking is a stronger risk factor for LEAD than for coronary artery disease. People who smoked had 4 times more risk to develop LEAD, compared to 2 times more to develop coronary heart disease or 1.8 more risk for stroke.[8]

In smokers, LEAD appears ten years earlier than in non-smokers.[9] Smoking has been shown to promote the progression of symptoms of intermittent claudication and more frequently leads to the development of critical limb ischemia (CLI) as well as the need for surgical intervention.[10] Multiple pathophysiologic mechanisms are involved in atherogenesis in cigarette smokers. This includes endothelial dysfunction[11] and the deterioration of lipoprotein metabolism, coagulation and platelet function. Continuing smoking in peoples with LEAD yields a threefold increased mortality and amputation risk.[12] Smoking cessation is one of the most effective interventions for prevention of adverse cardiovascular events.[9] Benefits of smoking cessation can be seen shortly after stop smoking, particularly in respect to cardiovascular morbidity and mortality. Nicotine replacement therapy has proven to be fairly effective and safe. Bupropion in combination with nicotine replacement therapy has been shown to provide additional advantage. Further, psychological support helps patients to quit smoking.[13]

Dyslipidemia

Dyslipidemia is an established risk factor for cardiovascular disease, including LEAD. Hypercholesterolemia nearly doubles risk for the development of LEAD.[14] The treatment of vascular patients with statins is associated with several beneficial effects including inhibition of progression of local disease and CV events.[15, 16] The guidelines of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) for the management of dyslipidemias in LEAD patients recommended the maximum acceptable dose of high-intensity statins (atorvastatin ≥40 mg/day or rosuvastatin ≥20 mg/day) plus ezetimibe or protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to reach target level of LDLC which is most effective in the prevention of atherosclerotic cardiovascular events.[17] The ESC/EAS guidelines for patients in the very high-risk category (≥10% risk of fatal cardiovascular events including LEAD patient which are at highest risk recommend LDL-C reduction by ≥50% from baseline and an LDLC goal of ≤1.4 mmol/L (≤55 mg/dL)[17] (Figure 1). For patients with a second vascular event in two years, while taking maximally tolerated statin-therapy, an LDLC goal ≤40 mg/dL (≤1.0 mmol/l) may be considered. Lowering of LDLC not only reduces cardiovascular events but also major adverse limb events, including amputations of the order of 25%. Recent systemic review and meta-analyses showed that routine treatment with statins reduced amputations for 41% compared with statin non-use in LEAD patients (P=0.08).[18] Addition of PCSK9 inhibitors to statin treatment results in further reduction in the risk of CV events as well as in the risk of major adverse limb events.[19] Therefore, patients with LEAD need aggressive lipid lowering therapy. Beside LDLC, Lp(a) was proven to be a significant independent risk factor for LEAD and higher levels of Lp(a) were associated with a severe form of the disease.[20] However, in the most of patients with LEAD, hyperlipidemia is undertreated.

Hypertension

Hypertension is one of the major risk factors for atherosclerotic disease, including LEAD. In patients with preclinical and clinical LEAD, hypertension was found in 50% to 92%.[21] The SHEP (Systolic Hypertension in the Elderly Program) study showed that low Ankle-Brachial Index (<0.9) in conjunction with hypertension predicted a two- to three-fold increased risk of CV mortality.[22] The ESC Hypertension guidelines[23] recommend the treatment of hypertension in general population to the target level of systolic blood pressure 120-129 mmHg and the target level of diastolic pressure should be 70-79 mm Hg. For some groups of patients, like subjects over 85 years and patients with significant frailty personalized blood pressure (BP) treatment should be instituted, usually higher target levels of BP are indicated. However, existing guidelines does not recommend different target levels of BP in patients with LEAD in whom intensive BP lowering may contribute to worsening of perfusion of diseased leg. The data indicate that systolic blood pressure <120 mmHg may worsen perfusion of the diseased leg and is related to the high rate of CV events. Similarly, patients with diastolic blood pressure <70 mmHg are at greater risk of LEAD events.[24] Therefore, there is a J-shaped relationship between systolic blood pressure and the rate of primary outcomes. Any class of anti-hypertensive drugs, including beta-blockers, can be used for the treatment of hypertension in patients with LEAD. Angiotensin converting enzyme (ACE) inhibitors may have some additional benefit over other anti-hypertensive drugs. They may improve perfusion of the diseased leg, walking distance and claudication symptoms.[25] Therefore, treatment of increased blood pressure is indicated also in patients with LEAD, but systolic BP<120 mmHg and diastolic BP<70 mmHg may contribute to adverse limb outcomes.

Consequently, LEAD patients most probably need different target levels of BP than general population.

Diabetes mellitus

Apart from smoking, hyperglycemia and diabetic metabolic disorders are the most important risk factors for lower extremity arterial disease (LEAD) progression. Type 2 diabetes (T2D) is a multifocal disease characterized by the occurrence of insulin resistance and endocrine dysfunctions (failure of β-cells, increased pancreatic alpha- cell function and decreased incretin secretion) resulting in hyperglycemia.[26, 27] Numerous mechanisms are involved in T2D development such as oxidative stress, endoplasmic reticulum stress, amyloid deposition in the pancreas or ectopic lipid deposition in skeletal muscle, liver and pancreas.[27] The occurrence of diabetes mellitus exposes the entire body to higher levels of glucose which are responsible of a series of biochemical, structural and functional changes in mature vascular endothelial cells leading to endothelial dysfunction (ED).[28] ED is usually observed early in the pathophysiology of DM and considered as a link between classical cardiovascular risk factors (smoking, hypertension, dyslipidemia, obesity, sedentary behavior) and diabetic microangiopathy.[29, 30] Diabetes elevates the risk of LEAD by a factor of 3 to 4 and the risk of clau-

dication by a factor of 2 which is also proportional to the quality of glucose control measured with HbA1c. Every HbA1c increase in the magnitude of 1% is associated with a 28% increase in the relative risk for manifest LEAD.[31] A subgroup analysis of United Kingdom Prospective Diabetes Study (UKPDS) showed a lower amputation rate with lower levels of HbA1c (23). Among people with type 2 diabetes (PWT2D) under intensified treatment the Steno-2 study observed a 25% relative risk reduction in amputation rates and a 10% decrease in vascular interventions over 7 years[32] and a median of 7.9 years gain of life.[33] The inverse relation is observed in case of active smoking, which is significantly associated with an increased risk of cardiovascular events and total mortality in case of T1D and T2D.[34] The relationship between active tobacco use and diabetic complications, cardiovascular events, and mortality is well established.[35] Pan *et al.* have even shown in a large meta-analysis among people with diabetes (T1D and T2D) that the higher adjusted relative risk associated with active smoking was for LEAD (2.15; 1.62-2.85; 95% CI).[36]

In case of diabetes the schematic representation of the cardiovascular continuum from normal condition to the presence of LEAD considers that ED is the earliest vascular abnormality which tends to worsen in parallel with the occurrence of diabetes related complications and the occurrence of cardiovascular risk factors, including chronic venous disease[37-39] (Figure 1). Finally, PWT2D suffering of LEAD tend not to receive optimal therapy for secondary prevention, meaning less aspirin, angiotensin-converting enzyme inhibitors and beta-blockers. Moreover, the first occurrence of major adverse cardiovascular events such as death from cardiovascular causes, nonfatal MI, or nonfatal stroke have been observed to occur more frequently in patients with LEAD.[40] Therefore, it is strongly recommended that patients with diabetes should be screened for LEAD and all LEAD patient should be screened for diabetes and effectively treated in the case of a proven diagnosis.

Therapeutic strategies

Lifestyle management remains the cornerstones of diabetes management which should be based on a person-center approach with the achievement of four main objectives: 1) medication for glycemic management with metformin as first line therapy; 2) weight management; 3) cardio-renal protection (with glucagon like peptide 1 receptor agonists: GLP-1 RAs and sodium glucose cotransporter-2 inhibitor(s): SGLT2i); and 4) cardiovascular risk factor management.[41-45] In patients with type 2 diabetes at high risk of cardiovascular disease rapid introduction of SGLT2i or GLP1-RAs independently of glucose control should become a standard of care.[41] In case of established atherosclerotic cardiovascular disease the introduction of GLP-1 RAs with cardiovascular benefits is strongly recommended. This class of anti-diabetic drugs has shown superiority in terms of care in PWT2D and concomitant LEAD comparatively to the other available drugs (Table I), and a combine therapy with iSGLT2 and GLP-1 agonist may be considered for additive reduction.

Management of different stages of LEAD

Atherosclerotic peripheral arterial disease is a part of systemic vascular disorder and predictor of CV morbidity and

Table I.—*Glucagon-like peptide 1 receptor agonists on lower extremity arterial disease in people with type 2 diabetes mellitus.*

Study name GLP-1 RAs	Type of study N. of patients	Primary outcome	Result and comment
STRIDE Semaglutide	RCT (phase 3) PWT2D and symptomatic LEAD	Change in maximum walking distance	End of study 5.07.2024
SUSTAIN Semaglutide	RCT PWT2D ≥50 years and established cardiovascular disease or chronic kidney disease (> stage 3) ≥60 years with at least one cardiovascular risk factor GLP-1 RA (N.=1648) Placebo (N.=1649)	First occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke Secondary outcome: revascularization (peripheral or coronary)	GLP-1 RA group had lower rates of peripheral or coronary revascularization (HR 0.65, 95% CI: 0.50-0.86; P=0.003)
SELECT Semaglutide[45]	RCT Patients' age ≥45 years; BMI ≥27 kg/m^2; prior myocardial infarction (MI), stroke, or peripheral arterial disease with claudication and Ankle-Brachial Index <0.85, prior revascularization, or amputation GLP-1 RA (N.=8803) Placebo (N.=8801)	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis	Reduced rate of primary cardiovascular endpoint in GLP-1 A group, (N.=569, 6.5%) *vs*. in the placebo group (N.=701, 8.0%; HR=0.80; 95% CI: 0.72-0.90; P<0.001) *Post-hoc* analysis may give further information about the patients with LEAD

mortality. Therefore, it should be treated as aggressively as coronary artery disease. Risk factors modification represents the cornerstone of treatment of all stages of LEAD.

Screening and diagnosis

Early detection of LEAD, before the onset of symptoms is mostly desirable for every patient and highly wanted among people with diabetes to prevent the occurrence of diabetic foot.[35] Despite inter-society consensus recommending to regularly inspect and examine the at-risk foot, clinical implementation remains low.[5, 6, 9] All specialties agree about the usefulness of performing an exhaustive interview including history of decreasing walking speed, leg fatigue, and claudication as well as a clinical evaluation of the vascular status.[3, 9] Foot examination should include inspection of the skin, examination of eventual deformities, and 10-g monofilament or vibration testing to evaluate the presence of sensory deficit. Vascular status should include palpation of pedal pulse and recent publications advocate for active screening of chronic venous disease (corona phlebectatica), the occurrence of LEAD been an independent risk factor for chronic venous disease.[46] Fontaine or Rutherford classification are common grading classification for LEAD and ischemia.[3] Candidates for ultrasound or advanced LEAD testing include those with 1) atypical LEAD symptoms or absence of pulse at lower extremities; 2) abnormal ankle-brachial index or any occurrence of foot problems.

Preclinical stages

Also, preclinical stages of LEAD are associated with increased risk for CV events. This group of patients should be treated as patients with symptomatic LEAD. Patients should be guided to benefit of preventive care services, smoking cessation counseling and nutritional therapy optimization. It includes a comprehensive approach to eliminate risk factors and to improve physical activity.

Glucagon like peptide 1 receptor agonists (GLP-1 RAs)

GLP-1 RAs are now extensively used to help people losing weight and to improve metabolic health independently of the occurrence of diabetes.[45] Data are still missing to confirm that GLP-1 RA use in patients with preexisting LEAD but without diabetes permit to reduce cardiovascular mortality and subsequent events,[43] however the results of the SELECT study confirmed that patients with preexisting cardiovascular disease and overweight/obesity gain to be treated with high dose semaglutide.[44]

Intermittent claudication (IC)

IC represents the most frequent form of symptomatic LEAD. These patients need intensive management of all modifiable risk factors, including smoking cessation, treatment of dyslipidemia, hypercholesterolemia, hypertension, modification of life style and supervised exercise.

Supervised exercise

Supervised exercise is the most effective conservative therapy for improving walking activity and preventing morbidity and disability in patients with IC. Supervised exercise therapy should be offered as first line treatment to all patients with symptomatic LEAD,[47] with the exception of critical limb ischemia. Also in patients undergoing revascularization supervised exercise programs should be included as adjuvant therapy. When walking is not an option, alternative training modalities including arm cranking, cycling and strength training should be performed. Physical exercise should be implemented several times per week and in progressive process increasing exercise intensity as tolerated.[47] The training program duration should last a minimum of 3 months.

Antithrombotic treatment

The management of symptomatic LEAD includes also antiplatelets monotherapy: either aspirin 75-100 mg daily or clopidogrel 75 mg daily. Antithrombotic Trialist Collaboration (ATC) study in patients with IC demonstrated a significant reduction in CV events with antiplatelet therapy.[48] The two years of treatment of 1000 high risk patients with aspirin 75-150 mg resulted in reduction of 22 CV events ($P<0.004$).[48] However, only one third of the LEAD patients included in this meta-analysis were treated with aspirin, while the rest received other antiplatelet drugs. Meta-analysis of randomised trials of the efficacy of aspirin for the prevention of CV events in LEAD patients, showed that aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary end points of CV events. Among 5269 participants, CV events were experienced by 251 (8.9%) of 2823 patients taking aspirin alone or with dipyridamole and by 269 (11%) in the control group (pooled relative risk 0.88, 95% CI, 0.76-1.04). Aspirin therapy was associated only with reduction in the secondary outcome of non-fatal stroke.[49] Similarly, also in the AAA[50] trial, aspirin did not significantly reduce CV events.[51] In the guidelines aspirin remains a basic antiplatelet drug for treatment LEAD, but with limited efficacy. Clopidogrel is an effective alternative to aspirin for prevention of CV events in symptom-

atic LEAD patients. In patients who are non-responders to clopidogrel ticagrelor is indicated. In the CHARISMA trial the dual antiplatelet treatment (aspirin plus clopidogrel) was not more effective than aspirin alone.[52] The COMPASS trial showed that a low dose new oral anticoagulant drug -rivaroxaban combined with aspirin in LEAD patients significantly reduced CV events including limb-threatening ischemia and limb amputation. Fewer CV events were observed in patients treated with rivaroxaban plus aspirin in comparison to aspirin alone group (379 patients [4.1%] *vs*. 496 patients [5.4%], HR 0.76; 95%, CI 0.66 to 0.86; P<0.001).[53]

Pharmacological treatment of gait capability in patients with IC

Different pharmacological agents were approved for treatment of IC. The first approved drug was pentoxifylline – a competitive non-selective phosphodiesterase inhibitor. Recently cilostazol, a phosphodiesterase inhibitor that also has antiplatelet and vasodilatory effects, is most frequently used. However, conflicting results were found regarding pharmacological treatment of IC.[54] Some studies and meta-analysis of 8 randomized studies showed that cilostazol improves claudication symptoms and walking distance in patients with LEAD.[55] Therefore, cilostazol can be used as an adjunctive therapy in patients with LEAD.

In recent years, sulodexide, as a mixture of glycosaminoglycans from porcine intestinal mucosa containing fast-moving heparin (80%) and dermatan sulfate (20%) is reaching a growing importance in LEAD treatment. The drug is targeting the inflammatory response, endothelial dysfunction, and the associated changes within the glycocalyx and the extracellular matrix as well as modulating the coagulability of blood.[56-58] *In-vivo*, sulodexide has been shown to promote arterial relaxation via a mechanism involving endothelium-dependent NO production.[59, 60] Results from clinical studies demonstrated that the activity of sulodexide is multidirectional and includes an effect on the hemostasis system, a reduction in thrombin generation, a profibrinolytic effect, and inhibition of pro-coagulation microparticle generation. It also has a documented effect on normalization of blood viscosity and lipid levels.[59-66] Clinical efficacy of sulodexide was documented in numerous vascular disorders, either venous or arterial.[67] Sulodexide has been shown to improve pain free and maximum walking distance in LEAD patients with intermittent claudication.[57, 58] Clinical efficacy of sulodexide include also alleviation of symptoms in patients with chronic arterial disease and a beneficial effect in diabetic complications as retinopathy, diabetic foot, trophic ulcers, and nephropathy.[56-67]

Treatment of critical limb ischemia

CLI represent clinical syndrome of ischemic pain at rest and tissue loss. CLI is related to high risk of limb loss and CV events, therefore it should be urgently treated. The overall aims of management of CLI are: relief of ischemic pain, heal ulcers, prevent limb loss and improve quality of life. Individuals with CLI are known to be at high risk of CV disease. They have a 1-year mortality rate of approximately 25%, but this is increased to 45% in those who have undergone amputation.[68] Therefore, they need aggressive risk factor management.

Patient with suspicion of CLI based on clinical presentation (rest pain in the distal food, pathological hemodynamic parameters in diseased leg-ankle systolic pressure <50 mmHg) need advanced diagnostics for determination of feasibility and approach to revascularization. Arterial lesions can be assessed using contrast enhanced tomography (CT), ultrasonography or magnetic resonance arteriography (MRA). Revascularization is the most effective treatment of CLI which in most cases provide immediate improvement of blood supply. Balloon angioplasty and stenting form the back-bone of endovascular treatment. In patients with multilevel disease surgical revascularization, preferably with autologous vein is indicated.[68] In patients unsuitable for revascularization, failed revascularization and in patients with extensive tissue loss or infection an amputation is indicated.

Medical treatment of CLI

Medical treatment of limb ischemia themselves is challenging. Prostanoids may have efficacy for treating rest pain and for ulcer healing. Prostanoids prevent platelet and leucocytes activation and protect the vascular endothelium. Iloprost showed favorable results in reducing the risk of mayor amputation, but long-term follow- up data regarding disease progression are lacking.[69, 70] In a subsequent double-blind placebo-controled trial of PGI2 analogue taprostene the effect of the drug was investigated.[71] However, there was not statistically significant effect on pain relief and healing of ulcers compared with placebo. Also, the number of angiogenic growth factors have been studied, but efficacy results have been mixed. Treatment with stem cells also showed some potential benefit, but further controlled studies are needed to demonstrate clear benefit[72] (Figure 2).

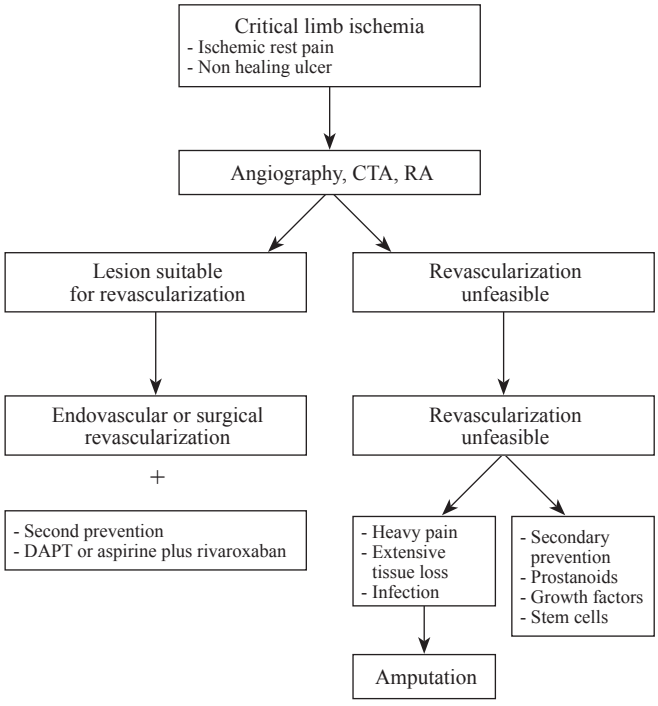

Figure 2.—Management of critical limb ischemia.

Therapy and surveillance after revascularization

To prevent thrombosis or restenosis after endovascular intervention low-dose aspirin is usually given for life to prevent thrombosis of treated segment and CV events. Dual antiplatelet therapy (DAPT) (aspirin plus clopidogrel) should be given for at least 1 month after drug-coated balloon angioplasty and for 3 months after either drug eluting or cowered stent implantation. Following the under- knee bypass grafting DAPT was shown to reduce the graft occlusion and above-knee amputation of the affected limb, but only in patients receiving prosthetic but not venous graft.[73] VOYAGER study which compared rivaroxaban 2.5 mg twice daily plus aspirin and aspirin alone in patients who had undergone lower extremity revascularization showed significant reduction in primary outcomes in the rivaroxaban group (acute limb ischemia, major amputation, myocardial infarction, ischemic stroke or cardiovascular death).[74] Therefore, combination therapy with aspirin and rivaroxaban should be considered for post-intervention period. Taken together, for patients with extensive LEAD, especially those who have undergone revascularization for LEAD addition of rivaroxaban to the treatment regimen may be considered.[75]

Emerging therapy

Despite many decades of exploratory attempts, medicinal interventions to enhance perfusion throughout the distal limb prove to be of poor value. The scene in which recent studies of anticoagulants (*e.g.*, rivaroxaban) and intensive lipid-lowering (which include PCSK9 [proprotein convertase subtilisin/kexin type 9] inhibitors) that have successfully lowered major cardiovascular and limb events in LEAD populations, chronic ischemia of the limb continues to be largely resistant to medical therapy. Experimental efforts to enhance limb results have included the infusion of angiogenic cytokines (such as those produced as recombinant proteins or in the form of gene therapy) and the use of cell treatments.[76] Although early angiogenesis as well as cell therapy research were encouraging, these studies lacked appropriate control groups, and bigger randomized clinical trials have failed to produce meaningful effects.

Promoting the creation of new blood vessels (angiogenesis) as well the production of wholly new ones (vasculogenesis) has great promise for restoring blood supply to ischemic limbs.[76] Gene therapy, cell-based therapeutics, and administration of growth factors are being researched in this field.[76] Early trials on utilizing plasmid DNA that encodes for VEGF (vascular endothelial growth factor) to stimulate angiogenesis in LEAD patients have shown some promise, with improved blood flow noted in roughly 30% of participants.[77]

Studies are currently being conducted regarding the creation and optimization of nanoparticle delivery systems specifically to gain LEAD treatment, with potential for enhancing blood flow by somewhere in the range of 20-30% in preclinical models.

Exosomes are gradually tiny membrane sacs released by cells that carry various molecules, which may involve proteins and RNA. These exosomes might have the potential to be harnessed for the transportation of therapeutic cargo that would encourage tissue repair as well as angiogenesis in PAD patients. Research is currently in its early stages, but additionally, initial results show promise for helping to increase new blood vessel formation by as much as 15% in animal models.[78]

The combination of existing therapies like revascularization and accepting medications, cell therapy, as well as gene therapy might make available synergistic benefits, throughout the process to more effective LEAD management.

Early clinical trials have shown that combining revascularization alongside cell therapy might raise the average walking distance by 30-40% when compared to revascularization alone.[78]

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The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
All authors read and approved the final version of the manuscript.

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