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GUIDELINES

PERIPHERAL ARTERIAL DISEASE

# Lower extremity arterial disease perspective: IUA consensus document on "lead management"

## Part 1

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## ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) is defined as coronary heart disease (CHD), cerebrovascular disease, or lower extremity arterial disease (LEAD) also named peripheral arterial disease (PAD). ASCVD is considered to be of atherosclerotic origin and is the leading cause of morbidity and mortality mainly for individuals with diabetes mellitus (DM). In this consensus document of the International Union of Angiology the authors discuss epidemiology, risk factors, primary and secondary prophylaxis, the correlation between diabetes mellitus and LEAD, conservative and surgical treatment.

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**Key words:** Lower extremity; Peripheral arterial disease; Atherosclerosis; Diabetes mellitus.

## Introduction

Atherosclerotic cardiovascular disease (ASCVD) is defined as coronary heart disease (CHD), cerebrovascular disease, or lower extremity arterial disease (LEAD) also named peripheral arterial disease (PAD). ASCVD is considered to be of atherosclerotic origin and is the leading cause of morbidity and mortality mainly for individuals with diabetes mellitus (DM).[1]

Atherosclerosis is considered a generalized disease. Similar or identical etiopathogenetic mechanisms and risk factors are involved in various atherosclerotic diseases, and the positive effects of preventive measures on atherogenesis in different parts of the arterial system were shown. However, until now, great emphasis has been placed on the aggressive pharmacological management of coronary artery disease (CAD), while less attention has been paid to the management of peripheral arterial disease (LEAD), despite its significant morbidity and mortality. Data on the efficacy of preventive measures in LEAD patients have mostly been gained from subgroup analyses from studies devoted primarily to the management of coronary patients. These data have shown that treatment of risk factors for atherosclerosis with drugs can reduce cardiovascular events also in patients with LEAD. However, effects of some preventive procedures in LEAD patients differ from coronary patients.[2]

Although the prognosis of LEAD is relatively benign regarding viability and survival of the affected limb, all patients with LEAD are at increased risk of myocardial infarction, ischemic stroke and cardiovascular death. Several studies indicated a two- to three-fold greater mortality in patients with LEAD than in age-matched controls with normal ankle-brachial index (ABI), with a five-year mortality of about 30% in patients with LEAD.[3]

## Epidemiology and risk factors

### Prevalence and incidence

LEAD affects over 40 million people in Europe[4] and appears to be 2 to 4 times more prevalent in people with type 2 diabetes (PWT2D) than in the general population.[5] Its prevalence ranges from 1.2% to 20% according to its definition. In the Action in Diabetes and Vascular Disease (ADVANCE) trial, the baseline prevalence of LEAD was 4.6%.[6] In the same trial, the incidence of LEAD was reported in 1.2 per 100 patient-years when it was 3.7 per 100 in the Fremantle Diabetes Study. The prevalence of LEAD rise up to 20% when its occurrence rely on an abnormal Ankle-Brachial Index (ABI).[7]

LEAD prevalence and incidence in PWT2D are strongly associated with the classical cardiovascular risk factors and diabetes duration.[7] The results of the UKPDS (UK Prospective Diabetes Study) have shown a prevalence of 1.2% at diagnosis and 12.5% after 18 years of diabetes evolution.[8]

### Prognostic and risk factors

LEAD is rapidly progressing worldwide due to demographic expansion, aging, increasing prevalence of tobacco smoking, sedentary behavior, hypertension, dyslipidemia, and type 2 diabetes.[4] Among PWT2D the occurrence of LEAD is associated with a high risk of morbidity compared with people without diabetes. The evidence show that LEAD is associated with a 4 to 5 folds increased risk of non-traumatic lower limb amputation (LLA), cardiovascular disease (CVD), and mortality.[9, 10] However, it remains less studied than other diabetes related complications and only rare randomized control trial have evaluated it as a primary outcome.

Among PWT2D, 5-year mortality after non-traumatic major amputations of the lower extremity is very high.[11] Whether it is a below-the-knee or above-the-knee amputation, mortality ranges from 40% to 82% to 40% to 90% respectively.[12]

## Primary and secondary prophylaxis

LEAD patients need intensive prevention and management of risk factors.

### Smoking

Cigarette smoking is one of the most important risk factors for peripheral arterial disease. Smoking increases the risk of LEAD by several fold and is a more influential risk factor for LEAD than for coronary artery disease. Smoking is associated with severity of LEAD, a higher amputation rate, peripheral bypass occlusion and mortality.[13] Multiple pathophysiologic mechanisms may account for the prevalence of atherosclerosis in cigarette smokers. These include abnormalities of endothelial function, lipoprotein metabolism, coagulation, and platelet function. Smoking cessation decreases the risk of cardiovascular morbidity and mortality, and may improve functional capacity in patients with LEAD. Therapies to promote smoking cessation include counselling, nicotine replacement, and bupropion. Smoking cessation as a modifiable risk factor in patients with LEAD is of utmost importance

### Lipid lowering

Hyperlipoproteinemia is also a relevant risk factor for LEAD. Hypercholesterolemia was found in 45% to 59%

of symptomatic LEAD patients, and a significant benefit of statin treatment on cardiovascular and cerebrovascular events has been shown in this group of patients. Routine statin use in vascular patients, either managed conservatively or undergoing open surgical or endovascular procedures, is associated with several beneficial effects.[14] A meta-analysis, the Cholesterol Treatment Trialists' Collaboration, showed that each 1.0-mmol/L decrease in low-density lipoprotein cholesterol by statin treatment is associated with a 12% reduction in all-cause mortality.[14]

The extent to which LDL values should be lowered in LEAD patients remains unclear, no prospective interventional studies have so far been carried out in LEAD alone patients. Beside statins PCSK9 inhibitors were shown to be effective in management of hypercholesterolemia in LEAD patients. The Fourier study[15] which enrolled 27,564 patients of which 13.2% (3,642) had symptomatic LEAD, all of whom were on statin therapy evaluated benefit in the preplanned LEAD subgroup. The full study of evolocumab, showed a significant decrease in the combined CV endpoints of MI, stroke, and death. In the LEAD subgroup, evolocumab significantly reduced the primary endpoints.[15]

European Society of Vascular Medicine has updated evidence on the management on dyslipidemia in patients with LEAD.[16] Guidelines recommend a low-density lipoprotein cholesterol (LDLC) goal of more than 50% reduction from baseline and <1.4 mmol/L (<55 mg/dL) in LEAD patients. As demonstrated by randomized controlled trials, lowering LDL-C not only reduces cardiovascular events but also major adverse limb events, including amputations, of the order of 25%. Addition of ezetimibe or a PCSK9 inhibitor further decreases the risk of cardiovascular events, and PCSK9 inhibition has also been associated with reduction in the risk of MALE by up to 40%. Furthermore, statin-based treatment improved walking performance, including maximum walking distance, and pain-free walking distance.[16]

## Managing hypertension

Hypertension is one of the most important risk factors for atherosclerotic disease, including LEAD. In patients with preclinical and clinical stages of LEAD, hypertension was found in 50% to 92%. Follow-up data from the Framingham Study found a 2.5- to 4-fold increased risk of LEAD in men and women with hypertension.[17] Nevertheless, not all studies have demonstrated a clear relation between hypertension and LEAD. However, most of the findings support that the presence of hypertension additionally increases the risk of cardiovascular events in LEAD patients, as was confirmed in the SHEP (Systolic Hypertension in the Elderly Program) study, where a low ankle-brachial index (<0.9) in an older population in conjunction with hypertension predicted a two- to three-fold increased risk of cardiovascular mortality.

Any class of antihypertensive drugs can be used to treat hypertension in most patients with LEAD, including beta blockers. Although a meta-analysis of 11 randomized control studies showed that beta (β) adrenergic blocker therapy did not worsen intermittent claudication,[18] starting the treatment of hypertension in LEAD patients with β blockers can provoke the onset of intermittent claudication and vasospasms. β Blockers should be carefully prescribed to LEAD patients with critical limb ischemia and vasospastic disorders. Dihydropyridine calcium channel blockers are appropriate for hypertensive patients with LEAD. Carvedilol and nebivolol are also effective drugs. However, in patients with LEAD, there is no conclusive, outcome-related data favoring the use of carvedilol or nebivolol over other beta blockers. ACE inhibitors exert various beneficial actions on the cardiac and vascular structure and function, beyond their blood pressure-lowering effects.[19]

The antiatherogenic effect of the ACE inhibitor ramipril was confirmed in the Heart Outcomes Prevention Evaluation (HOPE) study, where ramipril provided equal relative protection against myocardial infarction, stroke and cardiovascular death in patients with LEAD as in other high-risk groups.[11] The absolute benefit of ramipril was greater in patients with a reduced ankle-brachial pressure index than in those with a normal ankle-brachial pressure index.

In people with obesity, the accumulation of dysfunctional perivascular adipocytes is associated with an increased systemic inflammation and higher level of ED.[11] Hypertension is associated with higher circulating levels of paracrine factors like ET-1, a potent vasoconstriction factor, in response to endothelial cell damage[20] or exercise induced ischemia.[21]

## Diabetes mellitus

Apart from smoking, diabetic metabolic disorders are the most important risk factors for LEAD progression. Every $HbA_{1c}$ increase in the magnitude of 1% is associated with a 28% increase in the relative risk for manifest LEAD. Diabetes elevates the risk of LEAD by a factor of 3 to 4 and the risk of claudication by a factor of 2. A subgroup analysis of United Kingdom Prospective Diabetes Study (UKPDS) showed a lower amputation rate with lower levels of $HbA_{1c}$.[8] Among type 2 patients with diabetes 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.[22]

Therefore, it is 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 of diabetes.

### Antiplatelet drugs

Represent one of the basic options for the management of patients with various atherosclerotic diseases. Aspirin is the oldest and most often prescribed antiplatelet drug. The efficacy of aspirin depends probably on the type or location of atherosclerotic disease. It seems that it is most effective in coronary patients with clinically unstable disease, and its efficacy is uncertain in LEAD patients. One of the first meta-analyses[23] indicated that antiplatelet drugs also significantly reduce cardiovascular events in patients with LEAD. However, only one third of the LEAD patients included in this meta-analysis were treated with aspirin, while the rest received other antiplatelet drugs.

Also meta-analysis of randomized trials of the efficacy of aspirin for the prevention of cardiovascular events was performed in patients with LEAD only. Randomized trials of aspirin therapy with or without dipyridamole involved 5269 individuals. Aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary endpoints of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke and cardiovascular death). Only a significant reduction in non-fatal stroke was observed.[24]

The effect of aspirin on cardiovascular events in patients with preclinical LEAD was studied in the Aspirin for Asymptomatic Atherosclerosis (AAA) trial.[25] This double-blind randomized controlled trial included 3350 subjects with a low ankle-brachial index (ABI) (≤0.95). Participants were followed for 8.2 years. No statistically significant difference in endpoints was found between the subjects treated with aspirin (100 mg) and the placebo group.

Clopidogrel and ticagrelor were shown to be more effective than aspirin. Clopidogrel is thus an effective alternative to aspirin for prevention of cardiovascular events in symptomatic LEAD. In patients who are non-responders to clopidogrel, ticagrelor is indicated. Dual antiplatelet treatment (DAPT) with aspirin and ticagrelor in patients with coronary artery disease and concomitant LEAD significantly decreased the rate of major adverse cardiovascular events, including adverse limb events.[26] However, in the CHARISMA trial, aspirin and clopidogrel were not more effective than aspirin alone.[27]

The new antiplatelet drugs prasugrel, ticagrelor and picotamide seem to be more effective than aspirin in LEAD patients, particularly in diabetic patients with LEAD. A novel antagonist of protease-activated receptor (PAR)-1, to the primary receptor for thrombin on human platelets, on vascular endothelium and smooth muscle cells was used in patients with different atherosclerotic disease. Vorapaxar in LEAD patients did not reduce the risk of cardiovascular death, myocardial infarction or stroke.[28] However, vorapaxar significantly reduced the rates of hospitalization for acute limb ischemia and peripheral artery revascularization. The beneficial effects of PAR-1 antagonists on vascular events were accompanied by an increased risk of bleeding.[28]

### Anticoagulants and combination with antiplatelets

There is no indication for full dose INR lowering oral anticoagulation with vitamin K antagonists in patients with LEAD, provided that there is no acute embolic event. However, the effect of a low dose antithrombotic therapy with the new oral anticoagulants in combination with ASA has been investigated. In the COMPASS trial which included patients with CAD and LEAD, rivaroxaban and aspirin alone and in combination were studied. Those assigned to rivaroxaban (2.5 mg twice daily) plus ASA 100 mg daily, had a 24% better total survival and cardiovascular outcome but more major bleeding events than those assigned to aspirin alone.[29] Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. The net benefit was 22% overall risk reduction of the stable CAD/LEAD population. Besides the 28% general survival benefit, an additional significant (46%) reduction in major adverse limb events including major amputation for ASA 100 mg/d combined with rivaroxaban 2×2.5 mg/d compared to ASA 100 mg/d and placebo was seen.[29]

## LEAD patients and diabetes mellitus

### Pathophysiological mechanisms of LEAD in diabetes mellitus

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.[30, 31] 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.[32]

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.[33, 34] Endothelial dysfunction (ED) can be defined as an abnormal action of the endothelium toward reduced vasodilation, and pro-inflammatory and prothrombotic properties.[35] 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.[36] High fat diet, elevated protein intake as well as glucose excursions can trigger ED by stimulating increased generation of reactive oxygen species (ROS).[37, 38] Mechanisms leading to endothelial damage in DM, independent of the damage due to other cardiovascular risk factors, include insulin resistance, hyperglycemia and low-grade systemic inflammation.[35] Impaired endothelium-dependent vasodilation is highly prevalent in PWT2D and it is usually accepted that ED not only precedes atherogenesis, but also predispose to arterial thrombosis.[38] Moreover, all these factors lead to the activation of inflammatory pathways which further concur to worsen hyperglycemia[39] and the occurrence of DM related complications like LEAD.[40]

Nativel *et al*. have observed an association between an elevated concentration of TNFR1 and IMA and the risk of major LEAD confirming in PWT2D that ED is related to an excess-risk of LEAD.[41]

Finally, due to the frequent association of DM with other cardiovascular risk factors, including obesity, hypertension, and dyslipidemia, impairment of endothelium functions and the development of vascular disease can also be triggered by the secretion of paracrine factors. Perivascular adipocytes, not only endothelial cells, release paracrine factors in the vascular wall.

In conclusion, in PWT2D 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 (Figure 1).

## Screening and diagnosis

Early detection of lower extremity arterial disease (LEAD), before the onset of symptoms is mostly desirable in case of DM and highly wanted to prevent the occurrence of diabetic foot.[42]

There has been continued debate regarding the reliability of vascular screening in diabetes. International guidelines recommend to regularly inspect and examine the at-risk foot.[42] The American Diabetes Association suggests performing an exhaustive interview including history of decreasing walking speed, leg fatigue, and claudication as well as a clinical evaluation of the vascular status.[43] 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

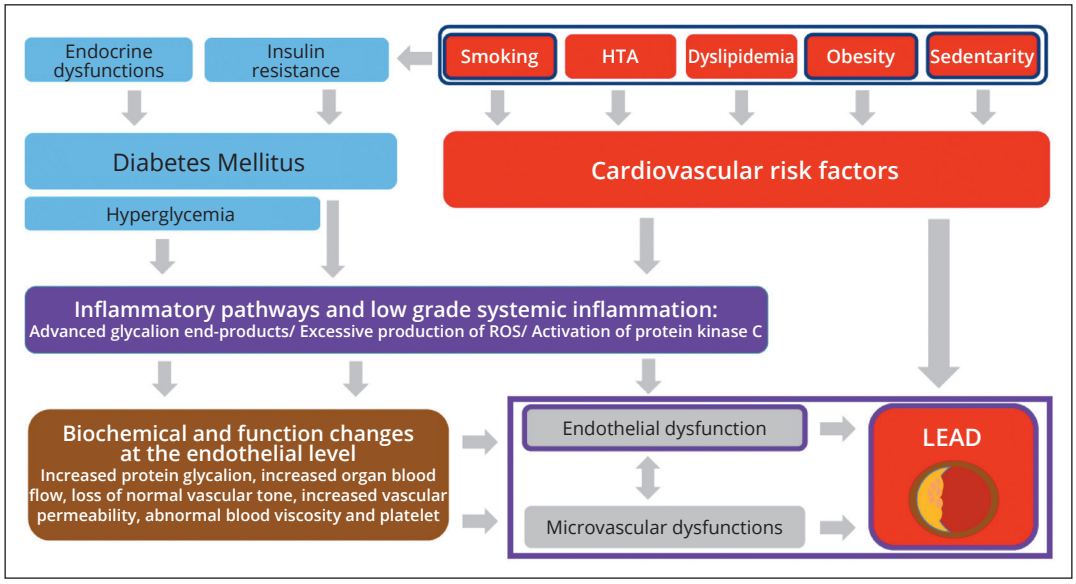


Figure 1.—Pathophysiology of LEAD and diabetes mellitus.

pulse. To grade LEAD presentation, ADA recommend using the Fontaine or Rutherford classification.[43]

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.

### Therapeutic strategies

Lifestyle management remains the cornerstones of diabetes management. Patients should be guided to benefit of preventive care services, smoking cessation counseling and nutritional therapy optimization. A comprehensive approach to the reduction in risk of diabetes-related complications is recommended.

### Anti-diabetic treatment

The targets of the treatment are the intensive *versus* standard glucose control and Insulin-sensitizing *versus* insulin-providing therapy.

In patients with type 2 diabetes metformin can be started as first line therapy if eGFR as long as eGFR is >45 mL/min and metformin should not be discontinued as long as eGFR is >30 mL/min/1.73 $m^2$.

Metformin should be stopped in case of severe intolerance, unstable heart failure or eGFR <30 mL/min/1.73 $m^2$. Metformin should be suspended when at risk of acute dehydration, acute kidney disease and before radiological procedure with iodine contrast.

In patients with type 2 diabetes and chronic kidney disease defined as (micro-albuminuria and eGFR <60 mL/min) and without known established atherosclerotic cardiovascular disease the introduction of iSGLT2 is recommended. These patients are at very high risk to develop LEAD.

In patients with type 2 diabetes and at high risk of cardiovascular disease (ACE guidelines) or with established atherosclerotic cardiovascular disease the introduction of GLP-1 agonist with cardiovascular benefits is recommended.

In patients with type 2 diabetes and multiple risk factors a combine therapy with iSGLT2 and GLP-1 agonist may be considered for additive reduction.

Despite younger age and substantial risk of future major CV events, PWT2D and established LEAD tend to receive less intensive secondary preventive therapy.[44]

## Conservative treatment of lower extremity arterial disease

The conservative treatment of LEAD should consist of two, following methods:

- non-pharmacological management;
- pharmacological management.

The non-pharmacological management of LEAD patient is the foundation of the therapeutic process and translates into reduced cardiovascular (CV) risk, improved prognosis, and better patients functioning.[45-47] Modification of the risk factors profile may contribute to the reduction of the severity and progression of atherosclerosis as well as to a delay in the onset of complications. Study results show that the management of LEAD patients, both non-pharmacological and pharmacological is less intensive than the management of patients with coronary artery disease or cerebrovascular disease.[48]

The non-pharmacological management for all types of atherosclerotic disease is mostly related to lifestyle modification, such as smoking cessation, improved physical activity and loos of body weight.[49-52]

### Smoking

Smoking cessation is recommended in all LEAD patients. Those who smoke or use other forms of tobacco should be educated at every visit regarding the need to quit smoking. Smoking LEAD patients should be helped with an established plan to quit smoking consisting of pharmacotherapy (*i.e.* varenicline, bupropion and/or nicotine replacement therapy) and/or referral for a smoking cessation program. LEAD patients should avoid exposure to environmental smoke at work, home, and public spaces.[52, 53]

### Physical activity

In patients with intermittent claudication the walking exercise is the most effective, non-invasive therapy for improving maximal and pain free walking distances. While both home-based and supervised treadmill walking exercise have been shown to improve pain-free and maximal walking distance in LEAD, most randomized trials of walking exercise in patients with PAD have studied supervised treadmill exercise.[54-56] Alternative cardio workout strategies such as upper body ergometry, cycling and walking until pain occur or low-intensity training, preventing moderate to maximum claudication, may be beneficial in symptomatic patients.[52] At least 150 minutes of moderate-intensity aerobic training per week (30 minutes 5 times a week) or 75 minutes of high-intensity aerobic training per week (15 minutes 5 times a weak) or a combination of the above are proposed.[57]

### Diet

LEAD patients are recommended to follow healthy diet. The low saturated fat content, with particular focus on

whole-grain products, vegetables, fruit, and fish should be the base of daily diet.[57]

Currently, no data from controlled, randomized clinical trials are available to suggest any benefits from any particular lifestyle modification dedicated to LEAD patients so as to reduce the mortality rate and incidence of CV events. Therefore, it is suggested that patients should follow the recommendations for the entire high cardiovascular risk population.

Pharmacological management in LEAD patients should include: lipid-lowering treatment, anticoagulant and antiplatelet treatment, vascular pleiotropic treatment and antihypertensive treatment. In this document we will focus only on the first three elements.

## Lipid-lowering treatment

According to ESC guidelines from 2019 in LEAD patients, lipid-lowering therapy with a maximum dose of statin or ezetimibe combined with PCSK9 inhibitor (if needed) is recommended to reduce cardiovascular risk (recommendation IA).[58]

Lipid profile analysis should be than performed in each LEAD patient and repeated at least once a year to assess the achievement of target LDL-C level. In addition, the assessments at 6–8-week intervals are suggested when treatment has to be modified and/or when target concentrations are not achieved. Target LDL-C values should be taken into account when assessing the outcomes of lipid-lowering treatment; once these are achieved, secondary therapeutic objectives (non-HDL cholesterol, triglycerides) may be sought after by means of the inclusion of appropriate omega-3 acids and/or fibrates in addition to non-pharmacological managements.

The 2019 ESC guidelines stated that all patients with LEAD and any additional risk factors should be classified to the extremely high-risk group where the target serum LDL-C levels are below 35 mg/dL (<0.9 mmol/L).[58] Other LEAD patients with no additional risk factors and diagnosis of peripheral artery disease alone, are classified to the group of very high risk with target LDL-C levels of below 55 mg/dL (<1.4 mmol/L).

Thus, the proposed management algorithm should include:

- patients should be persuaded to use phytosterols-containing products (margarines, yogurts) and possibly expand their diet with other products mildly reducing the LDL-C levels while not interacting with statin drugs;
- maximum-tolerated, high doses of statins should be used. The European guidelines require that strong statins (atorvastatin, rosuvastatin) are used; old statins with low effect on LDL-C levels (simvastatin, prevastatin, fluvastatin, lovastatin) should not be used;
- due to the pharmacological differences between atorvastatin (lipophilic) and rosuvastatin (hydrophilic), the former is used more commonly in patients with chronic renal disease while the latter is preferred in patients with signs of hepatic insufficiency;
- in every LEAD patient, target LDL-C levels should be aimed at by prescribing atorvastatin at the dose of 40–80 mg/day or rosuvastatin at the dose of 30-40 mg/day;
- in all cases when target LDL-C levels are not achieved using high doses of strong statins or when such high doses are not tolerated, ezetimibe should be included at the dose of 10 mg/day;
- in case the target LDL-C levels are not achieved using statins and ezetimibe, additional administration of an injectable drug (PCSK9 inhibitors: alirocumab) once every 2-4 weeks should be considered.

## Anticoagulant and anti-platelet treatment

Optimal medical treatment of patients with symptomatic LEAD includes antiplatelet and anticoagulation treatment. It may be provided both before potential revascularization (either open or endovascular) and in the post-procedural period. Management regimen consists of either antiplatelet drugs alone or antiplatelet drugs combined with anticoagulants. Notably, anticoagulants and anti-platelet drugs are used in LEAD patients to prevent ischemic incidents within the lower limb as well as to prevent generalized CV incidents. One should also keep in mind that none of the hitherto completed clinical studies evaluated the role of antiplatelet drugs in the entire LEAD spectrum (asymptomatic LEAD, intermittent claudication, and CLTI).

Four different scenarios can be taken into consideration as a possible mode of treatment for patients with LEAD:

- single antiplatelet therapy (SAPT);
- dual antiplatelet therapy (DAPT) or antiplatelet-anticoagulant treatment with low vascular doses of novel anticoagulants (rivaroxaban);
- antiplatelet-anticoagulant treatment following lower extremity arterial revascularization, either open or endovascular;
- treatment of patients with LEAD with coexisting indications for chronic anticoagulant therapy (*e.g.* artificial heart valve, atrial fibrillation, venous thromboembolism).

## Single antiplatelet therapy (SAPT)

Single antiplatelet therapy may be provided using acetylsalicylic acid (ASA dose 75-100 mg/24 h) or clopidogrel

(dose 75 mg/24 h). In LEAD patients, it is recommended only when clinical symptoms are present or after a revascularization procedure has been performed. According to CAPRIE study,[59] clopidogrel rather than ASA is the preferred antiplatelet drug in LEAD patients.

There are no convincing data on the superiority of new antiplatelet drugs (prasugrel, ticagrelor) over clopidogrel in a single antiplatelet therapy model in the group of patients with PAD, so such treatment is used only in selected cases, in patients with concomitant coronary syndromes and after acute coronary syndromes according to separate cardiological indications.

Optimization of SAPT management and the addition of sulodexide can be individually considered.

### Dual antiplatelet therapy (DAPT) or antiplatelet-anticoagulant treatment with low vascular doses of novel anticoagulants

There are currently no data on the routine use of DAPT in LEAD group of patients. Completed clinical trials do not indicate any superiority of DAPT over SAPT and in addition routine management of DAPT increases the risk of bleeding. However, currently published data from COMPASS study has demonstrated the benefit of using ASA 100 mg in combination with rivaroxaban 2x2.5 mg in the subgroup of patients with peripheral arterial disease.[29, 60, 61] Such management may be considered in patients with concomitant chronic coronary syndromes, diabetes mellitus, and other risk factors although the attention should be paid on group of patients with increased risk of bleeding. In such patients, therapy with one antiplatelet drug (clopidogrel preferred) with possible addition of sulodexide may be considered.

### Antiplatelet-anticoagulant treatment following lower extremity arterial revascularization, either open or endovascular

After open by-pass surgery of lower limbs, the regimen of clopidogrel or — if the risk of bleeding is acceptable — ASA with rivaroxaban at a dose (2x2.5 mg) may be used at the individual discretion of the operator, but not longer than a month. In the case of treatment with one antiplatelet drug (SAPT regimen), the addition of sulodexide may be considered.

Following endovascular interventions for patients with LEAD, the regimen of DAPT is recommended for at least one month after intervention regardless of the stent type (non-coated metal stent or drug-eluting stent).

Treatment below the groin has been recently tested prospectively, finding no need for more intensive or longer treatment. However, long-term treatment can be carried out using ASA + rivaroxaban 2x2.5 mg regimen, but only in the group of patients without an increased risk of bleeding. In case of high risk of bleeding — clopidogrel alone is recommended. Sulodexide can be added to it.

Three-component therapy consisted of ASA, rivaroxaban with clopidogrel is also possible, but only in selected patients.

In case of infrapopliteal artery stenting the dual antiplatelet therapy is frequently continued longer, although no evidence is available to support this management strategy.

### Treatment of patients with LEAD with coexisting indications for chronic anticoagulant therapy

Patients with LEAD who require long-term anticoagulant therapy do not need antiplatelet therapy. Only administration of optimal doses of new anticoagulants is recommending, if indicated. Treatment can be continued for life or for a limited period of time. If there is a very high risk of bleeding, sulodexide can be an option as treatment continuation.[62]

The antiplatelet treatment regimens recommended in the latest 2017 ESC guidelines for patients not requiring anticoagulant therapy (Figure 2) and for patients requiring oral anticoagulation (Figure 3) are shown below.[45]

The latest European cardiological guidelines for patients with LEAD from 2021 emphasize that:

- antiplatelet therapy is indicated only in symptomatic patients;
- treatment with 100 mg ASA with 2x2.5 mg rivaroxaban is reserved only for chronically symptomatic patients with LEAD and diabetes, without a high risk of bleeding, classifying such treatment as class IIb recommendation (selected patients only, individual consideration).

### Vascular pleiotropic treatment

Numerous groups of drugs were analyzed in terms of their vascular pleiotropic and protective character.

The most extensively studied for this indication are cilostazol, naftidrofuryl, pentoxiphylline, buflomedyl, carnitine, and propionyl-L-carnitine. The beneficial impact of the aforementioned substances is usually mild to moderate and highly variable depending on the type of the study. No evidence was provided for these agents to significantly alter the outcome prognosis.

In recent years, sulodexide, as a mixture of glucosaminoglycans from porcine intestinal mucosa containing fast-moving heparin (80%) and dermatan sulfate (20%) is

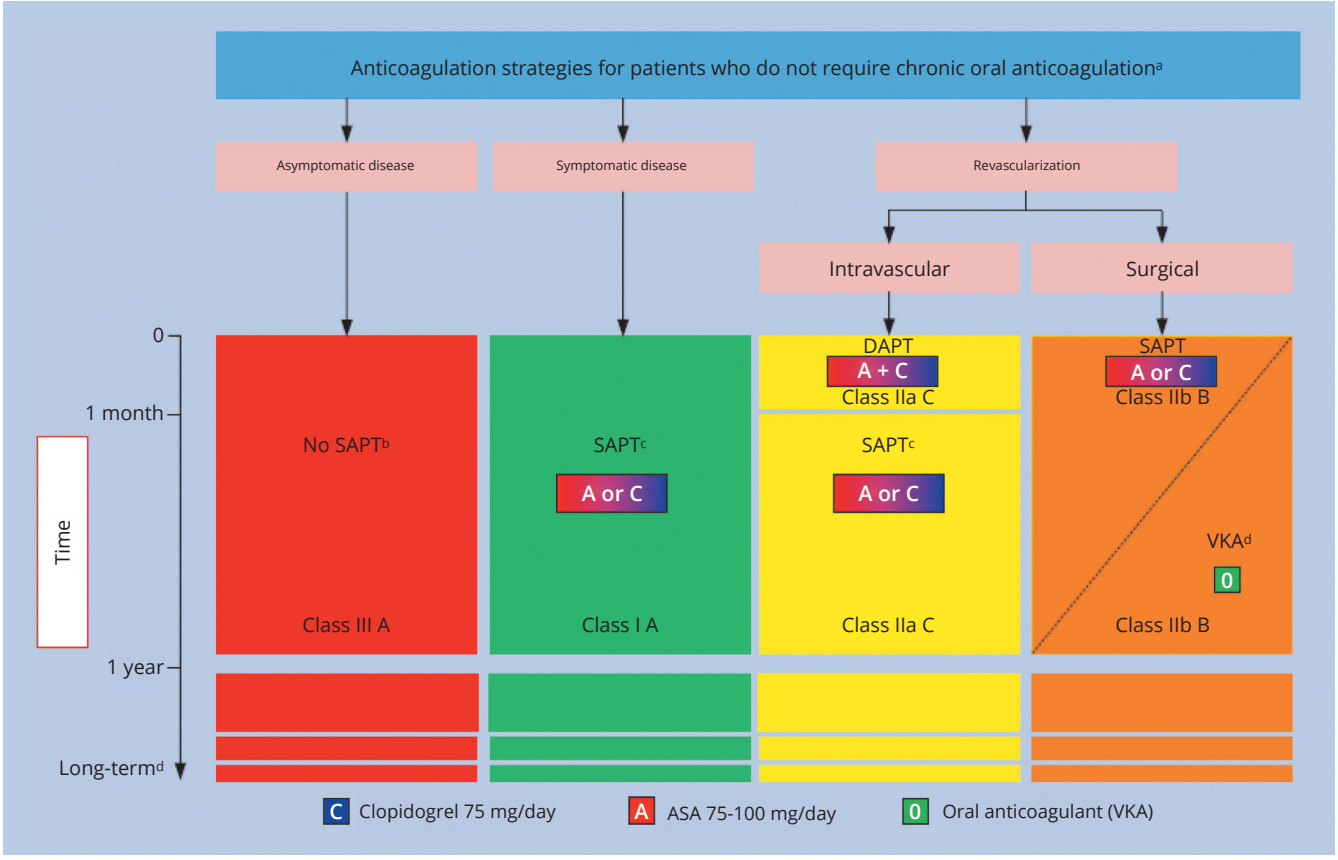


Figure 2.—Anticoagulation strategies for patients who do not require chronic oral anticoagulation (modified from Aboyans *et al*.).[45]
ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy; VKA: vitamin K antagonist.
a E.g., concomitant atrial fibrillation or mechanical valve prosthesis; b SAPT should be considered in cases of another concomitant atherosclerotic disease (*e.g.*, coronary artery disease); c DAPT may be considered in patients with recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization; d evidence is weak and bleeding doubles as compared to SAPT; "long-term" stands for as long as it is well tolerated.

reaching a growing importance in LEAD treatment. The drug is targeting the inflammatory response, endothelial dysfunction and the associated changes within the extracellular matrix as well as modulating the coagulability of blood.[11] *In vivo*, sulodexide has been shown to promote arterial relaxation *via* a mechanism involving endothelium-dependent NO production.[20] 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.[63-65]

Clinical efficacy of sulodexide was documented in numerous vascular disorders, either venous or arterial.

Sulodexide has been shown to improve pain free and maximum walking distance in LEAD patients with intermittent claudication.[65, 66]

Clinical efficacy of sulodexide include also alleviation of symptoms in patients with chronic venous disease, shortening the healing time of venous leg ulcers, improving treatment of venous thromboembolism, or prevention of cardiovascular events after myocardial infarction and beneficial effect in diabetic complications as retinopathy, peripheral arterial disease, trophic ulcers, and nephropathy.[67-76]

Statins are the other, well recognized group of drugs which has an important impact on pleiotropic and protective effect on vascular bed, reducing the risk of cardiovascular events and cardiovascular mortality in LEAD patients. Some, small randomized studies suggest that patients receiving statins may slightly improve their PFWD

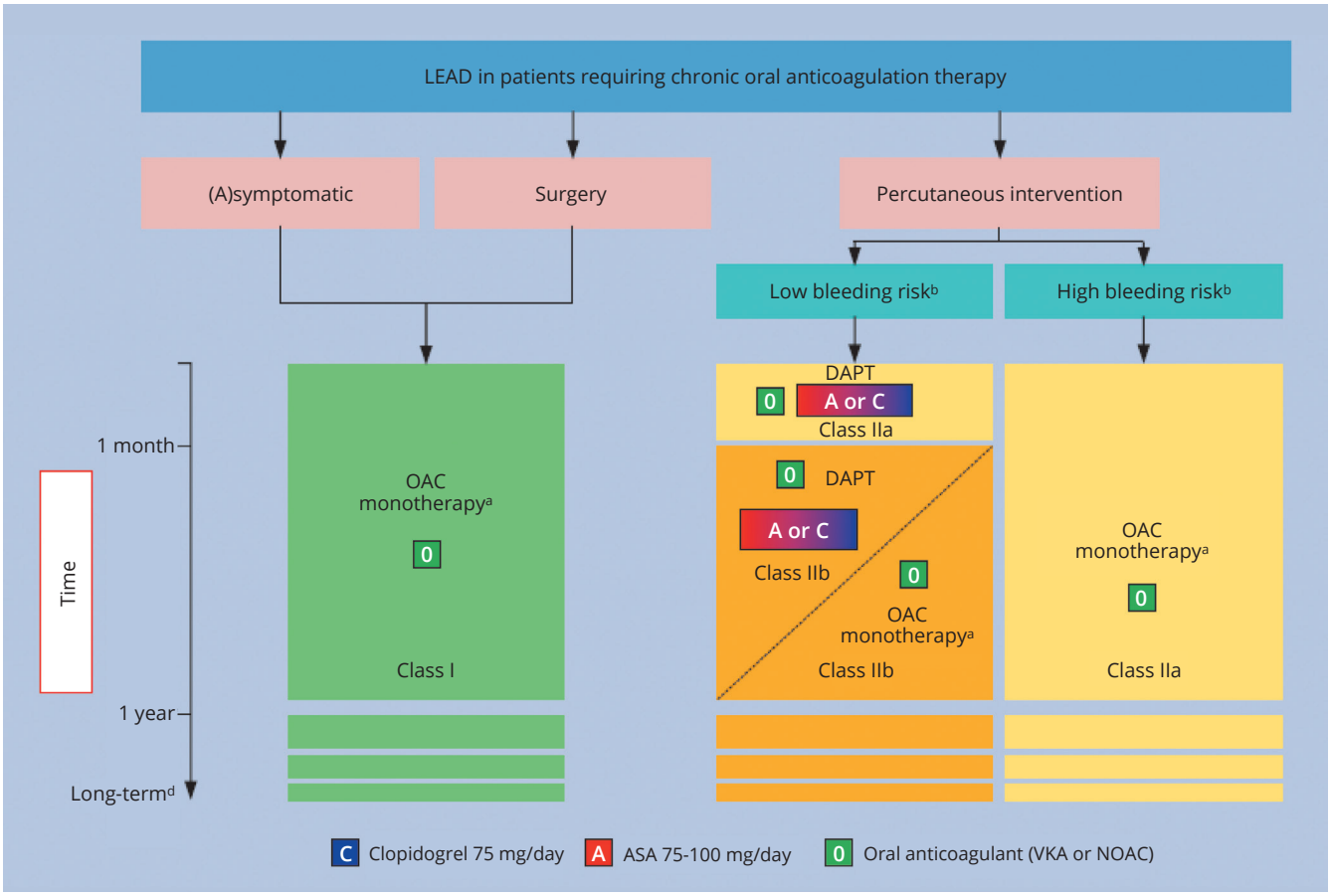


Figure 3.—LEAD in patients requiring chronic oral anticoagulant therapy (modified from Aboyans *et al.*).[45]
ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy (antiplatelet + anticoagulation); LEAD: lower extremity artery disease; NOAC: non-oral anticoagulant; OAC: oral anticoagulant; VKA: vitamin K antagonist.
[a] DAPT may be considered in patients at high risk of ischemic incidents defined as history of stent thrombosis, acute limb ischemia in the course of oral anticoagulation therapy or concomitant coronary artery disease (recent acute coronary syndrome, status post stenting of the last patent coronary artery, polyvascular coronary disease in diabetic patients after incomplete revascularization); [b] compared to the risk of brain stroke/chronic ischemia with a threat of limb loss due to stent/bypass occlusion; [c] stands for as long as it is well tolerated.

(pain-free walking distance) what relates to their vasoprotective activity independent of lipid lowering effect. Intensive statin therapy is associated with significant benefits combined with few adverse effects, thus statins are currently recommended in all LEAD patients regardless of their cholesterol levels and dyslipidemia status.

## Clinical and surgical management of patients with chronic limb-threating ischemia

Chronic limb-threatening ischemia (CLTI) is one of the most serious complications of LEAD, which can lead to amputation, mortality, and impaired quality of life.[77, 78] CLTI is a syndrome defined by the presence of rest pain, gangrene, or lower limb ulceration with a >2 weeks duration.[79] A suspect of CLTI has to be immediately reported to a vascular specialist who must accurately assess the degree of severity of the limb threat. If revascularization surgery becomes necessary, the options are to perform an open, endovascular or hybrid operation, otherwise to proceed with limb amputation.

### How to select the treatment

To facilitate the clinician's decision on how to intervene, global vascular guidelines (GVG) have proposed schemes and classification systems that come into help. GVG were first drawn up in 2013 following the recognition of the growing impact of CLTI on public health across Nations

and in different socio-economic areas. The reported recommendations refer to their most recent update in 2019.[78]

The first fundamental point to be addressed in CLTI patients is limb staging. GVG propose a grading based on Wound, Ischemia, and foot Infection (WIfI). Stage 1 of the classification indicates minimal ischemia, no or minor tissue loss; stages 2 to 4 reflect an increased severity of ischemia, wound, and infection, up to stage 5, where the foot is no longer salvageable due to the extent of the wound or the severity of infection.[78]

Once the severity of the condition has been established, an intervention for limb revascularization may be carried out. To provide evidence-based guidance for the revascularization strategy, GVG also propose a new integrated anatomic scheme for the threatened limb, named the Global Limb Anatomic Staging System (GLASS). The target arterial path (TAP) is first defined by the surgeon on the basis of appropriate angiographic imaging that allows the identification of the optimal arterial pathway to restore blood flow to the extremity of the limb (ankle or foot).[78] Once TAP is selected, the segmental femoropopliteal (FP) and infrapopliteal (IP) grades are determined from high-quality angiographic images. The combination of FP and IP grades allows the definition of the GLASS stages I to III, as illustrated in Table I. Each stage corresponds to the progressive technical complexity of the revascularization procedure. Finally, to aid clinical decision-making and to achieve effective revascularization, GVG authors propose a three-step integrated approach based on: Patient risk estimation, Limb staging, and Anatomic pattern of disease (PLAN). A CLTI patient is defined as average surgical risk level when the anticipated periprocedural mortality is <5% and the estimated 2-year survival is >50%, otherwise the patient is defined as high surgical risk (Recommendation Grade 2 and level of evidence C). In average-risk CLTI patients with infrainguinal disease, it is strongly recommended to base the decisions of endovascular intervention *vs*. open surgical bypass on the severity of limb threat (*e.g.*, WIfI), the anatomic pattern of disease (*e.g.*, GLASS), and the availability of autologous vein.

Whereas, in high-risk patients with advanced limb threat (*e.g.*, WIfI stage 4) and significant perfusion deficits (*e.g.*, WIfI ischemia grades 2 and 3) it is recommended to offer endovascular revascularization when technically feasible. If these high-risk patients also display an advanced complexity of disease (*e.g.*, GLASS stage III) or after prior failed endovascular attempts and unresolved symptoms of CLTI, open surgery should be considered.

## How to select the patient

Each type of patient must be selected for the most appropriate surgical procedure. To guide this selection, the establishment of a scoring selection system becomes an option to be considered. Some subgroups of CLTI patients worth examining into detail are patients with end stage renal disease (ESRD) in hemodialysis and patient ≥80 years.

The prevalence of CLTI in hemodialysis patients is 5-16%.[80] Some negative predictors for revascularization are age >80 years, the number of years on dialysis, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and dependent ambulatory status.[79] A retrospective study on 131 participants was conducted to define risk factors for clinical success (CS) after revascularization of CLTI in patients in hemodialysis and to transform findings into a prognostic score.[80] CS was evaluated as the amputation-free and reintervention-free survival of the patient. 180 limbs were treated, and primary major amputation (PMA) occurred in 7.8% of the cases (Table II). Revascularization procedures were performed

Table I.—*Assignment of Global Limb Anatomic Staging System (GLASS) stage (modified from Poredoš and Jezovnik).*[2]

| | | | | | | |
|---|---|---|---|---|---|---|
| Infrainguinal GLASS stage I-II | | | | | | |
| FP grade | 4 | III | III | III | III | III |
| | 3 | II | II | II | III | III |
| | 2 | I | II | II | II | III |
| | 1 | I | I | II | II | III |
| | 0 | NA | I | I | II | III |
| | IP grade | 0 | 1 | 2 | 3 | 4 |

FP: segmental femoropopliteal; IP: segmental infrapopliteal; NA: not applicable.

Table II.—*Assignment of Global Limb Anatomic Staging System (GLASS) stage (modified from Fowkes* et al.*).*[4]

| Operative treatment | N. (%) |
|---|---|
| Type of anesthesia | |
| Local-regional/local | 123 (71.5%) |
| General | 49 (28.5%) |
| PMA | 14 (7.8%) |
| Revascularization | 166 (92.2%) |
| Surgical | 52 (28.9%) |
| Isolated femoral-endarterectomy | 5 (9.6%) |
| Femoral-popliteal bypass | 24 (46.2%) |
| Femoral-distal bypass | 23 (44.2%) |
| Endovascular | 95 (52.8%) |
| Isolated iliac transluminal angioplasty | 4 (4.2%) |
| Isolated tibial transluminal angioplasty | 31 (32.6%) |
| Multilevel transluminal angioplasty | 60 (63.2%) |
| Hybrid | 19 (10.6%) |
| Femoral endarterectomy + transluminal angioplasty | 7 (36.8%) |
| Bypass + transluminal angioplasty | 12 (63.2%) |

PMA: primary major amputation.

by open (28.9%), endovascular (52.8%), or hybrid surgery (10.6%) (Table II). At 30 days, the overall mortality was 10.7%, limb salvage was 91.6%, cases of reintervention were 16.2%, and CS was 77%. At 6-, 12-, and 24-month follow-ups, CS progressively decreased to 47.9%, 30.8%, and 17.8%, respectively. The PMA group showed a significantly lower survival rate (25%) compared with the revascularization group (56%).

Based on the collected data, a formula has been established providing a score capable of predicting CS preoperatively: 0.026 × age (years) + 0.441 (if the patient has a history of CAD) + 0.59 (if the lesion is infected). If the score obtained is >2.07, it predicts a high-risk patient, whereas a score <2.07 predicts a low-risk patient.[80] In the population analyzed by this study,[79] CS at 1 year in the patients with a low-risk score was 51.6%, significantly higher than the 23.3% observed in the high-risk score cases (P<0.001).

Another study evaluated in-hospital mortality, PMA, and a predictive score of in-hospital mortality in patients ≥80 years affected by CLTI.[80] CLTI octogenarians often face in-hospital mortality and complications, especially if open revascularization is indicated. 283 octogenarians were evaluated, for a total of 375 limbs treated. The most common comorbidities were hypertension (92.0%) and dyslipidemia (68.0%). Patients arrived at the Operative Unit with 51% of limbs in Rutherford category 6 and with infected lesions in 24% of the cases. PMA occurred in 10% of the cases, while the endovascular approach was the most common among the revascularization strategies (48%), followed by the surgical approach (28%) and the hybrid approach.[79] Revascularization was successful in 91% of the cases, while in-hospital mortality accounted for 8.8%.

By performing multivariate analysis, four significant risk factors for in-hospital mortality were identified and points were assigned to each of these to obtain the final risk coefficient: hemodialysis (2 points), COPD (1 point), non-ambulatory status (1 point), and open revascularization (1 point). A score equal to 1 corresponds to a risk of 8%; if the score is 2 the risk is >37%; if the score is 3 the risk is >50%; if the score is >4.5 the risk is 100%. The identification of a preoperatively established score could assist clinicians in the decision-making process and to better inform the patient and their family.

The GVG Consensus was recently published to guide clinical and technical decisions in the management of CLTI. Further improvements may be implemented in the Consensus in the selection of patients with CLTI that may have a clinical success/benefit with revascularization.

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*Conflicts of interest*
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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