The position of Polish experts on conservative management in patients with artery diseases of lower limbs

Dear Readers,

Peripheral artery disease (PAD) is a common disease, though not very well known and often diagnosed on a very late stage, causing not only typical complications such as intermittent claudication, critical limb ischemia or amputations, but also to cardiovascular mortality. The risk of cardiovascular death can be even 11 times higher in patients with symptomatic PAD than in healthy patients. The risk of heart attack, stroke or cardiovascular death is even higher, reaching almost 4% within one year, nearly equal to the risk for patients with coronary artery disease (CAD). In those patients, the 5-year mortality risk is estimated at 10–15%, with cardiovascular disorders being the most likely cause of death. In patients with critical limb ischemia, the risk of cardiovascular death within one year can be as high as 25% and the risk of amputation — 30%.

It is estimated that the global population of patients with PAD is over 120 million. The incidence of the diseases is 3–10%, but in patients aged 70 and more, the incidence increases to 14–29%. In Poland, around 4,000 people are hospitalized every year for PAD of lower limbs. The number of PAD-related amputations is over 9,000 per year. Although the methods of PAD diagnosis (e.g. ABI) are often easy and non-invasive, they are scarcely used in clinical practice. Also, optimal conservative management in the form of quitting smoking, modifying the cardiovascular risk factors and supervised exercise is often overlooked.

PAD is a major issue not only for vascular surgery, but also for many other medical specializations, including angiology, general medicine, cardiology, or diabetology. As a result of long waiting times for the next visit and lack of access to patient programmes and reimbursed drugs, patients with PAD often report to the doctor when their condition is very serious. Despite the 2017 ESC guidelines on the diagnosis and treatment of peripheral artery disease, prepared together with ESVS, not all healthcare professionals have access to the latest knowledge on PAD diagnosis and treatment. Unfortunately, though published recently, the ESC's guidelines do not include some of the recent studies, among them the possibly breakthrough COMPASS trial which has the potential to change the paradigm of management of patients with PAD.

We must bear in mind that the population with PAD is a difficult patient group who need new treatment methods and optimization of the existing ones in order to visibly improve diagnosis, treatment and prognosis.

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Abbreviations:

ABI — ankle–brachial index
ACC — American College of Cardiology
ACE — angiotensin converting enzyme
ACEI — angiotensin-converting-enzyme inhibitors
ADP — adenosine diphosphate
AH — arterial hypertension
AHA — American Heart Association
Angio-MR — magnetic resonance angiography
ARB — angiotensin receptor blockers
ASA — acetylsalicylic acid
CAD — coronary artery disease
CLTI — chronic limb-threatening ischemia
CV — cardiovascular system
DAPT — dual antiplatelet therapy
EBM — evidence-based medicine
ESC — European Society of Cardiology
ESVS — European Society for Vascular Surgery
FDA — Federal Drug Administration
GLP-1 — glucagon-like peptide-1
GPS — good practice statement
HDL-C — high-density lipoprotein cholesterol

HIV — human immunodeficiency virus
INR — international normalized ratio
LDL-C — low-density lipoprotein cholesterol
LEAD — lower extremity artery disease
MACE — major adverse cardiac events
MWD — maximum walking distance
NNT — number needed to treat
NOAC — novel oral anticoagulants other than vitamin K antagonists
OAC — oral anticoagulants
PAD — peripheral artery disease
PAR-1 — proteinase-activated receptor 1
PCSK9 — proprotein convertase subtilisin/kexin type 9
PFWD — pain-free walking distance
PTD — Polish Diabetological Association
SAPT — single antiplatelet therapy
SGLT-2 — sodium/glucose cotransporter 2
TBI — toe–branchial index
TcPO$_2$ — transcutaneous oxygen pressure
TIA — transient ischemic attack of the central nervous system
VKA — vitamin K antagonist

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1. Introduction

The first decade of the 21st century has seen major progress in the diagnosis and treatment of peripheral artery disease (PAD). The introduction of new state-of-the-art techniques of intravascular treatment, new anticoagulants and new generations of statins resulted in a large number of new scientific reports and publications allowing a more objective assessment of the outcomes of various treatment and management methods. Given the new data available and the high risk of circulatory diseases in the Polish population, it appears necessary to develop Polish guidelines on the conservative management of the lower extremity artery disease (LEAD), focusing in particular on the pharmacotherapy of patients with intermittent claudication. The guidelines should take into account the results of the latest studies and trials, and the international guidelines on the management of LEAD. The purpose of this publication is to organize the available knowledge in an accessible manner so that it could be more efficiently used by all actors involved in PAD management. The Workgroup decided to restrict the scope of this study to the lesions in lower extremities secondary to atherosclerosis and the conservative management thereof, not including the issue of PAD in other areas of the vascular system, and to the indications for revascularization treatment and the methods of revascularization in patients with LEAD.

The authors had to choose the system of classification of the strength of the guidelines and the supporting scientific evidence, especially given that the literature of the subject, including the international guidelines on the management of patients with LEAD, had been using different approaches. Following the analysis of publications on the subject at hand from the preceding 10 years, the system applied in the guidelines of the European Society of Cardiology (ESC) was adopted. The system is based on 4 classes of recommendations indicating the strength of the recommendation (I, IIa, IIb, III), and 3 levels of evidence on which the recommendations are based (A, B, C). Both information should be provided together with a specific recommendation.

It should be pointed out that the position set out below, as well as the strength of individual recommendations, are not legally binding and thus the authors thereof cannot be legally liable for them. The following guidelines reflect the current state of the art in accordance with the principles of Evidence-Based Medicine (EBM) and are aimed at facilitating the standardization of medical care of patients with LEAD in Poland, in particular, the patients suffering from intermittent claudication. Much consideration was given to the complex issues related to anticoagulation therapy of patients with LEAD who often suffer from comorbidities which affect the indications for the use of anticoagulants (e.g. coronary artery disease or atrial fibrillation).

1.1. Purpose
The purpose of this publication on the conservative management of LEAD secondary to atherosclerosis is to organize the available knowledge and allow proper management of LEAD in line with the principles of EBM. The Workgroup's task of developing the guidelines involves not only reconciling the knowledge from the latest scientific studies, but also preparing educational tools and guideline implementation programmes, including abridged versions, summarizing slides, bulletins listing the main premises, summary cards for non-specialists, and digital versions for use in electronic appliances (such as smartphones). Digital versions of the source document will be abridged; therefore, the full text of the guidelines should be referenced.

1.2. Patient groups to whom the position applies
The developed position applies to patients with LEAD secondary to atherosclerosis.

1.3. Receivers of the position
The receivers of the position are doctors of all specializations who provide both general and specialized care for the aforementioned patients with LEAD.

1.4. Intervention types provided for in the position

The recommendations provided in the position include the diagnostic tests used for the diagnosis and atherosclerotic assessment of LEAD, as well as pharmacotherapy and non-pharmacological methods of management thereof (excluding interventional treatment).

1.5. Instructions on the use of the position

The position set out herein should not be viewed as a legally binding standard of care for all patients, since the document contains only guidelines for management, and the recommendations should aid doctors in making optimal decisions in everyday clinical practice. The proper patient care always depends on the individual conditions of the patient, the available and feasible methods of treatment, and many more factors; decisions on the applied management must always be made by the attending physician or the medical team, in consultation with the patient or, if necessary, the patient's guardian. The authors of the guidelines encourage doctors and medical professionals to implement and popularize the following guidelines for the management of adult patients with LEAD.

2. Methodology

2.1. Workgroup

The position was developed by the Polish experts/ /specialists in angiology, hypertension management, vascular surgery, internal medicine and cardiology. The Workgroup was composed of Professor Zbigniew Krasiński, DMSc, PhD (Head of Workgroup), Professor Zbigniew Gaciong, DMSc, PhD, Professor Tomasz Urbanek, DMSc, PhD, Filip Szymanski, DMSc, PhD, and Radosław Kowalewski, DMSc, PhD

2.2. Description of the process of developing the position and associated documents

Formulating the propositions of guidelines, the experts took into account the 2017 ESC guidelines on the diagnosis and treatment of PAD, developed together with the European Society for Vascular Surgery [1], the 2016 guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC) on the management of patients with LEAD [2], the 2015 guidelines of the Society for Vascular Surgery on the management of asymptomatic LEAD and intermittent claudication [3], and other scientific studies and publications from recent years, especially those released after the publication of the aforementioned guidelines.

Formulating the recommendations in the Polish position, the experts analyzed the source guidelines in terms of applying them in a Polish setting. The de-

veloped propositions for the recommendations were discussed in detail during meetings. Any disputes were discussed and settled. The preliminary version of the Polish position was then submitted for external consultations and reviews. Any justified comments on the substance of the guidelines were taken into consideration by the Workgroup. All experts in the Workgroup accepted the final version of the document.

2.3. Classification of the strength of recommendations and level of evidence

In this document, the system of classification of recommendations and levels of evidence proposed by the ESC was adopted (Tables 1A and 1B). The level of evidence was assessed as high (A), moderate (B) or low (C). The strength of a recommendation was classified based on the authors' opinion that the given management procedure was justified and would bring more benefits than harm. Class I ("it is recommended") and III ("it is not recommended") are strong recommendations, while class IIa ("it is reasonable") and IIb ("may be reasonable") are conditional/weak recommendations. In the absence of existing recommendations, related e.g. to the results of the latest studies, the Workgroup attempted to formulate the so-called good practice statement (GPS), i.e. a reconciled opinion of all experts.

3. Epidemiological data, clinical assessment, diagnosis

3.1. Prevalence and causes of chronic limb ischemia

The lower extremity artery disease (LEAD) is one of the most frequent peripheral artery diseases, the prevalence of which increases with the age of the observed population. On the basis of epidemiological data, the incidence of chronic limb ischemia is estimated at 3–10%, and in the population aged 70 or above, occurs 15–20%, more frequently in males [4]. In its initial stage, the disease is asymptomatic. In the studies based on the ankle-brachial index (ABI), which allows an objective diagnosis, the ratio of asymptomatic patients to the general number of confirmed cases ranges from 1:3 to 1:5 [1, 4–6]. The incidence of critical limb ischemia is 200–1,000 new cases per 1 million members of the population and is significantly higher in diabetic populations [1, 4, 5]. The key factors leading to LEAD include age, smoking, hyperlipidemia, the co-occurrence of diabetes or impaired glucose tolerance, and arterial hypertension [1, 4, 5]. Other factors which play a part in the development of chronic ischemia include sex, ethnicity, vascular lesions in kidney failure, as well as the C-reactive protein level, hyperfibrinogenemia and hyperhomocysteinemia [1]. Genetic factors are also

Table 1A. Classes of recommendations

I	Evidence from scientific studies and/or general agreement that a given procedure or treatment is beneficial, useful and effective **Is recommended**…
IIa	Weight of evidence and/or opinion is in favour of usefulness or efficacy of the given procedure or treatment **Should be considered**…
IIb	Usefulness or efficacy of the given procedure or treatment is less well established by evidence and/or opinion **May be considered**…
III	Evidence from scientific studies and/or general agreement that the given procedure or treatment is not useful or effective, and in some cases may be harmful **Is not recommended**…

Table 1B. Level (quality) of evidence

A — Data derived from multiple randomized clinical trials or meta-analyses
B — Data derived from a single randomized clinical trial or large non-randomized studies
C — Consensus of opinion of the experts and/or data derived from small studies, retrospective studies, registries

considered, although their identity and impact are still being studied [1, 5].

The lesions causing chronic limb ischemia are often accompanied by atherosclerotic lesions in other areas of the vascular system, which increase the cardiovascular risk, in particular, the risk of a heart attack and ischemic stroke [5]. In patients with atherosclerotic LEAD, the risk of mortality caused by coronary artery disease is increased 4-fold, and the incidence of brain ischemic episodes increases 2- to 3-fold [7–10]. In most cases, chronic lower limb ischemia is accompanied by atherosclerotic arterial lesions (95-98% of cases), although the chronic lower limb ischemia may also be caused by other diseases or clinical conditions [1, 4]. These include inflammatory vascular diseases, history of arterial embolism, vascular stenosis or occlusion in compressive lesions or sustained injuries and the consequences thereof, thrombosed popliteal artery embolism, complications of intra-arterial injections, or the less frequent vascular tumours [1, 4]. Diabetes is a key factor in the development of atherosclerotic lesions. Diabetic lesions usually coincide with the atherosclerotic process and lead to increased vascular wall rigidity not only by thickening but also by intravascular calcifications [4, 5]. In terms of symptomatology and treatment options, the involvement of lower leg arteries, a typical condition in diabetic patients, is of particular clinical importance, as it is a risk factor of critical ischemia in patients from this group [1, 4].

3.2. Symptomatology and classification of chronic limb ischemia

Most patients do not experience clinical symptoms and the condition can be identified on the basis of decreased ABI level (< 0.90) or the lack of pulse in leg arteries. The latest edition of ESC guidelines distinguishes a patient subgroup with "masked", i.e. a hidden form of LEAD. Those patients can suffer from severe disease but not report any symptoms due to the inability to cover a distance long enough for LEAD symptoms to manifest themselves (e.g. because of disability caused by another condition, such as heart failure), and/or reduced pain sensitivity (e.g. in patients with diabetic neuropathy) [1]. The patients in this group are usually elderly individuals, often suffering from neuropathy and other comorbidities. The subgroup with masked LEAD is exposed to high risk of limb-related incidents, which explains why some patients rapidly deteriorate from asymptomatic to sever LEAD.

One of the most typical symptoms of LEAD is intermittent claudication, which may affect different parts of the limb depending on the level of vascular occlusion/stenosis. The most frequent location of single-level stenosis in lower extremities is the femoral artery; however, as the disease progresses, multilevel atherosclerotic lesions develop. Clinically, the presence of occlusion and/or stenosis in the aorto-iliac or femoral-popliteal segment, and peripheral lesions involving the lower leg and foot can be distinguished [5]. The lesions are often

multilevel or located also in other areas of the vascular system. The occlusion of the femoral artery causes intermittent claudication which usually affects the lower leg muscles. The occlusion in the aorto-iliac segment can cause gluteal claudication — this condition usually accompanies the occlusion of the internal iliac artery. Stenosis or occlusion of iliac and/or pelvic vessels can also cause erectile dysfunction in men. In the case of occlusion of the lower leg vessels and impaired blood flow to the foot, the most typical symptoms, aside from lower leg pain, are observed in the foot [5, 11].

The severity of LEAD symptoms depends on factors related to both the location and extent of atherosclerotic lesions and the degree of development of collateral circulation [1, 4]. Aside from intermittent claudication, in the case of a chronic form of the disease, a number of irregularities can be observed in physical examination, such as muscular dystrophy, poor filling of superficial veins, loss of hair, weak capillary action, and paleness of the limb skin. If the ischemic symptoms deteriorate, necrotic lesions or ulceration can occur. Necrotic lesions (dry or liquefactive) initially affect the most distal parts of the extremity (toes, forefoot, calcaneal tuber area), and sites exposed to local chronic injuries (caused e.g. by compression), such as toes, heel and the 1st and 5th metatarsal bone heads. The progression of atherosclerotic lesions and deteriorating ischemia can lead to critical limb ischemia, which deteriorates prognosis. In patients with stable intermittent claudication, the risk of amputation over a 5-year follow-up period is relatively low; with proper management, it is approx. 2–3% within 5 years, and in 5–10% of those cases, critical limb ischemia will occur [4]. The risk of deterioration of the symptoms of intermittent claudication in the further 5 years of the disease is estimated at 10–20%, whereby the risk is highest in the first year following the diagnosis (6–9%) and reduced in subsequent years (2–3%/year) [12]. Differential diagnosis of intermittent claudication should take into consideration other potential causes of claudication, including claudication related to neurological diseases (e.g. nerve root or spinal cord compression), claudication of venous origin (occlusion, e.g. in the proximal segment of the venous system), chronic compartment syndrome, and other clinical conditions causing pain of the lower extremities [4]. A prerequisite for the diagnosis of critical limb ischemia is the confirmation of pain persisting for 2 weeks, or necrotic signs (stage III or IV ischemia according to Fontaine classification). Persistent pain in ischemia usually occurs with the blood pressure at the ankle below 50 mm Hg, or the pressure in big toe below 30 mm Hg. The level of partial oxygen pressure in percutaneous measurement ($tcPO_2$) considered to be critical is below 30 mm Hg [4]. The proposed and applied leg ischemia

Table 2A. Fontaine classification of chronic limb ischemia

Stage	Clinical symptoms
I	Asymptomatic
IIa	Mild claudication — claudication distance above 200 m
II b	Moderate or severe claudication — claudication distance below 200 m
III	Ischemic rest pain
IV	Ulceration or gangrene

Table 2B. Rutherford classification of chronic limb ischemia

Category	Clinical symptoms
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Ischemic rest pain
5	Minor tissue loss
6	Major tissue loss

classifications according to Fontaine and Rutherford are outlined in Tables 2A and 2B.

3.3. Diagnosis of chronic limb ischemia — clinical assessment and additional tests

The basic method for diagnosing chronic limb ischemia is a physical examination. Due to the possible lack of pulse in the limbs of some patients unrelated to LEAD, as well as the subjective nature of the ailments, the diagnostic algorithm must include additional tests [1, 4, 5].

Aside from assessing the pain and intermittent claudication, an important element of the physical examination is collecting the history of other atherosclerotic circulatory diseases, such as the coronary artery disease, stroke, transient ischemic attack, chronic mesenteric ischemia and other conditions of the circulatory system, such as arterial hypertension, arrhythmias (including atrial fibrillation) and heart failure. Equally important is the assessment of comorbidities, obesity and the patient's habits (physical activity, smoking, a diet with high fat or carbohydrate content) [1]. It is necessary to assess the cardiovascular risk factors identified mainly on the basis of laboratory tests, such as lipid disorders, diabetes or kidney failure, which affect the progression of ischemic lesions [1]. Aside from the assessment of

the site condition, the physical examination must also include measuring the pulse in typical sites on lower extremities (femoral artery, popliteal artery, dorsal artery of the foot, and posterior tibial artery).

In order to acquire an objective assessment of the stage of ischemia, the clinical assessment should be supplemented with additional tests. One of the most basic test methods is the measurement of ABI [1, 4]. Decreased ABI level correlates with the increase of cardiovascular risk [1, 4, 13–16]. It is generally accepted that ABI level ≤ 0.9 signals chronic limb ischemia (limit values 0.9–1.0; normal range: 1–1.4). In the event of measuring different pulse values in the dorsal artery of the foot and the posterior tibial artery of the same limb, the higher of the two values is used in the diagnosis of LEAD [4]. In patients with diseases causing increased arterial wall rigidity, e.g. diabetes, ABI level may increase to above 1.4; in such cases, the parameter cannot be used in the assessment of the severity of ischemia [1, 4, 5]. In patients with diabetes and the potential increase of lower leg arterial wall rigidity, the parameter allowing a more reliable assessment of the blood flow in the limb is the toe-brachial index (TBI). The measurement is taken by placing the sleeve on the big toe; the pressure value is read by the continuous-wave Doppler ultrasound transducer or a plethysmograph. TBI values below 0.7 are considered abnormal [17]. In patients with intermittent claudication, in order to objectively assess the distance covered without pain, a treadmill walking test can be performed. It is recommended to perform the standardized test, with the treadmill inclination of 12 degrees and speed of 3.2 km/h [1, 4, 5]. The $tcPO_2$ measurement may be useful both in the identification of chronic limb ischemia and the assessment of healing of wounds of ischemic origin. Other methods of assessing the microcirculation vessels, including laser Doppler flowmetry and capillaroscopy, are used much less frequently and mainly for scientific purposes.

The next group of additional tests performed in patients with LEAD are imaging test. In most cases, a duplex Doppler ultrasound examination is indicated, as it allows locating and assessing the stage of stenosis/ /occlusion. If the patient requires surgical treatment, a more objective and more comprehensive assessment of limb arteries is needed, including the aorta and iliac arteries. The first-line test is computed tomography (CT) angiography; however, as the method employs a contrast agent, it may deteriorate renal function, especially in patients who are already suffering from renal impairment. An alternative method is magnetic resonance angiography (MRA), but the availability of this test is still limited, the image recording time is much longer, and there is also the risk of contrast agent-induced complications [1, 4]. MRA can be performed without the contrast agent but at the cost of worse visibility of the lesions and a higher number of artefacts. Diagnosis of small vessels is challenging, especially an objective assessment of the vessels of the lower leg and the foot, particularly when vessel wall calcifications are present, e.g. in diabetic patients. The reference method providing the most accurate and precise image of the lower leg and the foot (in particular in patients with diabetic peripheral lesions) is still conventional angiography [1, 4].

Angiography using puncture technique is currently considered justified mainly when a simultaneous therapeutic procedure (revascularization) is planned. An exception is the aforementioned diagnosis of the vessels of the lower leg and the foot in diabetic patients with peripheral lesions since invasive angiography is able to image this vascular segment much more efficiently than other methods.

The recommendations for the medical interview, the physical examination and diagnostic tests in patients with atherosclerotic LEAD are outlined in Table 3.

4. General principles of management, treatment with exercise

The management of patients with LEAD involves two main elements: treatment in order to reduce the global cardiovascular risk, and treatment aimed at the symptoms and risk related to the occurrence of lesions in the arteries of lower extremities, in order to reduce the symptoms in the extremity and/or save the extremity from amputation. The management recommended for reducing the global cardiovascular risk, involving non-pharmacological methods and pharmacotherapy, is similar for all patients with PAD, regardless of the area of the vascular system in which the symptoms of atherosclerotic lesions occur. The treatment targeting local lesions in the arteries of lower extremities is typical for LEAD management.

Non-pharmacological methods — according to the 2017 ESC guidelines [1] on the management of patients with PAD, the following is recommended for all patients in this group:
1) quitting smoking (class of recommendation Ib);
2) healthy diet and physical exercise (class of recommendation Ic).

The notion-pharmacological prevention strategies can also be beneficial in terms of reducing limb incidents. In terms of both the improvement of the symptoms and the reduction of the cardiovascular risk, the most beneficial strategy is the combination of the recommended methods, i.e. quitting smoking alone will have little effect on the walking distance, but combined with exercise training, it will improve

Table 3. Medical interview, physical examination and diagnostic tests for patients with atherosclerotic lower extremity artery disease

Recommendations and instructions	Class of recommendation	Level (quality) of evidence
Medical interview and physical examination		
In the case of patients with increased risk of LEAD (see Table 4), medical interviews should be collected on the symptoms in lower extremities, among them intermittent claudication and unusual exercise symptoms, deterioration of walking efficiency, ischemic rest pain and non-healing wounds of lower extremities. Also, the presence of other circulatory diseases secondary to atherosclerosis and their risk factors should be assessed	I	C
In patients from the increased LEAD risk group (see Table 4) and/or with the symptoms suggesting LEAD, the vascular system of the lower extremities should be examined, including the assessment of pulse in the arteries of the lower extremities, murmurs above the femoral arteries, and visual examination of the lower extremities	I	C
Diagnostic tests		
ABI measurement is recommended for patients with clinically suspected LEAD on the basis of the medical interview or the physical examination	I	C
ABI measurement may be considered for patients in the increased LEAD risk group (see Table 4) without the clinical suspicion of LEAD on the basis of the medical interviews or the physical examination	IIb	C
ABI measurement is recommended as the first-line method for diagnosing LEAD	I	C
In the event of clinical suspicion of LEAD in patients with ABI > 1.4, or in the event of confirmed diabetes, the measurement of the toe-brachial index is recommended	I	C
In the patients with symptomatic LEAD who are considered for revascularization, anatomical imaging methods are recommended, such as duplex ultrasound (first-line method), computed tomography angiography or magnetic resonance angiography	I	C

ABI: ankle-brachial index; LEAD: lower extremity artery disease

Table 4. Patients with increased risk of atherosclerotic lower extremity artery disease (based on [1, 2])

Other atherosclerotic circulatory disease (coronary artery disease, peripheral artery disease in another area of the vascular system)
Heart failure
Abdominal aortic aneurysm
Chronic kidney disease
Age ≥ 65
Patients are aged < 65 with atherosclerosis risk factors (smoking, hyperlipidemia, arterial hypertension, diabetes), especially those in high and very high cardiovascular risk according to ESC guidelines on the prevention of circulatory diseases [18]
Patients aged > 50 with a family history of LEAD

ESC: European Society of Cardiology; LEAD: lower extremity artery disease

the walking distance considerably. On the other hand, smoking deteriorates LEAD in patients with intermittent claudication and increases the risk of amputation [18, 19].

Pharmacotherapy — each patient with PAD should receive pharmacotherapy as recommended in the guidelines in order to reduce the incidence of cardiovascular events and events related to ex-

Table 5. Recommendations on reducing the cardiovascular risk in patients with atherosclerotic lower extremity artery disease

Recommendation	Class of recommendation	Level (quality) of evidence
Non-pharmacological methods		
Quitting smoking is recommended for all patients with LEAD	I	B
A healthy diet and physical exercise are recommended for all patients with LEAD	I	C
Lipid disorders treatment		
Treatment with statins is recommended for all patients with LEAD	I	A
For patients with LEAD, it is recommended to reduce the LDL-C level to < 1.8 mmol/L (70 mg/dL), or ≥ 50%, if the initial LDL-C level is 1.8-3.5 mmol/L (70–135 mg/dL)	I	C
Anticoagulation treatment		
Long-term anticoagulation treatment is recommended for all patients with symptomatic LEAD or after revascularization due to LEAD (see Table 8)	I	A[a]
Arterial hypertension treatment		
Non-pharmacological methods should be applied according to the general standards	I	A
For patients with LEAD and arterial hypertension, the recommended target blood pressure is < 140/90 mm Hg[b]	I	A
All main classes of hypotensive drugs can be used, depending on the co-occurring clinical conditions	IIa	C
The inhibitors of the renin-angiotensin system (ACEI or ARB) should be considered as the first-line drugs for patients with LEAD and arterial hypertension	IIa	B
Beta-adrenolytics should be considered for patients with LEAD and indications for beta-adrenolytic therapy due to comorbidities (e.g. history of heart attack, heart failure with impaired left ventricular contractile function)	IIa	B
ACEI should not be combined with ARB in treating arterial hypertension	III	A
Diabetes treatment		
Strict glycemic control and standard treatment of diabetes are recommended for diabetic patients with LEAD	I	C

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; LDL-C: cholesterol in low-density lipoprotein fraction; LEAD: lower extremity artery disease
[a] Patients with symptomatic LEAD — the level of evidence A; patients after revascularization — the level of evidence C
[b] With the exception of patients, for whom higher target values might be indicated, e.g. elderly patients with frailty syndrome

tremities. The pharmacotherapy recommended for patients with PAD includes first of all anticoagulation drugs (mainly antiplatelet agents) and statins, and treatment related to any additional risk factors, such as co-occurring diabetes or arterial hypertension (see chapter 5).

The ESC guidelines emphasize that even if patients with LEAD are asymptomatic, the cardiovascular risk remains high and most strategies of cardiovascular events prevention are beneficial to them, in particular, strict control of the risk factors. An exception is an antiplatelet treatment which is recommended mainly for patients with symptomatic LEAD; no benefits to asymptomatic patients of administering antiplatelet agents have been confirmed.

The recommendations on the reduction of cardiovascular risk in patients with atherosclerotic LEAD are outlined in Table 5.

Symptomatic treatment — in patients with intermittent claudication, the treatment aimed at improving LEAD symptoms is based mainly on exercise training (see below). If the patient's daily activities are significantly disturbed, revascularization should be considered, combined with exercise therapy; this also applies to the situations when activity is significantly reduced despite the exercise therapy and other treatment methods. The details of the revascularization treatment of the arteries of lower extremities exceed the scope of this study. The drugs improving LEAD symptoms (mainly intermittent clau-

Table 6. Recommendations on symptomatic treatment of patients with intermittent claudication

Recommendation	Class of recommendation	Level (quality) of evidence
Statins		
Regardless of the benefits in terms of reducing cardiovascular risk, statins are also recommended to improve the walking distance	I	B
Exercise therapy		
Supervised walking training is recommended for all patients with chronic lower limb ischemia who are able to exercise. The patient should attend walking training sessions for at least 3 months, and the exercise on the treadmill should be intense enough to induce intermittent claudication; after each episode of claudication, the patient should rest	I	A
If supervised exercise training is not possible or available, unsupervised exercise training/physical exercise is recommended	I	C
Treatment extending the walking distance		
For patients with intermittent claudication, for whom elimination of risk factors and walking training is not bringing sufficient improvement, symptomatic pharmacotherapy may be considered to extend the patient's walking distance (See Table 11)	IIb	A
Revascularization		
If despite the exercise therapy and other methods, the patient's normal functioning remains disturbed, revascularization should be considered	IIa	C
If the patient's normal functioning remains severely disturbed, revascularization combined with exercise therapy and other methods should be considered	IIa	B

dication) play a supporting role and are discussed in detail in item 5.3.

The recommendations on the symptomatic treatment of patients with intermittent claudication are outlined in Table 6.

4.1. Exercise therapy

Aside from reducing cardiovascular risk, systematic physical exercise, in particular, walking, is essential in the treatment of the symptomatic LEAD. Walking training, preferably supervised, not only extends the walking distance by improving the efficiency of the local collateral circulation but is also beneficial to the circulatory system by improving the endothelial function, reducing inflammation, increasing the pain threshold, stimulating angiogenesis, improving cell metabolism and reducing blood viscosity. Exercise therapy improves the performance of the circulatory system and the overall quality of life [1, 20–23].

The ESC guidelines [1] recommend exercise therapy for patients with intermittent claudication, preferably in the form of properly supervised walking training (class of recommendation Ia), and if supervised training is unavailable, unsupervised training is recommended (class of recommendation Ic). In the case of supervised exercise therapy, exercise 3 times a week is usually recommended, starting with a 30-minute training and gradually extending its length to 60 minutes. As soon as the moderate (sub-maximal) pain severity is reached during training on the treadmill, the patient should rest until the pain disappears. The next exercise cycle should follow the same principles, and the total length of the training session should be gradually extended. As the claudication distance is gradually extended with exercise, the treadmill pace and incline may be increased (the recommended initial settings are based on the assumption that pain will appear after 3-5 minutes of walking) [4]. According to a review of data from the Cochrane database on 30 randomized trials, the walking training extended the maximum walking distance (MWD) and pain-free walking distance (PFWD) [24]. Exercise therapy also improved the overall quality of life. The ESC guidelines state that supervised exercise therapy is safe and that routine screening for heart diseases is not required prior to the therapy [25], however, the patient should undergo a clinical assessment of the cardiopulmonary reserve and comorbidities in terms of his/her tolerance of the planned exercise therapy. The minimum duration of exercise therapy is 3 months [24, 26]. The walking training also improves the long-term

treatment outcomes in patients undergoing revascularization [27].

Supervised exercise therapy is more efficient than unsupervised one [1, 26, 28, 29], but if appropriate supervision cannot be provided to the patient, then exercise therapy at home is a useful alternative, usually in the form of intensified walking, as this type of training also improves the overall quality of life and the walking performance [28, 30]. If the patient is unable to walk, alternative types of exercise can be used (e.g. bicycle riding, strength training or rowing machine for upper limbs — e.g. for patients after amputations), since those exercised have also been proven to be effective [29].

5. Pharmacotherapy

The objectives of pharmacotherapy in patients with LEAD include:
1. Reducing the risk of cardiovascular mortality and morbidity.
2. Reducing the risk of lower limb-related incidents.
3. Reducing the LEAD symptoms (mainly intermittent claudication).
4. Improving the treatment outcomes after revascularization (percutaneous or surgical).

In this patient group, pharmacotherapy involves two main elements: treatment to reduce cardiovascular risk and symptomatic treatment. Next, to the non-pharmacological methods, pharmacotherapy is the basic method of reducing the global cardiovascular risk in patients with LEAD, with a major impact on the overall prognosis. In order to reduce the risk of cardiovascular mortality and morbidity, mainly stating (see item 5.1.1) and antiplatelet drugs (see item 5.2) are used, and treatment for other risk factors, such as co-occurring diabetes (see 5.1.2) or arterial hypertension (see 5.1.3). Anticoagulation drugs are used mainly in patients with conventional indications for chronic oral anticoagulation, such as atrial fibrillation or venous thromboembolism. The data from the recently completed clinical trials indicate a potential role of direct oral anticoagulants (DOACs) in the management of LEAD (see 5.2). Some of the aforementioned drugs, in particular, the anticoagulants and statins, also reduce the risk of lower limb-related incidents and improve the outcomes of percutaneous or surgical revascularization.

Pharmacotherapy improving the LEAD symptoms (intermittent claudication) and/or improving the lower extremity function (see 5.3) is only supplementary to other methods of symptomatic treatment, such as walking training therapy and revascularization. Among the many tested pharmacological agents, the most significant improvement of the walking distance in patients with LEAD were achieved with cilostazol

and naftidrofuryl; the usefulness of other drugs is less well-confirmed or unconfirmed, and they are usually not recommended by international guidelines. Some drugs used mainly to reduce the global cardiovascular risk can also play a role in symptomatic treatment, in particular, statins.

5.1. Cardiovascular risk factors control

5.1.1. Hypolipidemic therapy in patients with lower extremity artery disease

Hypolipidemic therapy, mainly with the use of statins, which are pleiotropic drugs, reduces cardiovascular morbidity and mortality, and the overall mortality in patients with overt circulatory diseases, including patients with PAD. According to ESC guidelines, it is recommended for all patients with PAD to reduce the serum level of low-density lipoprotein cholesterol (LDL-C) to < 1.8 mmol/L (< 70 mg/dL), or by ≥ 50%, if the initial LDL-C level is 1.8–3.5 mmol/L (70–135 mg/dL) [1]. This corresponds to the objectives of treatment in patients from the very high cardiovascular risk group [3]. The recent recommendations of the Cardiovascular Pharmacotherapy Section (CPS) of the Polish Cardiac Society, published in the so-called 3rd Declaration of Sopot, specify that all patients with PAD (general atherosclerosis) and additional risk factors should be qualified into the highest risk group, called the extreme risk group in the CPS nomenclature, so their target serum LDL levels should be LDL < 35 mg/dL (< 0.9 mmol/L) (Table 7).

According to the current guidelines of the European Society of Cardiology and other scientific bodies, each patient with LEAD must receive statins from the attending physician (class IA recommendation) [1–3]. The results of the studies conducted thus far have shown that using statins reduces overall mortality and the incidence of cardiovascular events in patients with various stages of LEAD [31, 35]. Statins also significantly improve the walking distance until pain occurs and the maximum walking distance, and may reduce the incidence of adverse events in the limbs of patients with LEAD [34] (see 5.3).

In those patients who do not achieve the therapeutic goals with statins alone, statin therapy combined with ezetimibe can be beneficial [36]. A randomized clinical trial did not show a reduction of the cardiovascular risk in LEAD patients treated with bezafibrate as compared to placebo [37].

Recently, results of trials were published showing that the new, strong hypolipidemic drugs, proprotein convertase subtilisin/kexin type 9 (PCSK9), further considerably reduced the LDL-C levels and improved the clinical outcomes in patients with PAD. In the FOURIER

Table 7. Target low-density lipoprotein levels in relation to the cardiovascular risk profile (authors'original contribution).

Risk category	Presence of disease, risk factors or 10-year Pol-SCORE risk	Target LDL-C level
Extremely high	Stenting for left main coronary artery disease and/or multivessel coronary artery disease (complex percutaneous coronary intervention due to multivessel coronary artery disease) **Generalized atherosclerosis — involving multiple vascular beds with additional risk factors** Progression of atherosclerotic cardiovascular disease despite achieving and maintaining LDL-C level < 55 mg/dL (< 1.4 mmol/L)	**< 35 mg/d.** **(< 0.9 mmol/l)**
Very high	Progression of atherosclerotic cardiovascular disease despite achieving and maintaining LDL-C level< 70 mg/dL (< 1.8 mmol/L) Acute coronary syndrome, established coronary, carotid, or peripheral arterial disease Previous revascularization Pol-SCORE risk > 20% Diabetes or stage 3–4 chronic kidney disease with one or more risk factors Familial hypercholesterolemia History of premature atherosclerotic cardiovascular disease (< 55 years in men, < 65 years in women) Established cardiovascular disease in patients with diabetes or stage 3–4 chronic kidney disease	< 55 mg/dl (< 1.4 mmol/l)
High	≥ 2 risk factors and Pol-SCORE risk 10–20% Diabetes or stage 3–4 chronic kidney disease without other risk factors	**< 70 mg/dl** **(< 1.8 mmol/l)**
Moderate	< 2 risk factors and Pol-SCORE risk < 10%	**< 100 mg/dl** **(< 2.6 mmol/l)**
Low	No additional risk factors	**<115 mg/dl** **(< 3.0 mmol/l)**

LDL-C: low-density lipoprotein cholesterol; SCORE: Systematic COronary Risk Evaluation

trial, the PCSK9 inhibitor evolocumab combined with a statin reduced the incidence of cardiovascular events in patients with the atherosclerotic circulatory disease, as compared to the treatment with statins alone [38]. Similar results were achieved in the subgroup of patients with LEAD, for whom evolocumab reduced the cardiovascular mortality and the risk of heart attack, stroke, hospitalization due to angina, or the need for coronary revascularization [39]. Furthermore, treatment with evolocumab reduced the risk of adverse limb-related events (including amputations) by 42% compared to statins alone.

The recommendations on hypolipidemic therapy in patients with LEAD are outlined in Table 5.

5.1.2. Glycemic control in patients with lower extremity artery disease and diabetes

For patients with PAD and co-occurring diabetes, strict glycemic control is recommended according to the general standards [1, 40]. It is also believed that glycemic control is particularly important for improving the lower extremities treatment outcomes, including reducing the frequency of amputations in patients with critical limb ischemia and improving the patency after revascularization in the lower leg [41, 42].

According to the guidelines of the Polish Diabetological Association, the first-line drug for patients with type 2 diabetes is metformin (unless there are contraindications for use) [40]. Choosing the anti-diabetic medications, it should be taken into account that the benefit of reducing the cardiovascular risk has been confirmed for only a handful of those agents. The results of large randomized clinical trials published in recent years show a reduction of the overall and cardiovascular mortality by some GLP-1 receptor agonists (liraglutide among those available in Poland), and SGLT-2 inhibitors (empagliflozin) [40]. It appears that the most beneficial effects were achieved with empagliflozin which significantly reduced the overall mortality, cardiovascular mortality and morbidity (overall mortality caused by cardiovascular disorders, heart attack and stroke), and the risk of hospitalization due to heart failure [43]. In the

recently published review of the results of EMPA-REG OUTCOME trial it was shown that in patients with type 2 diabetes and co-occurring PAD, empagliflozin reduced the cardiovascular mortality by 43% and overall mortality by 38% [44].

The recommendations on the treatment of diabetes in patients with LEAD are outlined in Table 5.

5.1.3. Hypotensive therapy in patients with lower extremity artery disease

Arterial hypertension as a risk factor of the peripheral artery disease

Arterial hypertension is one of the key risk factors of atherosclerosis and its complications. The analysis of causes of death provided in the World Health Organization's report shows that AH is responsible for one-seventh of the overall mortality [45]. Similar conclusions have been formulated from the prospective epidemiological observations of over 8 million patients from around the world, conducted under the Global Burden of Disease study [46].

Globally, arterial hypertension affects around 30% of the adult population. In Poland, data from subsequent editions of NATPOL study show that the current number of patients exceeds 10 million; if the growth tendency is maintained, the population might increase by 50% over the next decade [47].

In the population of patients with abnormal ABI, the percentage of patients with AH is 60% (Rotterdam Study) [48]; similarly, in patients with arterial hypertension, lower ABI values are observed [49]. The risk of LEAD symptoms, such as intermittent claudication, is doubled in patients with AH than in normotensive patients [50] and usually affects untreated patients, or patients with insufficient arterial hypertension control [51]. Among all complications of atherosclerosis, PAD appears to be most closely related to the pulse pressure; each increase of systolic pressure by 20 mm Hg increases the risk of PAD by 63%. [52].

Next to smoking, arterial hypertension is the main PAD progression factor; however, there is insufficient data to confirm that arterial blood pressure control would affect the progression of lesions in the peripheral arteries [53].

Pharmacotherapy of arterial hypertension in patients with lower extremity artery disease

Reducing the arterial blood pressure reduces the risk of cardiovascular complications in patients with PAD. In the clinical trials on the efficacy of hypotensive therapy, the patients with PAD were a small group, but the available data indicate that they benefit from the therapy similarly to other groups [54]. Hence, the current guidelines recommend similar management

of patients with PAD as other groups of patients with arterial hypertension [1, 55]. In the ESC guidelines, the recommended target arterial blood pressure for patients with PAD and AH is < 140/90 mm Hg (class of recommendation Ia) [1]. On the basis of the results of INVEST trial, in which 12% of the population was diagnosed with PAD, it is not recommended to reduce the systolic blood pressure below 110–120 mm Hg due to the potential increase of the cardiovascular risk [56]. In elderly patients with frailty syndrome, it is recommended to reduce the arterial blood pressure in a careful and gradual manner, controlling the patients for orthostatic hypotension, and the aforementioned target arterial blood pressure levels should be achieved only if they are well tolerated by the patients and do not cause excessive pressure drop in standing position [57, 58].

An important element of the management of this patient group is the change of lifestyle (quitting smoking, physical exercise, body weight reduction, reduction of salt intake to < 5–6 g/day). All classes of hypotensive drugs are used in treating arterial hypertension in patients with PAD. As first-line drugs in monotherapy or combined therapy, diuretics, beta-adrenolytics, calcium antagonists, angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) can be used. The choice of the hypotensive drug may depend on comorbidities and co-occurring clinical conditions. The European and American guidelines [1, 2] state that for patients with PAD, ACEI or ARB should be considered as first-line drugs (class of recommendation IIa). The preference for renin-angiotensin system inhibitors arises from the data acquired in HOPE and ONTARGET trials which showed that ramipril or telmisartan reduced the cardiovascular risk in patients with PAD [59, 60]. Those drugs were also beneficial to patients with advanced ischemia (chronic limb-threatening ischemia, CLTI). In this patient group, treatment with ACEI or ARB reduced the incidence of major cardiovascular events and mortality, without affecting the outcomes of limb ischemia treatment [61].

Patients with PAD often have absolute indications for treatment with beta-adrenolytics, such as a history of heart attack or heart failure with impaired left ventricular contractile function. In the observational study, treatment of patients after myocardial infarction with beta-adrenolytics significantly reduced the risk of coronary events by 53% [62]. Using drugs from this class did not affect the claudication distance in patients with mild or moderate LEAD [63]. However, caution is recommended when using those drugs in patients with critical ischemia, despite the fact that in the observational studies, even in patients with CLTI the clinical outcomes of treatment were non-inferior among the patients treated with beta-adrenolytics to patients not receiving those drugs [64, 65].

Data on the beneficial effect of hypotensive drugs on intermittent claudication symptoms (walking distance) in patients with LEAD are limited. The ESC guidelines [1] state that, given the impact on intermittent claudication, calcium antagonists or ACEI/ARB are preferred for patients with PAD and arterial hypertension, due to their ability to dilate peripheral arteries. A randomized clinical trial showed that verapamil extended the walking distance in patients with LEAD [66]. Similar benefits were achieved in one randomized trial with ramipril [67]. The results of trials using ACE inhibitors are controversial, since of the six trials with ACE inhibitors compared to placebo which was included in the meta-analysis in 2013 [68], an improvement in the walking distance was observed in three trials with ramipril, two of which were subsequently retracted due to unreliable data [69], while three trials with other ACE inhibitors (captopril, cilazapril, perindopril), no benefits were achieved. In the new meta-analysis, which included only the four trials remaining after the two studies on ramipril had been retracted, no improvement of the walking distance was found [70].

Nebivolol was also hailed as a beta-adrenolytic drug with additional vasodilatory action [1], but the evidence of the potential superiority of vasodilatory beta-adrenolytics over the conventional beta-adrenalitis in patients with LEAD is very limited. Metoprolol and nebivolol were compared in a double-blind randomized clinical trial with 128 adrenolytic treatment-naïve patients suffering from intermittent claudication and arterial hypertension [71]. After 48 weeks of treatment, both drugs were found to be well-tolerated, exercising similar hypotensive effect and improving the maximum walking distance and ABI in both groups, without significant differences between the groups. Nebivolol was found to be superior only in terms of improving the walking distance until pain occurred.

The recommendations on the treatment of arterial hypertension in patients with LEAD are outlined in Table 5.

5.2. Anticoagulation treatment

Anticoagulation treatment is an important aspect of pharmacotherapy in patients with LEAD, aimed at both reducing the global cardiovascular risk and the risk of limb-related incidents, and improving the treatment outcomes after percutaneous or surgical revascularization.

Platelets play a crucial role in the pathogenesis of atherosclerotic and thrombotic complications in the arterial system, and the inhibition of platelet activation and aggregation is the basic mechanism of prevention of adverse cardiovascular events. The antiplatelet agent of choice is acetylsalicylic acid (ASA) which inhibits cyclooxygenase activity and thromboxane A2 synthesis. Other antiplatelet drugs include platelet P2Y12 receptor inhibitors which inhibit ADP-induced platelet activation, thienopyridine derivatives (ticlopidine, later replaced with clopidogrel and prasugrel), and ticagrelor which unlike clopidogrel is a non-thienopyridine, reversible inhibitor of the P2Y12 receptor. Among the currently used P2Y12 receptor inhibitor, large trials on patients with LEAD studied clopidogrel and ticagrelor, while prasugrel has thus far been studied mainly in patients with coronary artery disease. The new oral antiplatelets are PAR-1 thrombin receptor antagonists (e.g. vorapaxar and atopaxar) which inhibit thrombin-induced platelet activation [72]. Among those agents, vorapaxar was studied in large clinical trials on patients with LEAD. PAR-1 thrombin receptor antagonists are currently not available in Poland.

Anticoagulation drugs, including vitamin K antagonists (VKAs; warfarin and acenocoumarol) and direct oral anticoagulants (DOACs) other than vitamin K antagonists, are used mainly in patients with conventional indications for chronic oral anticoagulation, such as acenocumarol or venous thromboembolism; however, data from the recent clinical trials also indicate a potential role of rivaroxaban combined with ASA in a broader population of patients with LEAD, who do not have conventional indications for chronic oral anticoagulation.

Various anticoagulation therapy strategies are available, but the choice between specific strategies is not always clear [73]. The key international guidelines differ slightly in terms of indication for treatment and the choice of specific drugs [1-3]. Furthermore, no single strategy will be optimal for all disease stages and patient subgroups (i.e. asymptomatic LEAD, intermittent claudication, critical limb ischemia, patients after intravascular or surgical revascularization). In part due to those discrepancies and ambiguities, the anticoagulation treatment remains underused in patients with LEAD despite the high risk of atherosclerotic and thrombotic events in this patient group [73].

5.2.1. Asymptomatic lower extremity artery disease

In two randomized, placebo-controlled clinical trials, no benefits were found from using ASA in asymptomatic LEAD [74, 75]. One of the trials was conducted in a general population with ABI < 0.95, the other in a population of diabetic patients with ABI < 1.0. No benefits from using ASA were also found in subgroups with ABI < 0.9, although those studies might not have had the sufficient statistical power to detect benefits from using ASA in patients with lower ABI values [73]. On the basis of the results of those trials, the

ESC guidelines on the management of PAD [1] stated that antiplatelet therapy is indicated for patients with symptomatic LEAD or after revascularization (class of recommendation/level of evidence: I A/C), but is not routinely indicated in patients with asymptomatic LEAD who do not have indications for antiplatelet therapy due to another arterial disease (e.g. coronary artery disease). Authors of other guidelines believe, however, that antiplatelet therapy should be considered also for patients with asymptomatic LEAD (ABI ≤ 0.9), given the generalized nature of atherosclerosis and high cardiovascular risk in those patients (class of recommendation/ /level of evidence: IIa/C in 2016 AHA/ACC guidelines) [2]. Given the absence of evidence of the benefits of antiplatelet therapy in patients with asymptomatic LEAD, it is also unclear whether patients with masked LEAD (see 3.2) should be classified as patients with asymptomatic or symptomatic disease.

5.2.2 Symptomatic lower extremity artery disease
Single antiplatelet drug therapy
Acetylsalicylic acid — it is believed that the strongest evidence of the benefits of using ASA in symptomatic LEAD has been provided by the Antithrombotic Trialists Collaboration meta-analysis which showed that in 6, 200 patients with intermittent claudication, taking ASA significantly reduced the incidence of major adverse cardiovascular events (MACE; cardiovascular deaths, and non-fatal myocardial infarction and stroke), as compared to the control group [76]. Also, in the later randomized CLIPS trial which enrolled patients with asymptomatic LEAD or intermittent claudication (n = 366, 77% of patients with intermittent claudication), using ASA significantly reduced the incidence of MACE or critical limb ischemia [77]. However, some meta-analyses did not find significant benefits from using ASA in patients suffering mainly from symptomatic PAD [78].

Clopidogrel — in the *post hoc* analysis of the data from CAPRIE trial, it was found that in the subgroup of 6,452 patients with clinically overt LEAD clopidogrel significantly reduced cardiovascular mortality and the incidence of MACE as compared to ASA [79]. Indirect comparisons of various regimens using the meta-analysis of clinical trials also show the superiority of clopidogrel over ASA [80]. Based on the data from CAPRIE trial, the ESC guidelines considered clopidogrel to be more preferable than ASA, however, with a low class of recommendation and level of evidence (IIb/B) [1], while the other major international guidelines [2, 3] do not prefer clopidogrel over ASA as the antiplatelet drug of choice for symptomatic LEAD monotherapy.

Ticagrelor — the randomized EUCLID trial compared ticagrelor with clopidogrel in 13, 885 patients with symptomatic LEAD, finding no difference in the

incidence of MACE or major bleeding [81]. Treatment with ticagrelor was related to a significantly higher incidence of stroke, and also more frequent termination of treatment.

Dual antiplatelet therapy
It is believed that there is no direct evidence of the superiority of dual antiplatelet therapy (DAPT) with clopidogrel and ASA over ASA alone in patients with LEAD [82]. Dual antiplatelet therapy with clopidogrel and ASA was compared to ASA alone in CHARISMA trial. In the subgroup of patients with LEAD, using DAPT reduced the incidence of myocardial infarction, without affecting the overall incidence of MACE, and also increased 2-fold the incidence of minor bleeding, without affecting the incidence of major, fatal and moderate bleeding [83].

The comparison of PAR-1 thrombin receptor antagonist vorapaxar with placebo (in both groups, in combination with standard antiplatelet therapy) in the subgroup of patients with symptomatic LEAD in TRACER trial failed to demonstrate a significant reduction of the incidence of ischemic events, peripheral revascularization and amputations by that antiplatelet agent [84]. In larger TRA2°P-TIMI 50 trial, in the subgroup of patients with symptomatic LEAD, vorapaxar failed to reduce the risk of MACE but significantly reduced the risk of acute limb ischemia and peripheral revascularization as compared to placebo (in both groups in combination with standard antiplatelet therapy), however, at the cost of the increased bleeding risk [85, 86].

Dual antiplatelet therapy in patients with lower extremity artery disease and co-occurring coronary artery disease
The co-occurrence of LEAD and coronary artery disease is related to worse prognosis, and the presence of LEAD in patients might be an argument for a prolonged DAPT. In PRODIGY trial, which compared different durations of DAPT (clopidogrel and ASA) after coronary artery stenting, DAPT prolonged to 24 months reduced the risk of MACE in the subgroup of patients with co-occurring LEAD, as compared to a 6-month DAPT; however, for the entire group, no evidence of superiority of prolonged DAPT was found [87, 88]. PEGASUS–TIMI 54 trial assessed prolonged use of ticagrelor in the dose of 90 mg or 60 mg bid, combined with a low dose of ASA, in stable patients who had suffered from a myocardial infarction (1–3 years prior) [89]. In the subgroup of patients with the concomitant LEAD, ticagrelor was most beneficial in terms of reducing the incidence of MACE, and also significantly reduced the risk of major adverse events in the limb (acute limb ischemia and peripheral revascularization) [90]. The

ESC guidelines on the management of PAD [1] state that long-term treatment with ticagrelor combined with low-dose ASA may be considered in patients with LEAD who had suffered from a myocardial infarction more than 3 years prior (no class of recommendation specified).

Both the long-term use of ticagrelor combined with ASA after a heart attack in PEGASUS–TIMI 54 trial, and the prolonged DAPT with clopidogrel and ASA after acute coronary syndrome and/or coronary artery stenting, increased the incidence of major bleeding [89, 91]. The decision on prolonging DAPT must include a careful assessment of the risk of both ischemic events and bleeding. The duration of DAPT in patients with coronary artery disease and concomitant LEAD, who are receiving DAPT for acute coronary syndrome and/or percutaneous coronary intervention, should generally conform to the current guidelines on DAPT [92].

Combined antiplatelet and anticoagulation therapy

Conventional anticoagulation therapy does not play an important role for patients with symptomatic LEAD who have no other confirmed indications for such treatment, such as atrial fibrillation or venous thromboembolism. The efficacy of warfarin or acenocumarol (with the target values of the international normalized ratio [INR] of prothrombin time of 2.0–3.0) combined with antiplatelet therapy, as compared to antiplatelet therapy alone in patients with PAD was assessed by WAVE trial. The trial failed to demonstrate the superiority of the combined antiplatelet and anticoagulation therapy in terms of MACE prevention; on the other hand, this type of treatment increased 3-fold the incidence of life-threatening bleeding [93]. An interesting therapeutic option is combining antiplatelet therapy with small doses of new oral anticoagulants. The first observations suggesting a beneficial effect of this kind of combined treatment originate from the studies on the subgroups of patients who suffered from acute coronary syndrome and received small doses of new oral anticoagulants in addition to antiplatelet therapy (ATLAS ACS 2 TIMI 51 trial) [94].

The recent COMPASS trial assessed the new strategy of combined antiplatelet and anticoagulation therapy based on combining ASA with a small dose of DOAC, which was compared to the use of ASA alone and NOAC alone in patients with confirmed stable circulatory disease [95]. Since the results of COMPASS trial suggest new opportunities for combined anticoagulation therapy in patients with LEAD; because those results could not have been included even in the latest 2017 ESC guidelines on the management of PAD, the authors of this document have decided to discuss them in detail herein due to their potential impact on the future practice of management of patients with LEAD.

COMPASS trial

COMPASS was a large, multi-centre, randomized trial which compared the combined treatment with ASA (100 mg/day) and small dose of rivaroxaban (2.5 mg bid), and rivaroxaban alone (5 mg bid) or ASA alone (100 mg/day), in over 27,000 patients with stable coronary artery disease or PAD. The trial was terminated after an average of 23 months of observation due to the superiority of the combined treatment with ASA and rivaroxaban which significantly reduced the incidence of the composite endpoint of cardiovascular deaths, myocardial infarctions and strokes, and the reduction of cardiovascular mortality and overall mortality [95].

In the prospectively planned analysis of a subgroup of 7,470 patients with PAD (LEAD or carotid artery disease) it was determined that the combined treatment with ASA and rivaroxaban significantly reduced the incidence of the aforementioned composite endpoint, as compared to ASA alone (reduction of risk by 28%), and significantly reduced the incidence of major limb-related events, including amputations (reduction of risk by 46%) [96]. The overall risk of amputations due to vascular causes was reduced by 60%, and the risk of major amputations was reduced by 70% compared to the group treated with ASA only. The median treatment period was 21 months. The inclusion criteria for patients with LEAD included: previous percutaneous or surgical intervention, history of amputation, or intermittent claudication in patients with objectively documented LEAD (ABI < 0.9 or arterial stenosis ≥ 50%). Major limb-related incidents were defined as acute limb ischemia, severe chronic limb ischemia requiring vascular intervention, or amputation. The results in the subgroup with LEAD were similar to the entire group of patients with PAD. Monotherapy with rivaroxaban failed to reduce the incidence of the primary endpoint compared to ASA but reduced the incidence of major limb-related incidents, as well as the incidence of amputations. Rivaroxaban, both in monotherapy and in combination with ASA, increased the incidence of major bleeding, mainly from the gastrointestinal tract, but no increase of the incidence of fatal bleeding, intracranial hemorrhages and within the major organs.

Also, the results of a separate analysis were published concerning the incidence of major limb-related events in 6, 391 patients with LEAD who were enrolled in COMPASS trial [97]. Compared to the treatment with ASA alone, the combined treatment with rivaroxaban and ASA reduced the incidence of major limb-related events by 43%, all amputations by 59% and peripheral vascular interventions by 24%. The oc-

currence of a major limb-related event was related to poor prognosis (8.3% risk of death within 1 year; 20.5% risk of amputation within 1 year). The benefits of treatment with rivaroxaban were offset by the increased risk of major bleeding, although without a significant increase in the incidence of severing and fatal bleeding. The authors of the editorial note [98] pointed out that due to the fact that the absolute reduction of the risk of major limb-related events was more or less equal to the absolute increase of the risk of major bleeding, the assessment of the benefits to risk ratio related to the addition of rivaroxaban might be difficult. The risk of major limb-related events was highest in patients with a history of amputations or vascular interventions (3.8%), followed by patients with symptomatic LEAD but without prior amputations or vascular interventions (1.73%). The lowest risk was observed for patients with asymptomatic LEAD (0.5%). Thus, it appears that the benefits to risk ratio may be most favourable for patients with a history of prior amputations and vascular intervention, and the least favourable for patients with asymptomatic LEAD. Given the overall reduction of the risk of MACE in COMPASS trial, it was also concluded that the addition of rivaroxaban may be more beneficial to patients with concomitant coronary artery disease, especially those who had a previous heart attack.

5.2.3. Patients with lower extremity artery disease who underwent intravascular or surgical peripheral revascularization

Antiplatelet and anticoagulation therapy after surgical revascularization of LEAD

Acetylsalicylic acid compared to placebo — the meta-analysis (952 patients) revealed that the patency of the peripheral bypass was significantly improved in the ASA group compared to placebo. The beneficial therapeutic effect was particularly visible for bypasses made with synthetic materials. The incidence of amputations and bleeding and the survival rate were similar regardless of whether ASA was used or not [99].

Acetylsalicylic acid compared to oral anticoagulants — using VKAs after surgical bypassing of peripheral arteries is not well established in the clinical practice. In the trial titled "Dutch Bypass Oral Anticoagulants or Aspirin Study", a 2-year observation failed to demonstrate differences in the patency of the bypasses, mortality and incidence of amputations between the group receiving ASA (or ASA and dipyridamole) and the group receiving VKAs. The analysis of subgroups revealed, however, that in the group with a venous bypass, VKAs prolonged the patency of the bypass. The major bleeding risk was 2 times higher among the patients receiving VKAs [100]. Another study showed that combined therapy with VKA and ASA in the post-operative

period did not significantly impact the patency of the bypasses as compared to the patient group receiving only ASA, but increased the major bleeding risk 2-fold. The only group who benefited from the combined VKA+ASA therapy were the patients who had had a synthetic bypass with 6 mm diameter implanted. The benefit was not observed in patients with the bypass with 8 mm diameter [101]. Also, the use of dalteparin combined with ASA failed to benefit the patients who had undergone surgical revascularization due to LEAD [102]. The benefits from using warfarin and ASA compared to ASA alone were observed in a small study on patients with venous bypasses who were in the high bypass occlusion risk group (suboptimal bypass, poor reception of blood from the bypass, reoperation). The combined treatment was also related to increased incidence of bypass patency and limb preservation but at the cost of increased incidence of hematomas [103]. DAPT was also assessed in comparison to the combined treatment with VKAs and clopidogrel in patients who had undergone femoral-popliteal bypass surgery. A significant difference was found in the patency of the bypasses in favour of the patients treated with VKAs and clopidogrel; the incidence of MACE did not differ between the groups. Also, in that study, the use of VKAs increased the incidence of bleeding [104].

Acetylsalicylic acid compared to dual antiplatelet therapy — the randomized trial CASPAR compared monotherapy (with ASA) with DAPD (ASA + clopidogrel) in patients who had undergone bypass and peripheral shunt surgery below the knee joint. No differences were found between the groups in terms of the incidence of the composite endpoint of bypass occlusion, repeated revascularization, limb amputation above the knee joint, and death. A beneficial therapeutic effect of DAPT in terms of the endpoint specified above was found only in the prospectively defined subgroup of patients who had undergone femoral-popliteal bypass surgery with a synthetic bypass; no such benefits were found in patients with venous bypasses. At the same time, increased bleeding incidence was observed in the DAPT group, although the incidence of sever and fatal bleeding did not differ significantly between both groups [105].

Antiplatelet/anticoagulation therapy after intravascular interventions due to LEAD

Not much data is available on the efficacy and safety of various anticoagulation treatment regimens in patients who undergo intravascular interventions for LEAD. The current standard regimens after intravascular interventions in peripheral arteries are partially based on the results of studies assessing the regimens after coronary interventions.

Currently, the guidelines recommend DAPT for at least 1 month after the intravascular intervention, regardless of the stent type (uncoated metal stent or drug-eluting stents) [1, 3]. In clinical trials, DAPT is typically administered for at least 30-60 days, also in studies with drug-coated balloons [106, 107], although sometimes it is used for much longer periods — for example, in IN. PACT SFA study, in half of the enrolled patients DAPT was continued for over a year [108]. As specified in the ESC guidelines [1], DAPT is often administered longer after stenting arteries below the knee, but there is no evidence to support this strategy. Once DAPT is ended, regardless of its duration, the standard procedure after an intravascular intervention is indefinite treatment with a single antiplatelet agent (ASA or clopidogrel).

In MIRROR study, it was found that the use of clopidogrel and ASA for 6 months reduced the frequency of repeated interventions as compared to ASA alone, but that benefit of DAPT was not maintained after 6 months from discontinuing clopidogrel (i.e. after a total of 12 months of observation). The authors of the study concluded that for the patients who are in a high restenosis risk group, who would potentially benefit most from a prolonged DAPT, long-term treatment may be considered (> 6 months); currently, decisions on prolonging DAPT are often made on a case-by-case basis [109]. Prolonging DAPT may also be considered in the event of a coronary artery disease co-occurring with LEAD (see above). The ESC guidelines on the management of PAD [1] state that in patients with LEAD who have undergone percutaneous revascularization below the groin, DAPT may be prolonged to more than 1 month if the patient previously (i.e. within the previous year) suffered from acute coronary syndrome and/or underwent percutaneous coronary intervention, and also after stenting the last patent coronary artery, and in the event of a multi-vessel coronary artery disease with incomplete revascularization in diabetic patients.

Anticoagulants do not play any role in patients after intravascular interventions due to LEAD. Anticoagulation therapy was analyzed prospectively after percutaneous revascularization below the groin, finding no improvement of vascular patency, while the incidence of bleeding was significantly increased [110].

5.2.4. Summary — choosing the anticoagulation strategy

The anticoagulation therapy options for patients with LEAD can be divided into three main clinical categories: asymptomatic patients (ABI ≤ 0.9, without intermittent claudication), symptomatic patients (intermittent claudication), or patients undergoing intravascular or surgical revascularization. The main clinical trials related to anticoagulation therapy of patients with LEAD are summarized in Figure 1, while the proposed strategies of management are illustrated in Figure 2.

The recommendations on anticoagulation therapy of patients with atherosclerotic LEAD, without separate indications for chronic oral anticoagulation, are outlined in Table 8.
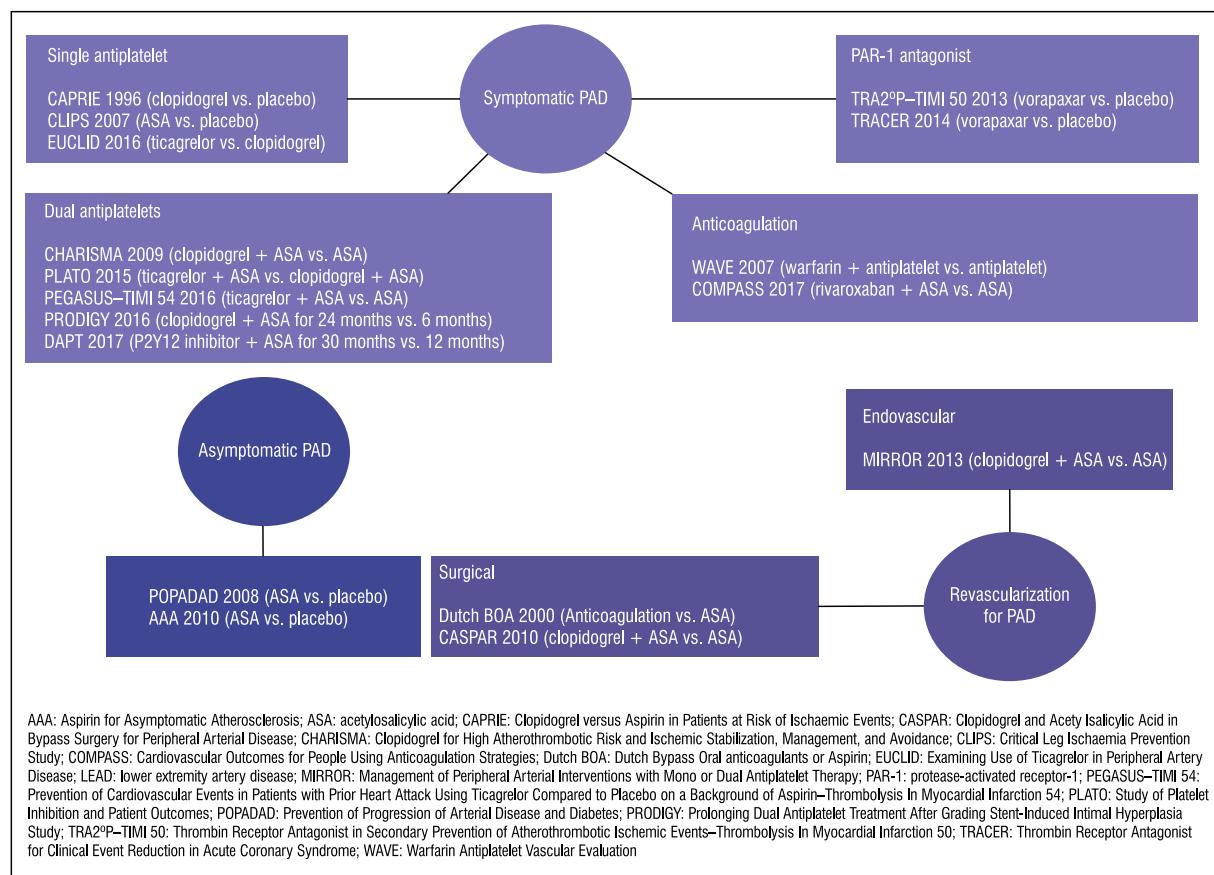
Asymptomatic lower extremity artery disease

In this patient group, treatment with the only single antiplatelet drug should be considered (ASA or clopidogrel). No clear evidence of the benefits of using ASA compared to placebo have been obtained in patients with asymptomatic LEAD, hence the difference of opinion between the experts on the indications for antiplatelet treatment in this group. The ESC guidelines do not recommend using antiplatelet agents in this group (class of recommendation/level of evidence: III/A) [1], while the 2016 AHA/ACC guidelines state that antiplatelet therapy is reasonable also in patients with asymptomatic LEAD (class of recommendation/level of evidence: IIa/C for patients with ABI ≤ 0.9) [2]. This opinion was reiterated in more recent studies by American experts [73]. Treatment with ASA may be considered especially in patients with co-occurring atherosclerotic lesions in other arterial beds. Indications for treatment with ASA may also arise from the co-occurring symptomatic coronary artery disease, or cerebrovascular disease (history of brain stroke or transient ischemic attack [TIA]).

Symptomatic lower extremity artery disease

In this patient group, antiplatelet therapy is clearly recommended (class of recommendation I in all major guidelines) to reduce the risk of cardiovascular events. Treatment with only one antiplatelet agent may be considered, choosing between ASA or clopidogrel; recently, in view of the results of COMPASS trial, also combined anticoagulation therapy with ASA and a small dose of rivaroxaban may also be put into consideration. On the basis of the data from CAPRIE study, which found that clopidogrel was more beneficial than ASA to patients with LEAD, the authors of ESC guidelines [1] have concluded that clopidogrel may be the drug of preference (class of recommendation/level of evidence: IIb/B); this opinion was shared by the authors of other guidelines: in the 2016 ACC/AHA guidelines [2], both drugs have identical class of recommendation/level of evidence (I/A), and the 2015 guidelines of the Society of Vascular Surgery [3] also do not specify preference for clopidogrel (ASA — I/A, clopidogrel as an alternative agent — I/B).

On the basis of the result of COMPASS study, an alternative strategy for anticoagulation treatment
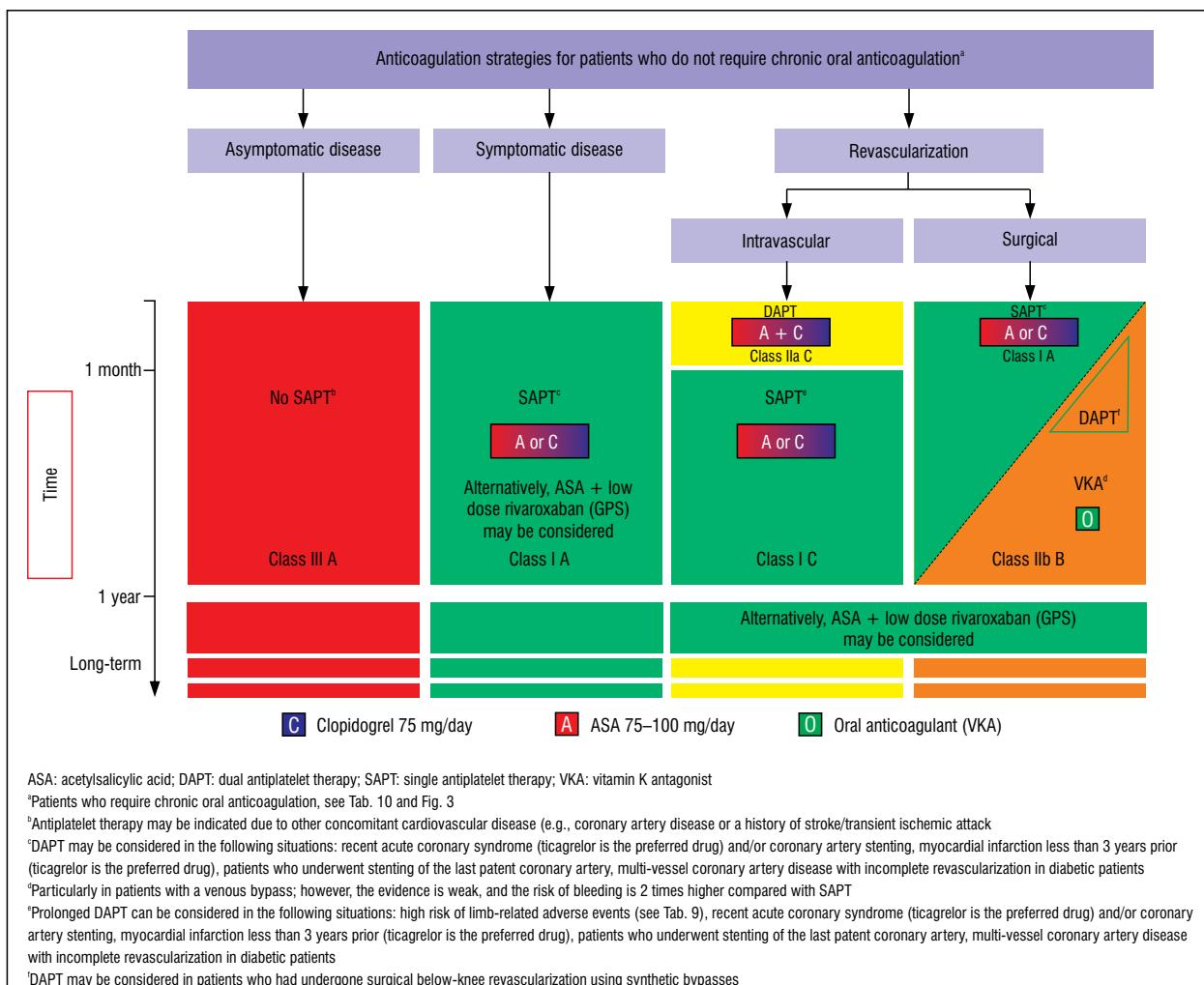
Figure 1. Main clinical trials related to anticoagulation therapy of patients with lower extremity artery disease [73]

in this group may be based on ASA combined with a small dose of rivaroxaban. Given the reduction of the MACE risk, both clopidogrel in CAPRIE study and the combination of ASA and a small dose of rivaroxaban in COMPASS study proved more efficient in patients with LEAD than ASA alone. However, a reduction of the risk of major adverse events in the limb, including amputation, was observed only for the combination of ASA and a small dose of rivaroxaban; there is no evidence of the similar effect of ASA or clopidogrel alone. The absolute reduction of the risk of MACE and major adverse events in the limb in COMPASS study was 1.54% per year (NNT 58) [73], whereas the absolute reduction of the risk of MACE in CAPRIE study was 1.15% per year (NNT 87) [79]. However, there is no direct comparison available between the small dose of rivaroxaban (± ASA) and clopidogrel in patients with LEAD. Taking into consideration the increase of the major bleeding risk, the absolute reduction of the composite incidence of MACE, major adverse events in the limb, fatal bleeding and symptomatic bleeding within the major organs (net clinical benefit) in COMPASS trial was 1.43% per year (NNT 70) [73]. In the

CAPRIE study, clopidogrel proved safer than aspirin in terms of bleeding [79]. Considering the use of ASA and a small dose of rivaroxaban in patients with symptomatic LEAD, the bleeding risk must be weighed carefully, all the more so that the patients in the high bleeding risk group were excluded from COMPASS study. Summing up, it appears that both strategies (clopidogrel and the combination of ASA and a small dose of rivaroxaban) may be considered as potentially more beneficial than ASA alone in patients with symptomatic LEAD.

Other possible anticoagulation strategies are not relevant for this patient group. Ticagrelor is not recommended, since in EUCLID study it did not prove superior to clopidogrel. Similarly, there are no indications for DAPT in patients who do not undergo revascularization due to LEAD, because CHARISMA study failed to demonstrate a clear superiority of the combined treatment with clopidogrel and ASA over single antiplatelet regimen. Vorapaxar is not available in Poland, since according to the clinical trials conducted thus far, vorapaxar's value when combined with standard antiplatelet therapy remains unclear and requires further study (in TRA2°P–TIMI 50 study, a reduction

Figure 2. Anticoagulation strategies for patients with lower extremity artery disease (modified according to [1, 73])

of the risk of acute limb ischemia and the incidence of peripheral revascularizations was shown, but at the cost of increased bleeding risk and without impact on MACE). Conventional anticoagulation therapy (with VKAs or NOACs in standard dosing regimens) should not be used to reduce the risk of cardiovascular/ischemic events in this patient group since no evidence was found of the benefits of such treatment [2, 3, 93].

Patients with LEAD and concomitant coronary artery disease — a separate group is formed by the patients with a history of the recent acute coronary syndrome and/or percutaneous coronary intervention, which should be treated with DAPT with clopidogrel or ticagrelor and ASA. The indication for DAPT arises from coronary artery disease, rather than LEAD. The previous standard therapy involved clopidogrel and ASA. In the current ESC guidelines on the management of patients with ACS, the newer P2Y12 receptor inhibitors (ticagrelor and prasugrel, and only ticagrelor in patients undergoing conservative

treatment) are preferred over clopidogrel [92]. On the basis of the results of PEGASUS–TIMI 54 study, long-term treatment with ticagrelor combined with a small dose of ASA may be considered for patients with LEAD after a history of myocardial infarction less than 3 years prior [1]. For patients with LEAD, prolonged DAPT may also be considered after acute coronary syndrome and/or stenting of coronary arteries. However, both strategies involve an increased risk of major bleeding, hence a careful assessment is necessary for the risk of both ischemic events and bleeding (Table 9). The duration of DAPT in patients with coronary artery disease and concomitant LEAD, who are receiving DAPT for acute coronary syndrome and/or percutaneous coronary intervention, as well as the choice of the P2Y12 receptor inhibitor (ticagrelor or clopidogrel), should generally conform to the current guidelines on DAPT [92]. Following the completion of DAPT, patients in this group receive a single antiplatelet drug (ASA or clopidogrel) indefinitely.

Table 8. Anticoagulation therapy (antiplatelet and antithrombotic) in patients with atherosclerotic lower extremity artery disease

Recommendation	Class of recommendation	Level (quality) of evidence
Asymptomatic LEAD		
Due to the lack of confirmed benefits, antiplatelet therapy is not routinely indicated for patients with isolated asymptomatic LEAD	III	A
Symptomatic LEAD		
Long-term SAPT is recommended for patients with symptomatic LEAD	I	A
Preference of clopidogrel over ASA may be considered	IIb	B
Instead of SAPT, a combined treatment with ASA and small dose of rivaroxaban[b] may be considered, especially in patients with high risk of ischemic events in the limb[c], provided that the bleeding risk is low	GPS	
DAPT is not recommended in patients who are not undergoing revascularization for LEAD	III	B
Oral anticoagulants in therapeutic doses are not recommended in patients who are not undergoing revascularization for LEAD and who have no other indications for long-term oral anticoagulation therapy	III	B
DAPT (ASA + clopidogrel or ticagrelor) may be considered in patients with LEAD who have indications for DAPT due to coronary artery disease[d]	IIb	B
Patients who underwent revascularization for LEAD		
Long-term SAPT is recommended for all patients who underwent revascularization	I	C
SAPT is recommended after surgical revascularization	I	A
VKAs may be considered (without antiplatelet therapy) after surgical revascularization in individual cases, especially in patients with venous bypasses, if the bleeding risk is low compared to the risk of bypass occlusion	IIb	B
DAPT may be considered after surgical revascularization in patients with synthetic bypasses implanted below the knee	IIb	B
DAPT (ASA + clopidogrel) should be considered for at least 1 month after intravascular revascularization	IIa	C
A longer DAPT may be considered after intravascular revascularization in patients with a high risk of an ischemic event in the limb[c]	IIb	B
After both surgical and intravascular revascularization, DAPT (ASA + clopidogrel or ticagrelor) may be considered in patients with LEAD who have indications for DAPT due to coronary artery disease[d]	IIb	B
After both surgical and intravascular revascularization, a combined treatment with ASA and a small dose of rivaroxaban[b] may be considered, especially in patients with a high risk of ischemic events in the limb[c], provided that the bleeding risk is low	GPS	

ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; LEAD: lower extremity artery disease; SAPT: single antiplatelet therapy; VKA: vitamin K antagonist.
[a]If there is no concomitant circulatory disease requiring antiplatelet therapy (e.g. coronary artery disease or a history of stroke/transient ischemic attack of the Central Nervous System)
[b]High risk of an adverse event in the limb can be defined as a synthetic bypass, bypass below the knee, suboptimal bypassing effect, poor blood reception from the bypass, widespread arterial lesions, or tissue loss [73]
[c]Recent acute coronary syndrome (ticagrelor is the preferred drug) and/or stenting of coronary arteries, heart attack < 3 years prior (ticagrelor is the preferred drug), status post-stenting of the last patent coronary artery, multi-vessel coronary artery disease in diabetic patients who have undergone incomplete revascularization

Revascularization due to lower extremity artery disease

Surgical revascularization — for patients who have undergone surgical revascularization, various strategies may be considered, including a single anti- platelet regimen (ASA or clopidogrel), DAPT, VKAs, and recently, given the results of COMPASS study, also the combined anticoagulation therapy with ASA and a small dose of rivaroxaban. Given the results of CASPAR study, it appears that for the entire population of patients who

Table 9. Risk factors of ischemic events, bleeding risk factors and increased risk factors for limbs which should be taken into consideration in making decisions on anticoagulation therapy in patients with atherosclerotic lower extremity artery disease [73]

Risk of ischemic events ↑	Bleeding risk ↑	Risk for limb ↑
History of heart attack	Anticoagulation treatment	Synthetic bypass
Diabetes	History of bleeding	Bypass below the knee
Old age	Old age	Suboptimal bypassing effect
Chronic kidney disease	Chronic kidney disease	Poor reception of blood from the bypass
Heart failure	Anaemia	Widespread arterial lesions
Smoking	Low body weight	Tissue loss

have undergone surgical revascularization, DAPT is not clearly superior over a single antiplatelet regimen. In the study, the benefits of DAPT were observed after bypass surgery below the knee in the patients with synthetic bypasses; no such benefits were found in patients with venous bypasses. The evidence of the benefits of VKA therapy is also limited and obtained mainly from patients with venous bypasses.

The ESC guidelines [1] generally recommend single platelet regimen for this group (ASA or clopidogrel; class of recommendation/level of evidence I/A); alternative strategies include: 1) treatment with VKAs of patients with venous bypasses (class of recommendation/level of evidence: IIb/B), although it is noted that the available evidence for anticoagulation therapy is weak and the bleeding risk increases twofold compared to antiplatelet agents; and 2) DAPT (ASA + clopidogrel) in patients with synthetic bypasses below the knee (class of recommendation/level of evidence: IIb/B). The authors of the guidelines also conclude that for patients with a history of recent acute coronary syndrome and/ /or percutaneous coronary intervention (less than 1 year prior), and after the stenting of the last patent coronary artery, and also in the case of multi-vessel coronary artery disease with incomplete revascularization in diabetic patients, DAPT may be considered [1]. Other major guidelines [2, 3] recommend single antiplatelet regimen (ASA or clopidogrel) or DAPT as an alternative; VKAs are either not recommended [3] or considered to be of uncertain usefulness [2].

In general, intensifying the anticoagulation therapy in this group should be considered firstly for the patients exposed to high risk of major adverse events in the limbs, such as bypass thrombosis or amputation. The risk factors related to the increased limb-related risk include synthetic bypass, bypass below the knee, the suboptimal effect of bypassing, poor blood reception from the bypass, widespread lesions in arteries, and tissue loss (Table 9) [73]. Among the three available

strategies (ASA + small dose of rivaroxaban, DAPT or VKAs), the strongest evidence in terms of reducing the risk of major adverse events in the limbs of patients with LEAD have been acquired for the combined anticoagulation therapy with ASA and a small dose of rivaroxaban. This strategy has not yet been included in the major international guidelines, since the results of COMPASS study were published later, but can be found in the latest expert studies [73].

All regimens of the intensified anticoagulation therapy are related to increased bleeding risk compared to the single antiplatelet regimen. Thus, a careful assessment is necessary for the risk of both limb-related events and bleeding (Table 9).

Intravascular revascularization (angioplasty with or without stenting)

The guidelines generally recommend DAPT (ASA + clopidogrel; ESC class of recommendation/level of evidence: IIa/C) for ≥ 1 month (1–6 months according to MIRROR study [73]); after DAPT is completed, the patients in this group are treated indefinitely with single antiplatelet regimen (ASA or clopidogrel), although in light of the results of COMPASS study, also ASA combined with small dose of rivaroxaban may be considered. Prolonged DAPT may be considered for patients exposed to high risk of major adverse events in the limbs, and also in the case of indications arising from the concomitant coronary artery disease (e.g. recent history of the acute coronary syndrome and/or stenting of coronary arteries). The combined anticoagulation therapy with ASA and a small dose of rivaroxaban may also be more beneficial to patients in the group exposed to high risk of major adverse events in the limb. All regimens of the intensified anticoagulation therapy are related to increased bleeding risk. Thus, a careful assessment is necessary for the risk of both limb-related/ischemic events and bleeding (Table 9).

There is insufficient evidence to differentiate the recommendations on the anticoagulation treatment regimen depending on the intervention type (conventional balloon angioplasty, drug-coated balloon angioplasty, metal stent implantation, drug-eluting stent implantation); the manufacturers' recommendations generally favour longer DAPT for therapies based on pharmacological technology — however, the aforementioned suggestions require confirmation in further studies on the revascularization of peripheral vessels.

5.2.5. Antiplatelet and anticoagulation therapy in patients with lower extremity artery disease and separate indications for chronic oral anticoagulation therapy

Patients with LEAD may have indications for chronic anticoagulation therapy arising from concomitant diseases rather than from LEAD. A typical example is the co-occurrence of atrial fibrillation. LEAD is one of the risk factors of atrial fibrillation, and this type of arrythmia affects between 10% and 20% of patients with PAD [111–113]. The co-occurrence of LEAD and atrial fibrillation is related to worse prognosis [113, 114].

Few data are available on the choice of specific anticoagulation therapy in patients with LEAD and indication for oral anticoagulation therapy, it is generally recommended to treat such patients only with an oral anticoagulant, without antiplatelet drugs (class of recommendation/level of evidence: IIa/B in ESC guidelines) [1]. This applies to patients with symptomatic or asymptomatic LEAD, patients who have undergone surgical revascularization for LEAD, and patients who have undergone intravascular revascularization a long time before, or in the event of high bleeding risk. The ESC guidelines recommend that in such situations, the indication for chronic oral anticoagulation should be verified. Typical indications for anticoagulation include paroxysmal, persistent or permanent atrial fibrillation in patients with stroke risk factors, prosthetic heart valve or recent or recurrent venous thromboembolism (deep vein thrombosis and/or pulmonary embolism). In patients with LEAD and atrial fibrillation, anticoagulant is unequivocally recommended (class of recommendation/level of evidence: I/A) in patients with ≥ 2 score on CHA$_2$DS$_2$-VASc scale (congestive heart failure; arterial hypertension; age ≥ 75 — 2 points; diabetes, history of stroke or TIA — 1 point; vascular disease, including coronary artery disease or PAD; age 65–75, female sex), and should be considered (IIa/B) for all other patients. It should be emphasized that the presence of LEAD accounts for 1 point on CHA$_2$DS$_2$-VASc scale and may affect the indication for chronic oral anticoagulation.

The decision to initiate an antiplatelet drug in patients who require long-term anticoagulation may depend on the concomitant coronary artery disease (recent acute coronary syndrome and/or percutaneous coronary intervention), or the need for intravascular revascularization as part of LEAD management. Combined treatment should be administered for the shortest possible time (at least 1 month is recommended), but decisions should be made on a case-by-case basis depending on the clinical indications and the bleeding risk [1]. In such situations, triple therapy (ASA, clopidogrel and anticoagulant) is advised against, with the exception of stenting arteries below the knee and complex lesions related to very high risk of thrombosis [1].

After intravascular revascularization, ASA or clopidogrel combined with an oral anticoagulant for at least 1 month should be considered, if the bleeding risk is low compared to the risk of stent/bypass occlusion (class of recommendation/level of evidence IIa/C in the ESC guidelines). After intravascular revascularization, only an oral anticoagulant should be considered if the bleeding risk is high compared to the risk of stent/bypass occlusion (class of recommendation/level of evidence IIa/C in the ESC guidelines). An oral anticoagulant combined with a single antiplatelet drug for longer than 1 month may be considered in patients with high risk of ischemic events, or in the case of another strong indication for long-term antiplatelet therapy (class of recommendation/level of evidence: IIb/C; the ESC guidelines define it as prior stent thrombosis, acute limb ischemia during treatment with oral anticoagulant, and indications arising from the concomitant coronary artery disease: recent acute coronary syndrome, stenting of the last patent coronary artery, multi-vessel coronary artery disease with incomplete revascularization in diabetic patients [1]). Based on the same indications, also a combination of an oral anticoagulant and a single antiplatelet drug may be considered for patients from the group with high bleeding risk compared to stent/bypass occlusion risk. The proposed algorithm of management, based on the ESC guidelines [1], is illustrated in Figure 3. It is recommended to protect the stomach mucosa with a proton-pump inhibitor; the intensity of the oral anticoagulation must be carefully monitored. The target INR values for patients treated with VKAs is 2.0–2.5, with the exception of patients with the prosthetic mitral valve. Patients who receive NOACs combined with an antiplatelet drug should be treated with the lowest dose tested in the trials which have been the basis for the drug's registration for stroke prevention [115, 116].

The recommendations on anticoagulation therapy of patients with atherosclerotic LEAD and separate

Figure 3. Anticoagulation therapy for patients with lower extremity artery disease who require chronic oral anticoagulation (modified according to [1])

indications for chronic oral anticoagulation are outlined in Table 10.

5.3. Symptomatic treatment

For patients with intermittent claudication, the key elements of therapy are the prevention of cardiovascular events and exercise training. If the patient's daily activities are significantly disturbed, revascularization should be considered (combined with exercise therapy; this also applies to the situations when activity is significantly reduced despite the exercise therapy and other treatment methods). Pharmacotherapy to improve LEAD symptoms is only supplementary.

It should be pointed out that the drugs used to reduce global cardiovascular risk do not significantly improve intermittent claudication. For this reason, for patients with intermittent claudication, pharmacotherapy to improve the LEAD symptoms is often based on drugs other than used in reducing the cardiovascular risk. Statins are an exception since a number of meta-analyses have shown a significant improvement of pain-free

walking distance (PFWD) and maximum walking distance (MWD) in patients treated with statins [31, 117]. Statins can also reduce the incidence of adverse events in the legs of patients with LEAD [34]. Limited data indicating an improvement of the walking distance have also been acquired for hypotensive drugs (ramipril, verapamil) and antiplatelet drugs (details — see Table 3).

It should also be emphasized that pharmacotherapy in intermittent claudication is not as efficient as exercise therapy or successful revascularization. The pharmacotherapy of intermittent claudication is also less efficient in patients who refuse to quit smoking and fail to adhere to exercise therapy. The objective of pharmacotherapy of claudication is to reduce the severity of LEAD symptoms and increase the walking distance for patients with intermittent claudication which affects the quality of life, particularly when modification of the risk factors and exercise therapy are unsuccessful and the patient is not eligible for revascularization, does not consent to such treatment, or there are contraindications for revascularization [1–3].

Table 10. Anticoagulation therapy for patients with lower extremity artery disease who require chronic oral anticoagulation

Recommendation	Class of recommendation	Level (quality) of evidence
For patients with LEAD and atrial fibrillation, OACs: — are recommended for patients with ≥ 2 score on CHA_2DS_2-VASc scale — should be recommended for all other patients	I	A
	IIa	B
For patients with LEAD and indication for OACs (e.g. atrial fibrillation, prosthetic heart valve or venous thromboembolism), treatment only with OACs should be considered	IIa	B
For patients with LEAD and indication for OACs after surgical revascularization, treatment only with OACs should be considered	IIa	C
For patients with LEAD and indication for OACs after intravascular revascularization, SAPT (ASA or clopidogrel) combined with an oral anticoagulant for at least 1 month should be considered, if the bleeding risk is low compared to the risk of stent/bypass occlusion	IIa	C
For patients with LEAD and indication for OACs after intravascular revascularization, treatment only with OACs should be considered, if the bleeding risk is low compared to the risk of stent/bypass occlusion	IIa	C
A combination of OAC and SAPT (ASA or clopidogrel) for longer than 1 month may be considered for patients with a high risk of ischemia, or with another strong indication for long-term SAPT[a]	IIb	C

ASA: acetylsalicylic acid; LEAD: lower extremity artery disease; OAC: oral anticoagulant; SAPT: single antiplatelet therapy
The CHA_2DS_2-VASc score is calculated as follows: congestive heart failure — 1 point, arterial hypertension — 1 point, age ≥ 75 — 2 points, diabetes — 1 point, stroke — 2 points, vascular disease — 1 point, age 65-74 — 1 point, female sex — 1 point
[a]Defined as prior stent thrombosis, acute limb ischemia during oral anticoagulation or concomitant coronary artery disease (recent acute coronary syndrome, status post-stenting of the last patent coronary artery, multi-vessel coronary artery disease with incomplete revascularization in diabetic patients)

A number of pharmacological agents have been assessed in the treatment of intermittent claudication of patients with LEAD. The most promising data, showing an increase in PFWD and MWD in randomized, controlled clinical trials, were acquired for cilostazol and naftidrofuryl [118]; however, only the former is available in Poland. Other assessed agents, which have also been claimed to increase the walking distance in patients with intermittent claudication, include pentoxifylline, carnitine, propionyl-L-carnitine, prostanoids (prostaglandins I2 and E2), buflomedil, L-arginine, maidenhair tree (*Ginkgo biloba*) and sulodexide [117–120]. The ESC guidelines on the management of patients with LEAD emphasize however that only limited objective documentation of the effect is available, and the beneficial impact on the walking distance, if any, is usually minor to moderate, and varies considerably between patients [117]. Also, no additional benefits of those drugs are known when combined with exercise therapy and treatment with statins. Consequently, in the ESC guidelines [1], class of recommendation/level of evidence I / A/C was assigned only to exercise therapy and treatment with statins (for revascularization, class of recommendation//level of evidence IIa / B/C was assigned); no formal recommendations were formulated for other drugs. Among those other drugs, cilostazol and naftidrofuryl

were identified as potentially useful. For other pharmacological agents, i.e. pentoxifylline, prostanoids, buflomedil, L-arginine and maidenhair tree (*Ginkgo biloba*), it was concluded that insufficient data from randomized, controlled clinical trials were available to recommend them to patients with intermittent claudication [119–122]. In the 2016 ACC/AHA guidelines [2], the use of cilostazol as an efficient drug improving the symptoms of LEAD and increasing the walking distance of patients with intermittent claudication was assigned class of recommendation/level of evidence I/A; naftidrofuryl was not included in the guidelines, as it is not available in the United States. The use of pentoxifylline was not recommended (class/level III/B). In the 2015 guidelines published by the Society of Vascular Surgery [3], cilostazol was recommended (class/level 2/A); if the drug is not tolerated or contraindicated, pentoxifylline was recommended as an alternative (class/level 2/B).

Cilostazol is a type III phosphodiesterase inhibitor registered for the treatment of intermittent claudication. Several clinical trials showed that cilostazol increased the MWD and PFWD as compared to placebo [123, 124]. A systematic review comparing cilostazol with naftidrofuryl and pentoxifylline revealed that cilostazol was slightly less efficient than naftidrofuryl but more efficient than pentoxifylline [118]. Due to its

Table 11. Drugs with confirmed or potential efficacy in treating intermittent claudication

Drug	Characteristics and evidence of benefits
Drugs with confirmed clinical efficacy in treating intermittent claudication, recommended by international claudication [1, 2]	
Cilostazol (dosing: 100 mg BID)	Type III phosphodiesterase inhibitor which increases the volume of cyclic AMP, thus inhibiting the contraction of smooth muscles and platelet aggregation. It reduces the proliferation of smooth muscles, which might play a role for patients undergoing angioplasty, and stimulates angiogenesis. Cilostazol also affects the serum levels of lipids, reducing the triglyceride levels and increasing the HDL-C
	It is registered by the FDA for treatment of intermittent claudication and improves MWD and PFWD compared to placebo. It is also more efficient than pentoxifylline [118, 123, 124], but its effect may vary [118, 133]
	Frequent side effects include headache, diarrhoea and other gastrointestinal disorders. Due to its mechanism of action, cilostazol can reduce arterial blood pressure and induce arrhythmia. In randomized clinical trials, cilostazol reduced the incidence of restenosis but increased the incidence of hemorrhagic complications in patients who had undergone intravascular treatment [125]
	Main contraindications include: congestive heart failure, hemorrhagic stroke/unstable angina//heart attack/coronary intervention in the previous 6 months, history of significant ventricular arrhythmia, simultaneous use of ≥ 2 other anticoagulants (antiplatelets or antithrombotics), sever renal impairment (CrCl ≤ 25 mL/min)
	For patients who are simultaneously taking strong CYP3A4 inhibitors (e.g. certain macrolide antibiotics, azole antifungal agents, HIV protease inhibitors), or CYP2C19 inhibitors (e.g. omeprazole), it is recommended to reduce the dose by half (to 50 mg BID)
Naftidrofuryl (dosing: 200 mg TID)	Serotonin-2 receptor antagonist which reduces the aggregation of red blood cells and platelets Not registered by FDA; available only in Europe, but currently not available in Poland Systematic review and meta-analysis revealed that it increased MWD and PFWD [134]. In the systematic review, naftidrofuryl showed slightly higher efficacy than cilostazol [118] Side effects: mainly gastrointestinal, such as nausea, vomiting, diarrhoea, flatulence, abdominal discomfort. Causes less adverse events than cilostazol
Statins	Registered for use in reducing cardiovascular risk, with the restriction that they are not registered for the treatment of intermittent claudication. The statins' effect on claudication is unknown; they might impact vascular tension or stimulate angiogenesis
	Side effects: headache, gastrointestinal symptoms (abdominal pain, constipation, flatulence, diarrhoea), muscular pain or myositis, increased liver enzyme activity, rarely cholestatic hepatitis, rhabdomyolysis
	A number of meta-analyses have shown that statins significantly improve the PFWD and maximum walking distance (MWD) [31, 117]. In the randomized CLEVER trial, conservative treatment, including the use of statins, did not significantly improve the walking efficiency or reduce the symptoms in patients with intermittent claudication, as compared to supervised exercise training or stenting [135]
Drugs with potential, but insufficiently confirmed efficacy in treating intermittent claudication	
Pentoxifylline	A methylxanthine derivative, improving oxygenation by increasing the deformation of red blood cells. Pentoxifylline can inhibit platelet aggregation and affect blood coagulation, especially when combined with anticoagulants
	It is registered by the FDA for treatment of intermittent claudication. Some studies have shown pentoxifylline to increase PFWD and MWD compared to placebo [136], but a systematic review revealed vastly discrepant results in terms of increasing the walking distance [137]. Its clinical application is thus limited due to the difficulty in identifying patients who would benefit from treatment [137]
	The ESC and ACC/AHA guidelines [1, 2] do not recommend using pentoxifylline, while the 2015 guidelines of the Society of Vascular Surgery [3] recommend using pentoxifylline if cilostazol is not tolerated or contraindicated. Given the unavailability of naftidrofuryl in Poland, it seems that pentoxifylline may be sometimes considered as an alternative drug for improving the walking performance if cilostazol cannot be used and other methods (quitting smoking, exercise therapy, statins, revascularization) fail to improve the patient's condition or cannot be used

Table 11 (cd). Drugs with confirmed or potential efficacy in treating intermittent claudication

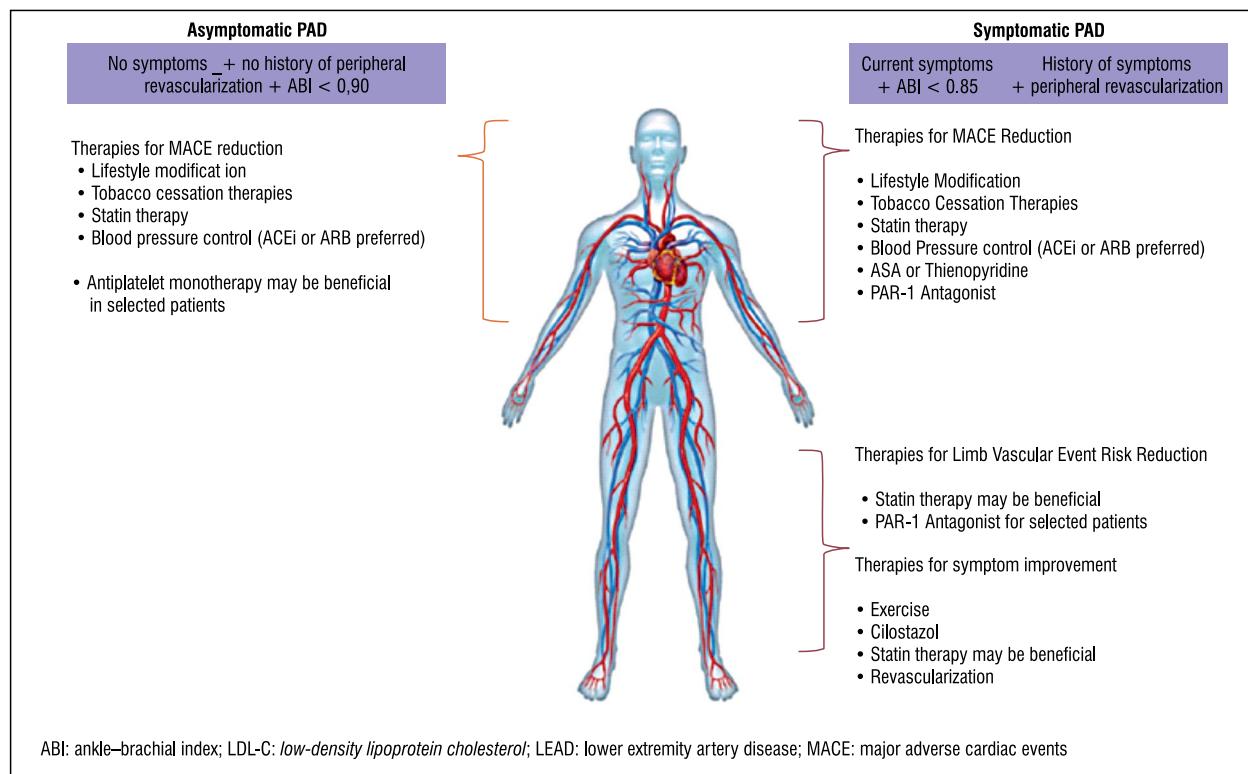| Lek	Charakterystyka i dowody korzyści
Drugs with potential, but insufficiently confirmed efficacy in treating intermittent claudication	
Antiplatelet drugs	A systematic review revealed that antiplatelet therapy significantly increased PFWD compared to placebo [138], but the improvement of the walking distance was achieved mainly for older antiplatelet drugs, such as ticlopidine, while no evidence of the beneficial effect on LEAD was achieved for acetylsalicylic acid or clopidogrel. In one small trial, the combination of acetylsalicylic acid and dipyridamole increased PFWD and resting blood flow in the limbs of patients suffering from intermittent claudication [139]
L-carnitine and propionyl-L-carnitine	Improve energy metabolism in ischemic muscles. Both propionyl-L-carnitine and L-carnitine were studied in clinical trials, showing a slight increase of PFWD and MWD compared to placebo, but finding no benefits compared to walking training [140–144]
L-arginine	The drug has an indirect vasodilatory effect on the smooth muscles of the vessels. Administered intravenously, L-arginine increased MWD compared to placebo, however, no improvement was found in a 6-month study with an oral preparation [145, 146]
Prostanoids (prostaglandins E1 and I2)	Prostanoids have a vasodilatory and antiplatelet effect. Prostaglandin E1 increased MWD compared to placebo [119, 147]; however, in the trials with beraprost (prostacyclin analogue), inconsistent results were obtained [148, 149]
Angiotensin-converting-enzyme inhibitors (ACEI)	May be preferable for treatment of patients with PAD and arterial hypertension due to their vasodilatory effect and improvement of endothelial function, as well as the confirmed reduction of cardiovascular risk in patients with PAD through the renin-angiotensin system inhibitors A randomized clinical trial showed that ACEI increased the walking distance in patients with intermittent claudication [67] The results of trials using ACE inhibitors are controversial, since of the six trials with ACE inhibitors compared to placebo which was included in the meta-analysis in 2013 [68], an improvement in the walking distance was observed in three trials with ramipril, two of which were subsequently retracted due to unreliable data [69], while three trials with other ACE inhibitors (captopril, cilazapril, perindopril), no benefits were achieved. In the new meta-analysis, which included only the four trials remaining after the two studies on ramipril had been retracted, no improvement of the walking distance was found [70]
Verapamil	Calcium antagonist which does not belong to dihydropyridine derivatives. A randomized clinical trial showed that verapamil extended the walking distance in patients with LEAD [66]
Maidenhair tree (*Gingko biloba*)	The mechanism of action of the maidenhair tree has not been fully explaining, but is likely an antioxidant and anticoagulant, inhibiting vascular injuries. A meta-analysis of 11 clinical trials only showed a trend towards the improvement of MWD [150]
Sulodexide	A substance with a broad spectrum of effects (anticoagulant, profibrinolytic, anti-inflammatory, inhibiting fibrosis and protecting vascular endothelial cells) The major international guidelines [1–3] do not list sulodexide among the drugs which are potentially useful in treating intermittent claudication, but in a randomized, double-blinded, placebo-controlled SUAVIS clinical trial, an improvement of MWD and PFWD was shown at 6 months of treatment. The results of treatment in patients with and without diabetes were similar [120]
Padma 28	Padma 28 is a traditional Tibetan medicine containing 22 herbal ingredients. The review of trials in the Cochrane database yielded some data indicating an improvement of the walking distance, at least in short-term trials [151]. Long-term treatment effects are unknown. The available data have limited methodological value and the clinical significance of the observed walking performance improvement is questionable

All abbreviations in the text

antiplatelet action which increases the bleeding risk, care must be taken when combining cilostazol with other antiplatelets and anticoagulants, and also when using the drug in patients with other bleeding risk factors (e.g. active ulcer or improperly controlled arterial hypertension). In randomized clinical trials, cilostazol reduced the incidence of restenosis but increased the incidence of hemorrhagic complications in patients who had undergone intravascular treatment [125]. Frequent side effects include headache, diarrhoea and other gastrointestinal disorders. Due to its mechanism of action, cilostazol can reduce arterial blood pressure and induce arrhythmia. Main contraindications include congestive heart failure, history of significant ventricular

Table 12. Recommendations on drugs improving the walking distance

Recommendation	Class of recommendation	Level (quality) of evidence
Cilostazol is recommended as a first-line symptomatic treatment drug to increase the pain-free walking distance in patients with LEAD and intermittent claudication provided that there are no contraindications for use	I	A
Pentoxifylline may be considered as an alternative drug to increase the walking distance if cilostazol cannot be used The clinical efficacy of pentoxifylline in treating intermittent claudication has not been clearly confirmed and exhibit inter-individual variability	IIb	B
Sulodexide may be considered in the treatment of intermittent claudication in patients with LEAD	IIb	B
The efficacy of other agents, such as L-arginine, L-carnitine/propionyl-L-carnitine, maidenhair tree (*Gingko biloba*) and prostanoids have not been unequivocally confirmed	GPS	
Chelation therapy is inefficient in treating intermittent claudication and may have harmful side effects	III	B

LEAD: lower extremity artery disease

Asymptomatic PAD

No symptoms _+ no history of peripheral revascularization + ABI < 0,90

Therapies for MACE reduction
• Lifestyle modificat ion
• Tobacco cessation therapies
• Statin therapy
• Blood pressure control (ACEi or ARB preferred)

• Antiplatelet monotherapy may be beneficial in selected patients

Symptomatic PAD

Current symptoms   History of symptoms
  + ABI < 0.85   + peripheral revascularization

Therapies for MACE Reduction

• Lifestyle Modification
• Tobacco Cessation Therapies
• Statin therapy
• Blood Pressure control (ACEi or ARB preferred)
• ASA or Thienopyridine
• PAR-1 Antagonist

Therapies for Limb Vascular Event Risk Reduction

• Statin therapy may be beneficial
• PAR-1 Antagonist for selected patients

Therapies for symptom improvement

• Exercise
• Cilostazol
• Statin therapy may be beneficial
• Revascularization

ABI: ankle–brachial index; LDL-C: *low-density lipoprotein cholesterol*; LEAD: lower extremity artery disease; MACE: major adverse cardiac events

Figure 4. Key information in the comprehensive approach to the treatment of patients with atherosclerotic lower extremity artery disease (modified from [152])

arrhythmia and simultaneous use of ≥ 2 other anticoagulants (antiplatelets or antithrombotics).

The treatment methods, for which no clinical benefits in terms of improving claudication and which are not recommended, include antithrombotic agents (warfarin and low molecular weight heparin) [126], hormone replacement therapy [127, 128], garlic [129], vitamin E supplementation [130] and chelation therapy [131, 132].

Drugs with confirmed or potential clinical efficacy in treating intermittent claudication are listed in Table 11. The recommendations on the use of drugs improving the walking distance are listed in Tables 11, 12.

6. Summary

The objective of the comprehensive treatment of LEAD is to reduce the risk of cardiovascular events and limb-related incidents and to improve the LEAD symptoms. The main treatment methods for patients with LEAD are provided in Figure 4. Following the review of the available evidence from scientific studies and formulation of the therapeutic recommendations, the Workgroup proposes the following 10 principles of conservative treatment of patients with LEAD:

1. Quitting smoking and using other non-pharmacological methods to reduce cardiovascular risk (healthy diet, exercise).
2. Administering statins to patients with LEAD in order to achieve the target LDL-C level < 1.8 mmol/L (70 mg/dL), or reduce it by ≥ 50%, if the initial LDL-C level is 1.8–3.5 mmol/L (70–135 mg/dL).
3. Treating the concomitant arterial hypertension and diabetes.
4. Anticoagulation therapy for patients with symptomatic LEAD or who have undergone revascularization.
5. In most patients, the basic treatment method is a single antiplatelet drug (ASA or clopidogrel, whereby clopidogrel may be preferable).
6. A promising new treatment strategy, providing an alternative to single antiplatelet therapy, is the combined anticoagulation therapy with ASA and a small dose of rivaroxaban.
7. Dual antiplatelet therapy is applied mainly in the initial period (≥ 1 month) after intravascular revascularization, and in patients with an indication for dual antiplatelet therapy arising from the concomitant coronary artery disease.
8. Oral anticoagulation is applied mainly in patients with separate indications for such therapy (such as atrial fibrillation with stroke risk factors), usually as monotherapy, i.e. without the antiplatelet therapy, or in combination with a single antiplatelet drug, provided that there are other indications (e.g. int he first month following the implantation of a stent in peripheral vessels).
9. The basic method of symptomatic treatment of intermittent claudication is exercise therapy, i.e. walking training.
10. Cilostazol is the drug of choice to supplement the treatment increasing the claudication distance.

Conflict of interest

None.

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