ISSN 1234–950X

ACTA ANGIOLOGICA

2019, Vol. 25, No. 4

POLISH JOURNAL OF VASCULAR DISEASES

JOURNAL OF POLISH SOCIETY FOR VASCULAR SURGERY

JOURNAL OF POLISH ANGIOLOGICAL SOCIETY

Recommendations for the management of lower extremity artery disease (LEAD) based on ESVS/ESC 2017 guidelines. Position document of PTChN, PTNT, PTLR and SFSN PTK experts

Arkadiusz Jawień, Krzysztof J. Filipiak, Andrzej Bręborowicz, Beata Mrozikiewicz-Rakowska, Filip M. Szymański, Piotr Terlecki, Tomasz Zubilewicz

VIA MEDICA

www.journals.viamedica.pl/acta_angiologica

ACTA ANGIOLOGICA

www.journals.viamedica.pl/acta_angiologica

JOURNAL OF POLISH SOCIETY FOR VASCULAR SURGERY

JOURNAL OF POLISH ANGIOLOGICAL SOCIETY

Acta Angiologica (ISSN 1234–950X) is published by VM Media sp. z o.o. VM Group sp. k., Świętokrzyska 73, 80–180 Gdańsk, Poland, tel: (+48 58) 320 94 94, fax: (+48 58) 320 94 60, e-mail: viamedica@viamedica.pl, www.viamedica.pl

Editorial Address: Department of Vascular Surgery and Angiology, Medical University of Lublin, S. Staszica 11, 20–081 Lublin, Poland

Advertising: For details on media opportunities within this journal please contact the advertising sales department, Świętokrzyska 73, 80–180 Gdańsk, Poland, tel: (+48 58) 320 94 52; e-mail: marketing@viamedica.pl

18-0238.004.001

Acta Angiologica is indexed at: Thomson Reuters (Emerging Sources Citation Index), Index Copernicus (114,76), Scopus, EMBASE, EBSCO, Google Scholar, CrossRef, Ulrich's Periodicals Directory, Ministry of Education (20) and Polish Medical Bibliography (GBL). Website www.journals.viamedica.pl/acta_angiologica is certified by Health On the Net Foundation (www.hon.ch)

VIA MEDICA

ORIGINAL ARTICLE

Acta Angiol
Vol. 25, No. 4, pp. 219–269
Doi: 10.5603/AA.2019.0015

ISSN 1234–950X
www.journals.viamedica.pl/acta_angiologica

Recommendations for the management of lower extremity artery disease (LEAD) based on ESVS/ /ESC 2017 guidelines. Position document of PTChN, PTNT, PTLR and SFSN PTK experts

Authors:
Prof. Arkadiusz Jawień MD, PhD[1]
Prof. Krzysztof J. Filipiak MD, PhD[2]
Prof. Andrzej Bręborowicz MD, PhD[3]
Asst. Prof. Beata Mrozikiewicz-Rakowska MD, PhD[4]
Asst. Prof. Filip M. Szymański MD, PhD[2]
Asst. Prof. Piotr Terlecki MD, PhD[5]
Prof. Tomasz Zubilewicz MD, PhD[5]

[1]Department of Vascular Surgery and Angiology, Nicolaus Copernicus University Medical College in Bydgoszcz
[2]1st Department of Cardiology, Medical University of Warsaw
[3]Department of Pathophysiology, Poznań University of Medical Sciences
[4]Department of Diabetology and Internal Medicine, Medical University of Warsaw
[5]Department of Vascular Surgery and Angiology, Medical University of Lublin

*The authors wish to thank Mr. Szymon Jędrzejczyk of the Medical University of Warsaw for his help in the final edition of this positions

Key words: LEAD, guidelines, Polish guidelines

TABLE OF CONTENTS

Address for correspondence: Marek Iłżecki, Chair and Department of Vascular Surgery and Angiology, Medical University of Lublin, Staszica 11, 20–081 Lublin, Poland, e-mail: milzecki@interia.pl

1. Introduction — premises for the position

The Polish term "choroba tętnic obwodowych", derived from the term "peripheral artery disease" (PAD), is becoming increasingly popular in Polish medical articles and refers to the disorders of all peripheral arteries (carotid, vertebral, subclavian, renal, visceral, iliac, upper- and lower limb arteries), nearly always of atherosclerotic background.

From epidemiological standpoint, atherosclerosis of lower limbs is the most common form of peripheral artery disease; hence, an idea was proposed to develop a set of concise guidelines for the management and care provided to patients with lower extremity artery disease (LEAD)

The position of experts drawing up these guidelines for Polish physicians was largely based on the 2017 guidelines of two major societies, namely The European Society of Cardiology (ESC) and the European Society for Vascular Surgery (ESVS). Classes and levels of evidence for individual recommendations are based on these guidelines (Tables 1, 2).

It is the hope of the article's authors that it would contribute to expanding the knowledge regarding the diagnostics and treatment of LEAD among physicians of various specialties and prove helpful in their everyday medical practice. The ideal scenario would include

Table 1. Recommendation classes as routinely used in the European Society of Cardiology's guidelines

Recommendation class	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/ /indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/ /efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

Table 2. Levels of evidence as routinely used in the European Society of Cardiology's guidelines

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

Table 3. General recommendations on the management of patients with peripheral arterial disease (PAD) according to the 2017 ECS and ESVS guidelines

Recommendations	Recommendation class	Level of evidence
In healthcare centers, it is recommended to set up a multidisciplinary Vascular Team to make decisions for the management of patients with PAD	I	C
It is recommended to implement and support initiatives to improve medical and public awareness of PADs, especially cerebrovascular and lower extremity artery diseases	I	C

Table 4. Lower extremity artery diseases — Fontaine and Rutherford's classifications

Fontaine classification		Rutherford's classification		
Grade	Symptoms	Grade	Category	Symptoms
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	I	Mild claudication
IIb	Moderate or severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Minor tissue loss
		III	6	Major tissue loss

the establishment of multidisciplinary vascular teams focused on the treatment of peripheral artery diseases as outlined in the ESC and ESVS guidelines (Table 3).

2. LEAD Epidemiology and risk factors

2.1. LEAD epidemiology in Poland

Lower extremity artery disorder (LEAD) is one of the most commonly overlooked of the most prevalent diseases.

It is rarely diagnosed in subjects below the age of 55; however, its incidence increases with age to reach 8–10% in individuals above the age of 65 and about 20% in individuals above the age of 80 [1].

Due to the variety of disease forms (Table 4) and high variability of risk factors in individual countries, epidemiological data are difficult to interpret and usually pertain to particular clinical forms of LEAD.

The wealth of the residents of individual countries and continents is also important in the epidemiology of LEAD. In high-income societies, LEAD is more prevalent in males whereas in low- and medium-income areas, the total incidence is higher in female rather than in male subjects [2].

There is now a growing conviction that the most reliable source of epidemiological data for the assessment of LEAD prevalence consists in ankle-brachial index (ABI) measurements. As shown by the results of a German study carried out in 6880 subjects above the age of 65, LEAD defined as LEAD of less than 0.9 was detected in 18% of the study population whereas the symptomatic form of the disease, as manifested by intermittent claudication, was observed in as little as 1/10 of this number [3]. These data differ from those in most of other publications where the rate of symptomatic cases ranges between 1/3 and 1/5 of all LEAD patients.

The prevalence of severe LEAD, i.e. critical lower limb ischemia is low and amounts to 0.4%, which corresponds to annual incidence of 500–1000 cases per million individuals; it is higher in diabetic patients. The risk of lower limb amputation is high, with annual rate being estimated as 120–500 cases per million, symmetrically distributed between amputations above and below the knee [4].

Table 5. Overall prevalence of lower extremity artery diseases (LEAD/1000 person-years (Holland — observation period 7.2 years)

	Overall	Males	Females
Asymptomatic LEAD	9.9	7.8	12.4
Symptomatic LEAD	1.0	0.4	1.8

Table 6. Number of life years lost to LEAD/100,000 individuals in 2010

Western Europe	Central Europe	Eastern Europe
31.7	15.1	3.7

Long-term observation studies carried out in Holland provided an additional insight in the epidemiology of LEAD. Table 5 illustrates total LEAD morbidity in symptomatic and asymptomatic patients per 1000 person-years.

Lower extremity artery disease may be fatal in outcome. The mortality rates directly due to LEAD have increased in Europe to reach 3.5/100,000 individuals in 2010. The numbers of life years lost due to LEAD are different in different regions of Europe and depend on numerous risk factors. Table 6 provides interesting epidemiological data from 3 different regions of Europe [6]. However, one should keep in mind that most LEAD patients die from complications of coronary artery disease or brain stroke.

In Poland, precise and comprehensive epidemiological data on the incidence and prevalence of LEAD are unavailable, and hence extrapolation of European or global data is required in many cases. The only available information consists in that each year, about 40,000 patients present for the first time with early symptoms of LEAD.

As unambiguously shown by the results of epidemiological data, there is a need to improve the diagnostic and therapeutic protection of LEAD patients; however, for reasons hitherto unknown, care provided to LEAD patients is of lower standard and markedly differs from that provided to coronary artery disease patients. As shown by the recently published PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study, individuals with LEAD had not been timely and properly diagnosed and, as a consequence, failed to receive optimum conservative treatment similar to that provided to CAD patients [7].

2.2. Risk factors

Atherosclerosis leading to limb ischemia is the most common cause of lower extremity artery disease. Additional risk factors, markedly increasing the risk of ischemic disease, are also at play, and include:

- **Smoking** — a particularly strong LEAD risk factor [7]. Its population share in total risk was estimated to be about 44%. Notably, the connection between LEAD and smoking is maintained after cessation of smoking, albeit it is reduced significantly after more than 10 years from discontinuation of the habit [8].
- **Diabetes** — strongly correlated with LEAD; the odds ratio (OR) in population studies ranged between 1.9 and 4 [7, 9]. The risk increases with the duration of the disease. In diabetic patients, LEAD prognosis is usually worse than in non-diabetic patients. The risk of amputation is fivefold due to the specific location characteristics of atherosclerotic lesions which are frequently formed in distal arteries as well as to common comorbid neuropathy and increased risk of infections [10].
- **Arterial hypertension** — leading to increased incidence of LEAD, with the OR as observed in large epidemiological studies ranging from 1.32 to 2.20 [7, 9]. Arterial hypertension in men aged 40–79 was associated in a 2.42-fold increase in LEAD morbidity [7]. In an analysis encompassing a total of 4.2 million individuals and 44,329 new cases of LEAD, a 20-mm Hg increase in systolic blood pressure (SBP) was correlated with LEAD risk being increased by 63% [11]. In a prospective populational study encompassing 92,728 subjects, arterial hypertension was the strongest predictor of all acute forms of PAD, including acute mesenteric ischemia, acute limb ischemia, and chronic limb-threatening ischemia (CLTI), as well as of their respective treatment outcomes [12].
- **Dyslipidemia** — high prevalence of hypercholesterolemia is an important factor contributing to LEAD. In most studies, total cholesterol levels were correlated with LEAD in multivariate analyses [13–15]. In a prospective study in 51,529 males aged 40–79 years and followed up for 2 decades, hypercholesterolemia was shown to be strongly, gradually, and independently related with clinically

overt LEAD [8]. Protective effects of low-density lipoprotein cholesterol (LDL-C) were observed in all large epidemiological studies. In a comparison of new LEAD cases with a healthy control, the strongest relationship with the disease was observed for the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio [16]. Lipoprotein(a) levels were correlated with the presence and progression of LEAD [17, 18].

- **Age** — the risk of atherosclerosis increases with age; first symptoms develop usually after the age of 40 [19].
- **Gender** — the development of the disease is more common in male patients; however, the risk in postmenopausal women is the same as in males within the same age group due to hormonal changes [19].
- **Increased homocysteine and fibrinogen levels** — both substances promote endothelial damage [16].

2.3. New findings from basic research on the pathogenesis of PAD

Dysfunction of vascular endothelium is one of the main factors initiating the development of atherosclerotic lesions within the arterial system. It is a multifactorial process resulting from natural changes in endothelial function due to aging as well as from adverse environmental factors and factors related to the metabolic status of the system. Although the aging of arteries is unavoidable, appropriate lifestyle, diet, or selection of medications may slow down the process [20].

Despite the fact that the findings from clinical studies are frequently contradictory, increasing the antioxidative potential of endothelial cells is still believed to delay their aging. Increased activity of arginase I in endothelial cells accelerates their aging by means of uncoupling endothelial nitric oxide (NO) synthase subunits with simultaneous oxidative stress and inflammatory reaction among other factors. These processes were inhibited in the presence of N-acetylcysteine (NAC) — a substrate for glutathione synthesis [21]. As demonstrated earlier, long-term supplementation with NAC inhibits endothelial cell aging in patients with peripheral artery atherosclerosis [22]. An important approach to slowing down the development of atherosclerotic lesions consists in maintaining appropriate endothelial NO production and its availability within the vascular bed. As shown in *in vitro* studies, inhibition of arginase II in endothelial cells increased the availability of NO [23]. Another approach consists in supplementation with L-arginine but also with L-citrulline to slow down endothelial aging, inhibit oxidative stress, and increase NO production [24].

The aging of arterial endothelial cells exposed to serum collected from patients with peripheral atherosclerosis is inhibited by sulodexide (Vessel Due F®): a blend of heparin and dermatan sulphate — natural constituents of cell glycocalyx. Sulodexide reduced the prothrombotic and pro-inflammatory properties of arterial endothelium cells caused by their aging at both gene expression and secretion levels [25]. Other studies revealed that sulodexide contributes to reconstruction of damaged glycocalyx layer on the endothelial surface, normalizes the plasma concentration of adhesion proteins, and reduces total and LDL cholesterol levels while increasing HDL-C levels [26]. The protective effect of sulodexide on endothelial cells was also demonstrated in hyperglycemic conditions [27].

Another approach to treatment or correction of atherosclerotic lesions consists in administration of endothelial cell growth factors to stimulate new vessel formation or in a transfer of genes to stimulate the systemic production of these substances. Research is also under way to assess the applicability of autologous stem cells or endothelial progenitor cells for *in vivo* vessel reconstruction. Results of preliminary clinical trial suggest the efficacy of these novel therapies as reflected by reduction of pain and faster ulcer healing. A supplement to these studies is provided by research aimed at preparation of biocompatible substrates facilitating implantation and growth of stem cells for faster initiation of the formation of new blood vessels [28].

2.4. Prognosis

As atherosclerosis is a generalized process, one should keep in mind that patients with lower extremity artery disease may also be at risk of cardiovascular (CV) and cerebrovascular incidents. Numerous studies suggest increased rates of morbidity and mortality related to myocardial infarction of brain stroke in patients with symptomatic or asymptomatic LEAD [7].

ABI is used not only for the diagnosis of LEAD as it is also a strong prognostic factor for CV incident (Fig. 1). ABI values of less than 0.90 are associated with a more-than-twofold increase in the rates of coronary incidents, CV-associated deaths, and overall deaths over ten years [29]. Over a five-year follow-up period, myocardial infarction or brain stroke were observed in 20% of patients with intermittent claudication, while the mortality risk was as high as 10–15% [30]. Figure 2 illustrates the markedly increased risk of fatal incidents for ABI values of less than ABI 0.9 or more than 1.4 [31].

While LEAD is a progressive disorder, its clinical course may be surprisingly stable in many cases. As suggested by long-term study results, significant deterioration of clinical status is observed only in about 25% of patients with intermittent claudication. Limb amputation is performed only in about 1.0– 3.3% of patients with intermittent claudication. Figure 3 presents

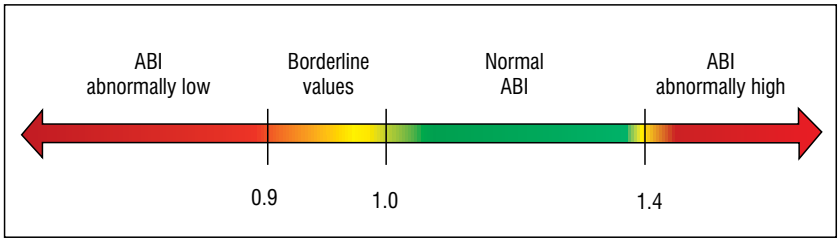


Figure 1. Interpretation of ankle-brachial index (ABI) measurements

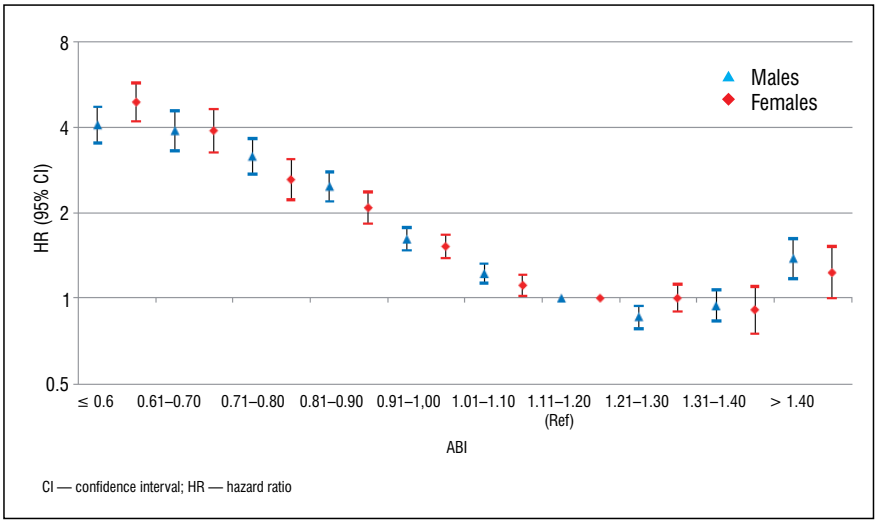


Figure 2. Risk of fatal events in males and females depending on the ankle-brachial index (ABI) value [31]

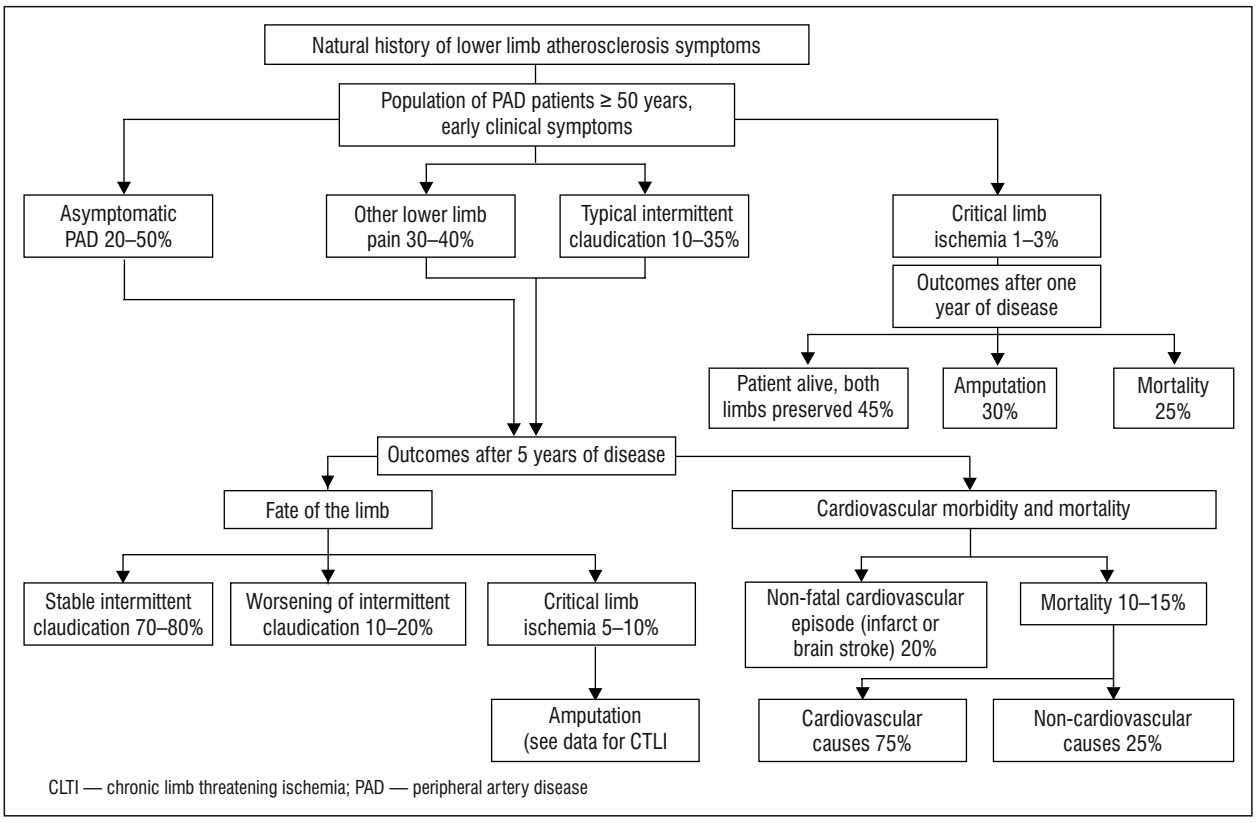


Figure 3. Natural history of lower extremity artery disease

Table 7. Vascular, non-atherosclerotic causes of chronic lower limb ischemia

Vasculitis	1.3%
Peripheral arterial embolism, embolizing aneurysm	0.6%
Fibromuscular dysplasia, compression syndromes (e.g. popliteal artery entrapment syndrome), vascular trauma, chronic venous insufficiency	0.1%

the natural history of LEAD indicating that significant mortality is due to CV incidents of brain stroke rather than to limb amputation [32].

3. Diagnostic Management

3.1. Interviews

Medical interview consists in the collection of information on the presence of clinical symptoms of lower extremity artery disease (LEAD), cardiovascular risk factors, history of surgeries and concomitant diseases. The interview outline should be aimed at obtaining information on current major pain disorders, the onset and the natural history of the disease, other concomitant disorders, and the treatment to date together with the information on patient's lifestyle, diet, physical activity, smoking status and alcohol intake.

Pain disorders due to chronic lower ischemia of lower limbs in the course of atherosclerosis should be differentiated from the frequently concomitant neurological symptoms originating from lumbosacral spine, osteoarthritis, or other vascular symptoms as listed in Table 7.

Considering the generalized character of the disease and the possibility of symptoms of ischemia being previously evident in another body region, particular attention should be paid to the presence of symptoms of coronary artery disease, central nervous system ischemia, abdominal angina, or erectile dysfunction.

Due to the dynamic civilizational progress associated with reduced physical activity of humans, typical symptoms of lower limb ischemia such as intermittent claudication may be diagnosed very late into the course of the disease.

Properly collected medical interview should be included in medical records for easier analysis of the efficacy of future treatment.

The American Heart Association (AHA) AHA PAD Symptom Checklist [33] may come in useful when carrying out interviews with LEAD patients (Table 8).

Table 8. AHA PAD Symptom Checklist [33]

Age above 50	☐
Smoking	☐
Concomitant diseases • diabetes • chronic renal insufficiency • arterial hypertension • hypercholesterolemia	 ☐ ☐ ☐ ☐
Family history of peripheral artery disease	☐
Have you ever been diagnosed for peripheral artery disease, ischemic heart disease, or brain stroke?	☐
Do you ever experience leg fatigue, heaviness, or muscle cramps, particularly during activities?	☐
When looking at your toes and feet, do you see that they are pale, discolored, or blueish?	☐
If you feel leg pain, does it disturb your sleep?	☐
Have you ever had slowly-healing or non-healing ulcers on your toes, feet, or shanks?	☐
Do you regularly have the impression that one of your limbs is colder than the other?	☐
Have you noticed slow growth of toenails and reduced hair growth on your toes and feet?	☐

3.2. Physical examination

Heart rate palpation is the primary component of physical examination. Within the lower extremities, palpation is performed in a comparative manner on both limbs — within the groin (common femoral artery), within the popliteal fossa (infrapopliteal artery), beyond the medial malleolus (posterior tibial vein) and on the dorsum of the foot (anterior tibial/dorsalis pedis artery) (Fig. 4).

Despite its simplicity, the technique has certain diagnostic limitations, particularly in obese patients, patients with concomitant limb edema, and patients with low blood pressure. Palpation of infrapopliteal artery may be particularly difficult due to the anatomical location of the vessel. However, its is not possible to unambiguously rule out LEAD on the basis of the presence of palpable pulse in the arteries of feet. Wrong assessments are made in more than one third of cases due to examiner error. Characterized by sensitivity of 20%, palpation alone is insufficient for the diagnosis of LEAD and, when used as the primary examination, should be combined with auscultation (sensitivity of 75%, specificity of 40%) [34]. Combination of pulse palpation and auscultation with the presence of intermittent claudication increases the efficacy detecting a clinically significant arterial stenosis to 84% [35].

Another, equally important element of physical examination consists in visual inspection of the limbs. In

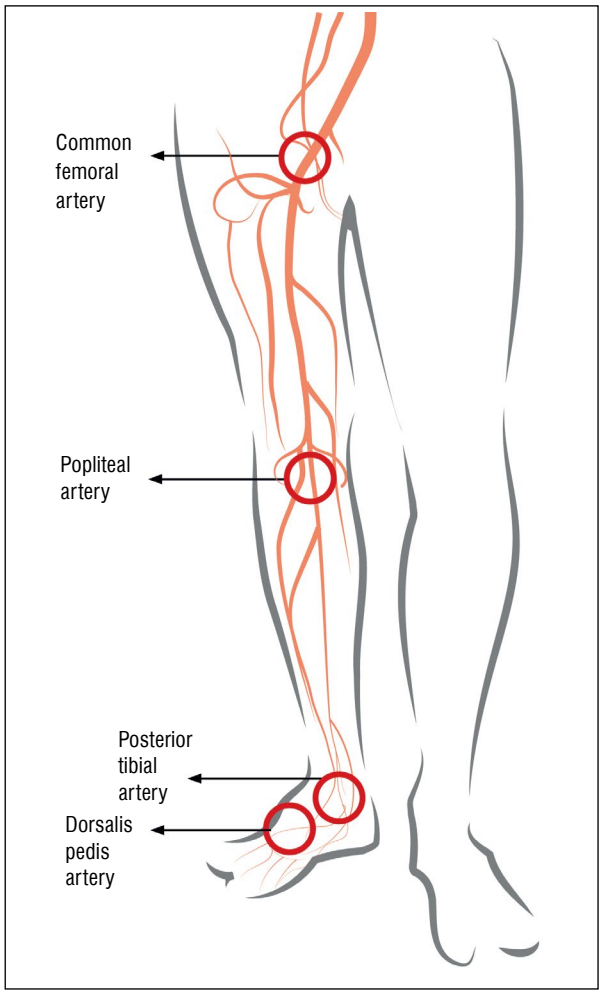


Figure 4. Anatomy of arterial vasculature within the lower limbs with identification of places for pulse palpation

the course of the examination, attention should be paid to the condition of hair and the appearance of toenails. Chronic ischemia is associated with the loss of hair and dull, thickened toenails. Changes in skin coloration manifested as either pallor or redness provide valuable information on the degree of blood supply restriction. Muscular atrophies are typical symptoms of chronic lower limb ischemia; however, one should also keep in mind that disproportionate limb circumferences may also be due to chronic insufficiency or thrombosis of veins.

Combination of all the above elements of physical examination facilitates an objective assessment of the degree of limb ischemia, management strategy and prognosis.

3.3. Laboratory investigations

Laboratory investigations are helpful in the assessment of the risk factors of atherosclerosis and cardiovascular diseases. According to the ECS/ESVS guidelines [36], recommended analyses include peripheral blood counts, electrolytes, albumins, fasting glycemia, lipid profile (total cholesterol, LDL-C, HDL-C and triglycerides), uric acid and creatinine including calculation of estimated glomerular filtration rate (eGFR) as presented in Table 9.

Table 9. Laboratory investigations supporting the assessment of the risk factors of atherosclerosis and cardiovascular diseases

Routine analyses
Fasting plasma glucose
Fasting serum lipid profile: • Total cholesterol • Triglycerides • High-density lipoprotein cholesterol • Low-density lipoprotein cholesterol
Serum creatinine and creatinine clearance
Urinalysis: proteinuria dipstick test, microalbuminuria
• Peripheral blood counts • Uric acid
Additional investigations depending on the findings in the interview, physical examination, and routine laboratory tests.
If fasting plasma glucose > 5.6 mmol/L (101 mg/dL), hemoglobin A_1c or oral glucose tolerance test
Lipoprotein(a) in cases of premature cardiovascular diseases in family history
Quantitative proteinuria in cases of positive dipstick tests

Inflammatory markers and coagulation factors constitute the group of "novel" cardiovascular risk factors. C-reactive protein (CRP), fibrinogen, homocysteine, matrix metalloproteinases (MMP-2, MMP-9), interleukins (IL-6, IL-1), and micro-RNA are among those most commonly examined. Correlations were demonstrated between these factors and the function of platelets and coagulation system, fibrinolysis, endothelial function, and generalized inflammatory response [37]. In recent years, particular attention was drawn to the assessments of micro-RNA — one of the major post-transcriptional regulators of gene expression. Numerous reports confirm the particular role of micro-RNA in the pathogenesis of ischemic heart disease and lower limb atherosclerosis. The increase in the values of the aforementioned factors is prognostic for the risk of both atherosclerosis and its complications [38, 39].

3.4. Methods for LEAD diagnostics

3.4.1. Ankle-brachial index

The ankle-brachial index (ABI) is the ratio of systolic blood pressure recorded at foot arteries (anterior tibia/

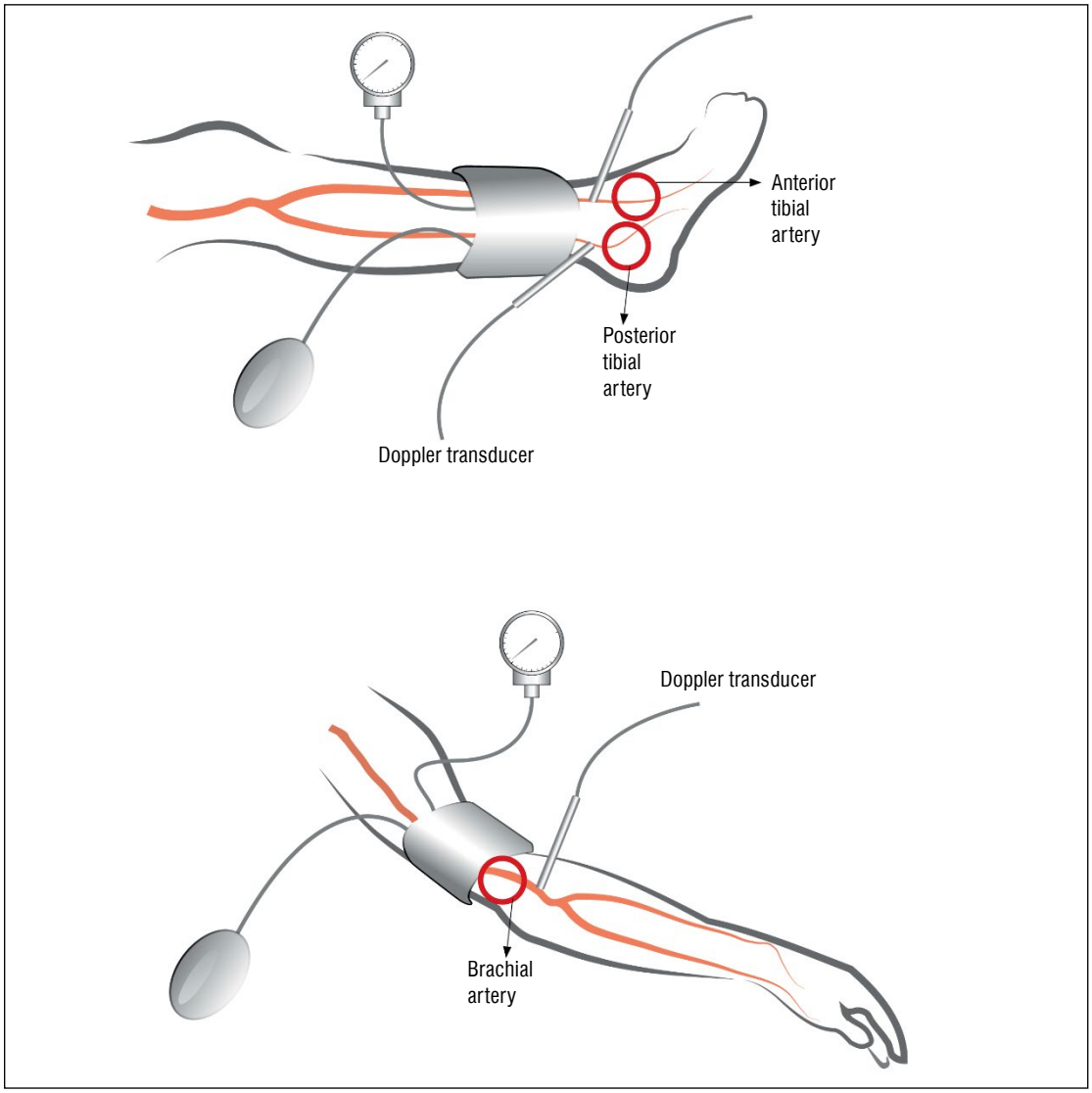


Figure 5. Principles of proper ankle-brachial index measurements

/dorsalis pedis artery and posterior tibial artery) to that recorded at brachial arteries of both upper extremities. Proper measurement consists in dividing the larger pressure as measured within the foot by the larger pressure as measured within the upper extremities. ABI is determined using a standard blood pressure gauge and a Doppler flow detector ("blind Doppler") or a Doppler ultrasound apparatus with an 8–14 Hz transducer.

To make the results more objective, the measurements should be performed after the patient has been at rest for about 10 minutes. According to the guidelines of numerous scientific associations, including ESC, ESVS, Society for Vascular Surgery (SVS), American College of Cardiology/American Heart Association (ACC/AHA) and TransAtlantic Inter-Society Consensus (TASC II), ABI of 0.9 is considered to be a threshold value. Values below 0.9 are indicative of clinically significant LEAD [40–44].

In patients with intermittent claudication, ABI values range between 0.5 and 0.9 and drop below 0.5 in patients with critical ischemia.

Results higher than 1.4 should be interpreted with caution.

Usually, these are due to the presence of strongly calcified atherosclerotic lesions within the arteries of patients with diabetes and advanced chronic renal insufficiency [45].

Figure 5 illustrates the principles of ABI measurements, whereas Tables 10 and 11 provide the list of indications and principles for the interpretation of results according to the ASC/ESVS guidelines [36].

Table 10. Indications for ankle-brachial index (ABI) measurements

Who should be subjected to ABI measurements in clinical practice?
Patients with clinical suspicion of LEAD: • No pulse within lower limb arteries and/or vascular murmur • Typical intermittent claudication or symptoms suggestive of LEAD • Non-healing wound within a lower limb
Patients in the LEAD risk group due to the following clinical conditions: • Diseases of atherosclerotic background: CAD, any PAD • Other conditions: AAA, CKD, heart failure
Asymptomatic individuals from LEAD risk groups: • Males and females aged > 65 • Males and females aged < 65 in the high cardiovascular risk group according to ESC guidelines • Males and females aged > 50 with family history of LEAD

AAA — abdominal aortic aneurysm; CAD — coronary artery disease; CKD — chronic kidney disease; ESC — European Society of Cardiology; LEAD — lower extremity artery disease; PAD — peripheral artery disease

Table 11. Ankle-brachial index (ABI) measurement interpretation rules

How to interpret the ABI readings?
For a LEAD diagnosis to be made, ABI values should be interpreted separately for each lower limb (one ABI value per limb) For stratification of cardiovascular risk, the lowest ABI value as measured in both limb is taken into account Interpretation: • ABI abnormally low — < 0.9 • Borderline values — 0.9–1.0 • Normal ABI — 1.0–1.4 • ABI abnormally high — > 1.4

3.4.1.1. How to measure the ABI?

For the purpose of ABI measurements, patients should be brought to recumbent position and the cuff should be placed just above the ankle while avoiding any wound regions. After 5–10 minutes of rest, a Doppler transducer (5–10 MHz)is used to measure SBP within the posterior and anterior tibial arteries (or the dorsalis pedis artery) of each lower limb and within the brachial arteries of each upper limb. Automated blood pressure cuffs are usually not validated for ankle pressure measurements; in cases of low ankle pressure, the readings may be overestimated. For each lower limb, the ABI is calculated by dividing the highest SBP value in the ankle region by the higher of the SBP values measured within the upper limbs (Fig. 5).

American Diabetes Association recommends ABI screening tests in all diabetic patients above the age of 50; if the results are within the reference range, the test should be repeated every 5 years. Diabetic patients below the age of 50 should undergo screening tests if other risk factors are present such as smoking, arterial hypertension, hyperlipidemia, or the duration of diabetes being longer than 10 years [46].

According to the ACC/AHA guidelines, ABI measurements are indicated in patients aged 65 or more yeas as well as in patients aged 50 or more years presenting with additional risk factors such as diabetes, smoking, or intermittent claudication [32, 47].

Recommendation classes and levels of evidence for the ESC/ESVS guidelines [36] are presented in Table 12.

3.4.1.2. Toe-brachial index

In diabetic patients in whom ABI was found to exceed 1.4, the toe-brachial index (TBI) should be determined for better objectivization of results. The measurement is made by placing the cuff on the big toe and the determining the pressure value using a "blind Doppler" or a Doppler ultrasound device with a linear probe. TBI values of less than 0.7 are considered abnormal [48].

The toe pressure measurement is mainly a measure of perfusion via the posterior tibial artery. In case the measurement results are inadequate for the clinical symptoms of ischemia, additional measurements are recommended within the remaining toes as the perfusion of the lateral part of the foot is achieved via the anterior tibial artery and can't be assessed by the TBI measured on the big toe.

Toe arteries are rarely calcified allowing for diagnosis of LEAD in cases of ambiguous ABI results [33, 49].

Table 12. Recommendations for ankle-brachial index (ABI) measurements

Recommendations	Recommendation class	Level of evidence
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD	I	C
In the case of incompressible ankle arteries or ABI > 1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated	I	C

Supportive methods such as TBI should be used whenever the ABI results are considered inappropriate.

TBI measurements are recommended in patients with trophic disorders, diabetic patients and all patients with ABI of above 1.4.

3.4.2. Exercise tests

In case of ambiguous ABI measurements, functional exercise stress test should be performed as part of LEAD diagnostics.

When performed after 10 minutes of rest, ABI measurement may fail to reflect the less intense symptoms of chronic limb ischemia. Second measurement taken at rest immediately following physical exercise increases the sensitivity of LEAD screening by 10%. If no treadmill is available, the measurement may be taken after an intensive series of standing on one's toe or after a quick stroll along a predefined length of a corridor.

The treadmill test consists in ABI being measured at rest and then after exercise load exerted by walking at the speed of 3 km/h on a treadmill set at 12% incline. The patient walks at a steady pace and at a steady incline as long until they feel pain in their limb or until the predefined test duration has elapsed. A 20% drop in the ABI value confirms the diagnosis of LEAD [50].

Exercise tests are also for objectivization of treatment outcomes. The 36-Item Short Form Health Survey (SF-36) pr the (Walking Impairment Questionnaire (WIQ) are helpful tools for recording treatment efficacy [51].

In case of ambiguous ABI measurements, functional exercise stress test should be performed as part of LEAD diagnostics.

3.4.3. Imaging studies

3.4.3.1. Duplex ultrasonography (DUX)

Doppler ultrasonography is the primary tool for the diagnostics of cardiovascular diseases. Thanks to its non-invasive character and relatively low cost, it is an attractive alternative to other methods used in the diagnostics of LEAD such as angio-CT, angio-MR, or arterography. Doppler ultrasound provides precise information on the degree of arterial stenosis or obstruction and the extent of lesions as well as on the morphological nature and stability of atherosclerotic plaque. The flow rate measurement and the character of the Doppler spectrum provides additional information on lesion severity with the sensitivity of 87–92% and specificity of 94–99% compared to angiography [52, 53].

Examination of lower limb arteries starts with the assessment of the abdominal aorta and iliac arteries using a 3.5 MHz convex transducer.

Infra-inguinal arteries are assessed using linear transducers with the frequency of 5–7.5 MHz. Transducers with higher frequencies may also be used albeit at the cost of examination quality, particularly in obese patients or patients with extensive muscle buildup. The assessment of the degree of arterial stenosis is based on calculating the Kohler's ratio of peak systolic flow velocities or Cosman's absolute peak systolic velocity as presented in Tables 13 and 14.

A limitation to Doppler ultrasound evaluation of lower limb arteries consists in difficult morphological assessment of low-diameter infrapopliteal arteries and iliac arteries in obese patients. However, this limitation is of no clinical importance when the examination is carried out by an experienced operator.

Careful photographic documentation of the examination should be provided in all cases so that the images fully reflect all information contained within the summary.

Routine contrast administration is not recommended in patients undergoing ultrasound diagnostic examination of lower limbs due to LEAD [54].

Duplex ultrasonography is used in preliminary diagnostics of LEAD.

Its diagnostic value depends on the operator's skill, technical parameters of the device, and individual patient-related factors (Fig. 6).

3.4.3.2. Computed tomography angiography (angio-CT)

Multi-slice computed tomography angiography (angio-CT) is a non-invasive diagnostic method facilitating detection of aortoiliac stenoses larger than 50% with the sensitivity of 96% and specificity of 98%, and femoro-subpoliteal stenoses with the sensitivity of

Table 13. Kohler's ratio of peak systolic flow velocities-based criteria

1	Unremarkable vessel — triphasic flow, no spectrum widening
2	Stenosis < 20% — triphasic flow with slight spectrum widening, slight increase in peak systolic velocity not exceeding 30% compared to the proximal segment. Proximal and distal flow spectra unremarkable
3	Stenosis 20–49% — triphasic flow maintained at the stenotic site with regurgitation wave decreasing with the increase in lesions, marked widening of flow spectrum with fill-in of the spectrum window, PSV at stenosis increased by 30–100% compared to the proximal segment. Distal flow spectrum unremarkable
4	Stenosis 50–99% — monophasic flow at the stenotic site, no regurgitation wave, spectral widening (with marked turbulences at more severe stenoses), PSV at stenosis increased by more than 100% compared to the proximal segment. Peripheral flow monophasic, with velocity reduction dependent on the degree of stenosis
5	Vessel obstruction — no color signal or flow within the vessel lumen. Upstream flow slow, with increased resistance, peripheral vessels with slow, monophasic flow. Collateral circulation vessels with non-physiological flow directions are frequently detectable near the lower margin of obstruction. In cases of iliac vessel obstruction, reversed flow may be observed in larger vascular trunks (e.g. deep femoral artery)

Table 14. Cosman's absolute peak systolic velocity-based criteria

	PSV cm/s	Velocity ratio
Unremarkable	< 150	< 1.5:1
30–49%	150–200	1.5:1–2:1
50–75%	200–400	2:1–4:1
> 75%	> 400	> 4:1
Obstruction	No flow	

97% and specificity of 94% when using a 64-slice CT apparatus [55].

The examination is characterized by short duration, low number of artifacts, and the possibility of spatial imaging by means of 3D reconstruction. Despite the ongoing technological progress in computed tomography, interpretation of examination results may sometimes be difficult with regard to low-diameter infrapopliteal arteries with significant degree of calcification [56].

A disadvantage and limitation of angio-CT consists in X-ray exposure, nephro- and thyreotoxicity, and hypersensitivity reactions to contrast agents. For this reason, determination of creatinine, eGFR and thyroid stimulating hormone levels is recommended not later than 7 days prior to the examination. Patients with low renal parameters should be properly hydrated both before and after the examination.

Pregnancy is an absolute contraindication to angio-CT scans; they may be performed only when maternal or fetal life is at risk. Hypersensitivity to iodine is another absolute contraindication to angio-CT scans. Particular care should also be taken in patients with renal, hepatic, or thyroid diseases and allergies [57] (Fig. 7).

3.4.3.3. Magnetic resonance angiography (angio-MR)

Just like computed tomography angiography, magnetic resonance angiography (angio-MR) is a non-invasive, operator-independent imaging technique. High-quality 3D reconstructions may be generated with high sensitivity and specificity of 86% and 93%, respectively, as compared to standard angiography. An advantage of the technique consists in the use of non-ionic contrasts (gadolinium) which are much less nephrotoxic. Gadolinium contrasts are also 6 to 8 times less allergenic (1%).

Significant limitations of angio-MR include the long duration of the examination, possibility of patient experiencing claustrophobia, contraindication in patients with pacemakers or other metallic implants, and significant impact of motion artifacts.

Angio-MR scan may be acquired without administration of the contrast agent; however, this is associated with poorer visualization of lesions and larger number of artifacts [58] (Fig. 8).

3.4.3.4. Digital subtractive angiography

Digital subtraction angiography (DSA) is considered the gold standard in vascular imaging; however, the method has lost much of its value as a diagnostic method due

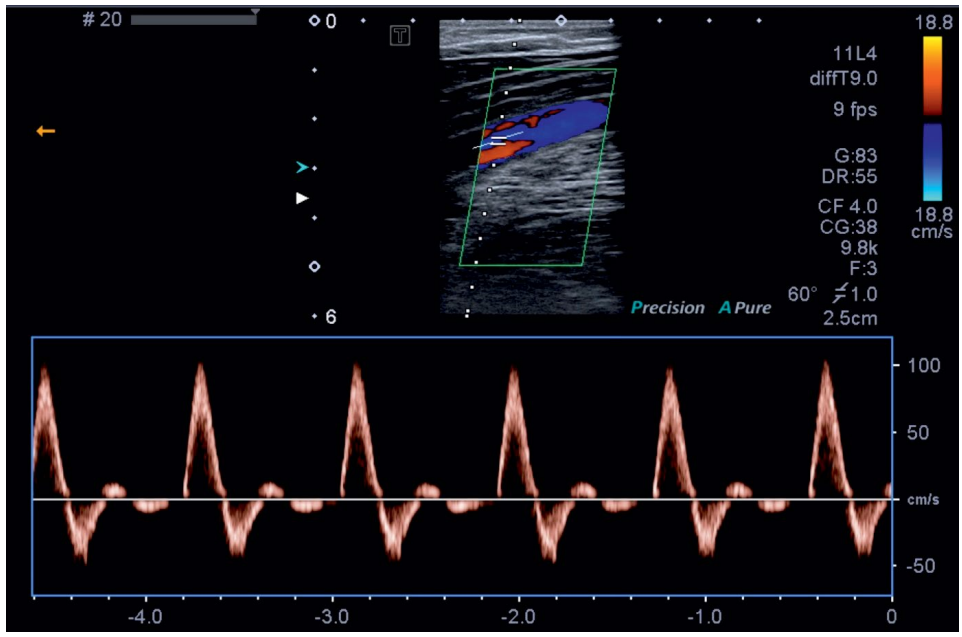


Figure 6. Duplex imaging scan from the records of the Department of Vascular Surgery and Angiology, Medical University of Lublin

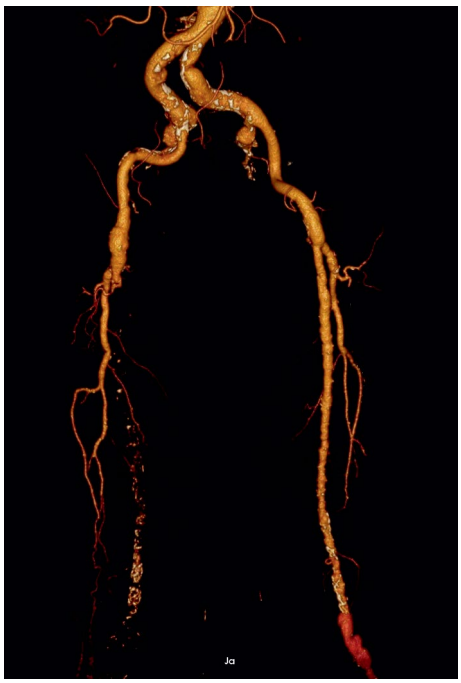


Figure 7. Computed tomography angiography (angio-CT) scan — courtesy of prof. Witold Krupski, z from the records of the 2nd Department of Medical Radiology, Medical University of Lublin

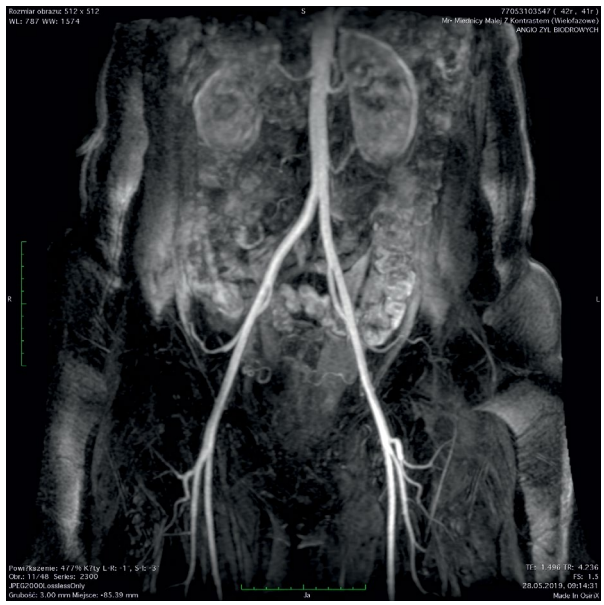


Figure 8. Magnetic resonance angiography (angio-MR) scan — courtesy of prof. Radosław Pietura, from the records of the Department of Interventional Radiology and Diagnostic Imaging, Independent Public Clinical Hospital no. 1 in Lublin

to its invasiveness and potential of serious, sometimes life-threatening complications. Potential iatrogenic complications such as hematoma, pseudoaneurysm, bleeding, arteriovenous fistula, arterial thrombosis and contrast-induced complications are observed in 0,7% of cases and are associated with a 0.16% mortality rate [40].

The greatest advantage of DSA, responsible for its superiority over angio-CT i angio-MR, is the quality of

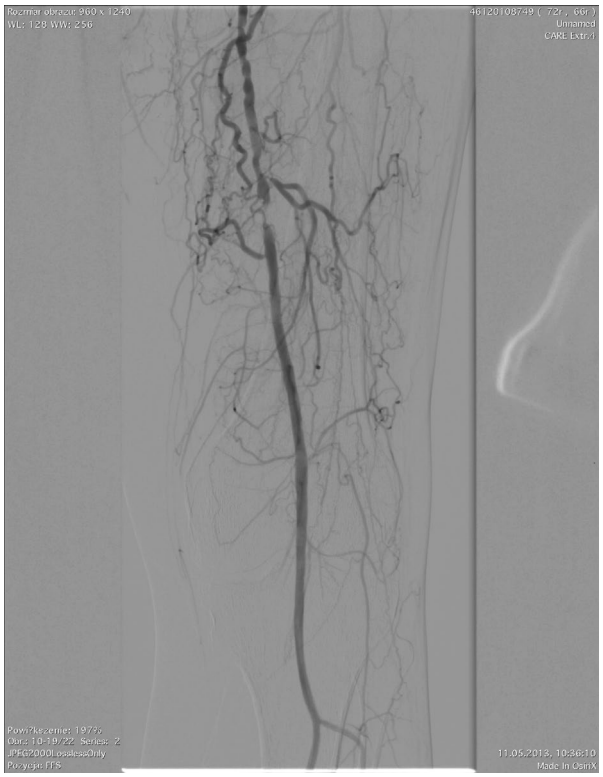


Figure 9. Digital subtractive angiography (DSA) scan — courtesy of prof. Radosław Pietura, from the records of the Department of Interventional Radiology and Diagnostic Imaging, Independent Public Clinical Hospital no. 1 in Lublin

images of small caliber arteries, particularly the foot arch vessels. In addition, DSA facilitates visualization of collateral circulation and measurement of pressure gradients for determination of hemodynamic significance of stenoses subject to investigation.

Subtractive angiography facilitates combining the diagnostic procedure with an artery repair intervention. In patients with intermittent claudication, subtractive angiography should be performed only as direct prelude to an intervention as part of the same procedure (Fig. 9).

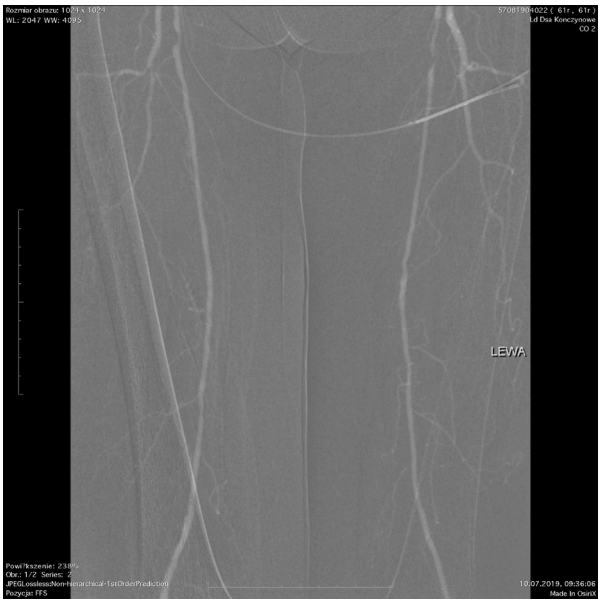


Figure 10. Carbon dioxide angiography scan — courtesy of prof. Radosław Pietura, from the records of the Department of Interventional Radiology and Diagnostic Imaging, Independent Public Clinical Hospital no. 1 in Lublin

3.4.3.5. Carbon dioxide angiography

In patients with chronic renal insufficiency not requiring hemodialysis, carbon dioxide (CO_2) angiography provides a valuable alternative to conventional angiography involving the use of contrast agents. The use of a nephrotoxic contrast agent at this stage of renal insufficiency might lead no irreversible damage and requirement of continuous dialysis therapy. Carbon dioxide angiography provides good imaging of large vessels from the aorta down to the popliteal artery; it may be insufficient for proper assessment of infra-popliteal vessels or potential in-stent stenosis. In such cases, supplemental examination with a small quantity of iodine-based contrast is recommended [59] (Fig. 10).

Table 15 presents ESC recommendations for radiological diagnostics of chronic lower limb ischemia.

Table 15. European Society of Cardiology and European Society of Vascular Surgeon's recommendations for radiological diagnostics of chronic lower limb ischemia

Recommendations	Recommendation class	Level of evidence
DUS is indicated as a first-line imaging method to confirm LEAD lesions	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy	I	C
Data from an anatomical imaging test should always be analyzed in conjunction with symptoms and hemodynamic tests prior to a treatment decision	I	C
DUS screening for AAA should be considered	IIa	C

angio-CT — computed tomography angiography; angio-MR — magnetic resonance angiography; DUS — duplex ultrasonography; LEAD — lower extremity artery disease

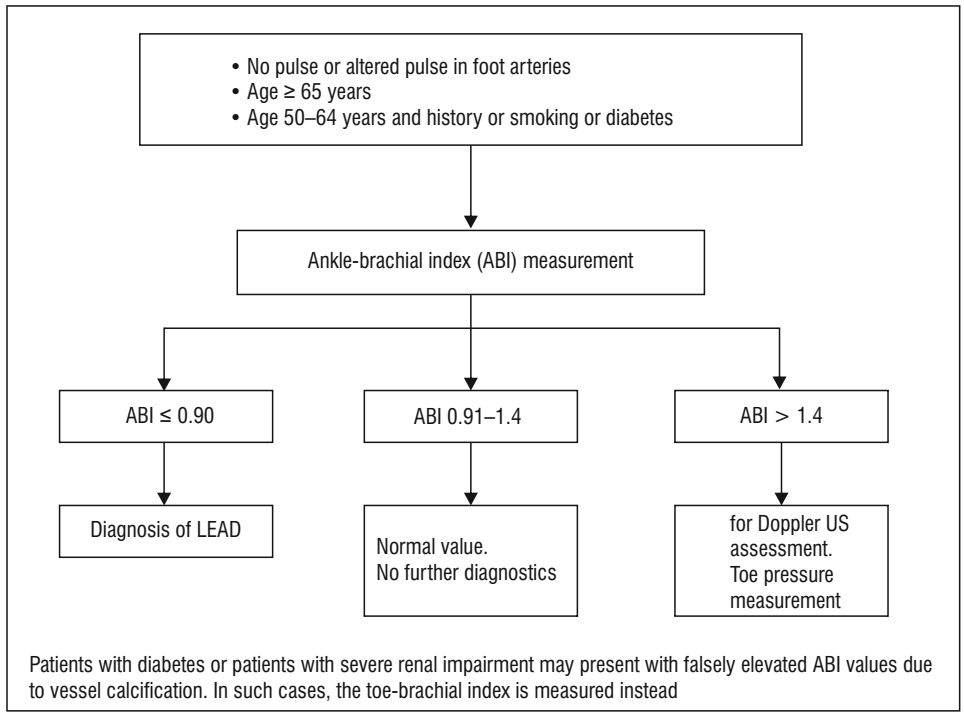


Figure 11. Algorithm for the management of asymptomatic lower extremity artery disease (LEAD)

3.4.4. Other investigations

Other examinations used in the diagnostics of LEAD include plethysmography, transcutaneous oxygen pressure measurements, and near infrared spectroscopy (NIRS).

Due to the limited specificity and sensitivity of these methods, combination of several diagnostic procedures may be required. As the result, the clinical importance of individual methods remains rather low [60, 61].

3.5. Summary

Principles for interviews, physical examinations, and diagnostics of patients with chronic lower limb ischemia were presented in this chapter.

Figures 11 and 12 present the proposed algorithms for the management of asymptomatic and symptomatic lower limb ischemia based on the SVS guidelines for the diagnostics of chronic lower limb ischemia modified so as to correspond to ABI values and patient age ranges defined in European guidelines.

4. Treatment

4.1. Non-pharmacological management (smoking, physical activity, diet)

4.1.1. Background

Non-pharmacological management of LEAD patients is the foundation of the therapeutic process and translates into reduced CV risk, improved prognosis, and improved functioning of patients [62]. Modification of the risk factors profile may contribute to the reduction of the severity and progression of atherosclerosis as well as to a delay in the onset of complications. PAD is associated with significantly elevated CV risk profile. Study results show that the management of LEAD patients, both pharmacological and lifestyle-related, is less intensive than the management of patients with coronary artery disease brain vessel diseases [63].

4.1.2. General recommendations

With regard to the populations of patients with all types of atherosclerotic diseases, non-pharmacological management consists in broadly understood lifestyle modifications. Usually, this relates to cessation of smoking, taking up physical exercise, improvement in patient's diet and loss of body weight [14, 64-66]. Compared to pharmacological treatments, the efficiency of individual types of non-pharmacological interventions is more difficult to assess in a randomized clinical study setting, for example due to the different degrees of patient compliance. However, data suggesting a preference for particular interventions as being superior to others are available.

4.1.3. Smoking [67]

- Smoking is associated with the development of atherosclerosis and, by its contribution to endothelial

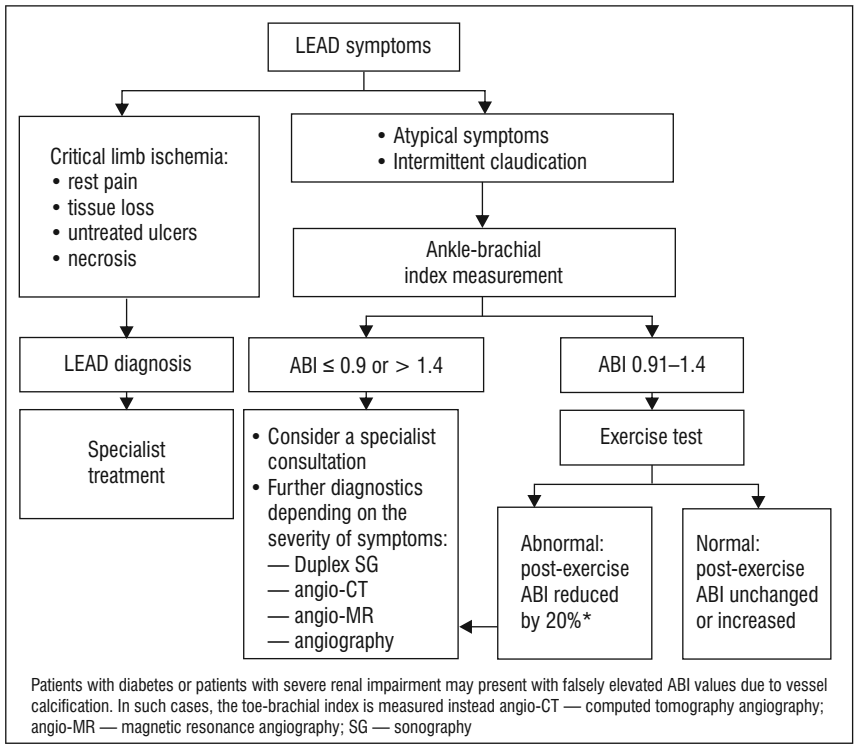


Figure 12. Algorithm for the management of symptomatic lower extremity artery disease (LEAD)

damage and blood flow disturbances, constitutes the strongest risk factor of intermittent claudication and LEAD.

- Statistically, diagnosis of LEAD is made about 10 years earlier in smokers as compared to non-smokers. The larger the number of cigarettes a patient smokes every day, the higher the intensity of symptoms. In addition, nicotinism is a risk factor of asymptomatic forms of LEAD diagnosed in population screenings.
- As shown by the study results, surgical vascular reconstruction procedures were more than three times more common in patients with intermittent claudication and history of smoking involving at least 40 packet-years as compared to patients who smoked less. In smokers diagnosed with LEAD, the frequency of major amputations ranges from 6 to 11% while being sporadic in non-smokers. The rate of procedural failures is also higher in smoking patients.
- Switching to heat-not-burn devices, such as IQOS®, is a sort of an alternative for smoking patients.

4.1.4. Physical activity [68–70]

- The risk of LEAD is inversely proportional to previous physical activity levels suggesting a protective effect of prophylactic exercise.
- Studies showed that the ability to walk, the maximum walking distance (MWD) and other competence parameters in patients with intermittent claudication are markedly improved by regular training which also contributes to the modification of risk factors.
- Regular exercise is also important in the context of other atherosclerotic diseases that are concomitant to LEAD as well as in the context of increased CV risk in LEAD patients. Numerous meta-analyses are indicative of the benefits of physical exercise in patients with ischemic heart disease and chronic heart failure.

4.1.5. Diet [71, 72]

- Patients with any type of atherosclerotic disease should be on a diet including a reduced intake of saturated fats, trans fats and fats of animal origin.
- Evidence is available on the benefits of Mediterranean diet rich in fruit, nuts, vegetables, fish, and unsaturated vegetable fats.
- However, no studies on the supplementation with individual nutrients provided any evidence on their potential benefits in LEAD patients.
- Therefore, dietary recommendations suggest a broadly understood healthy, low-fat diet aimed primarily at the reduction of cholesterol levels and inhibition of atherosclerosis.

Table 16. Summary of recommendations regarding non-pharmacological pro-health interventions in patients with lower extremity artery disease (LEAD) as suggested by major scientific associations — European Society of Cardiology (ESC) and American Heart Association (AHA)

	ESC Guidelines (LEAD)	AHA Guidelines (LEAD)	ESC Guidelines (prevention)
Smoking	Smoking cessation is recommended in all LEAD patients	LEAD patients who smoke or use other forms of tobacco should be educated at every visit regarding the need to quit smoking. Smoking LEAD patients should be helped with the establishment of a plan to quit smoking consisting of pharmacotherapy (i.e. varenicline, bupropion and/or nicotine replacement therapy) and or referral for a smoking cessation program. LEAD patients should avoid exposure to environmental smoke at work, home, and public spaces	Avoiding exposure to any form of tobacco smoke is recommended
Diet	Patients are recommended to follow healthy diet		With low saturated fat content, with particular focus on whole-grain products, vegetables, fruit, and fish
Physical activity	Cardio workout supervised by medical personnel is recommended. When supervised workout is not possible or accessible, non-supervised training is recommended	In patients with intermittent claudication, supervised workout program is recommended to improve functional status and quality of life as well as to reduce the disease symptoms. A supervised workout program should be discussed as an option for the treatment of claudication prior to revascularization. In Lead patients, structured group or home-based workout program may be beneficial in terms of improving walking ability and functional status. Alternative cardio workout strategies such as upper body ergometry, cycling and walking until pain or low-intensity training, preventing moderate to maximum claudication, may be beneficial in symptomatic patients	At least 150 minutes of moderate--intensity aerobic training per week (30 minutes 5 times a week) or 75 minutes of high-intensity aerobic training per week (15 minutes 5 times a weak) or a combination of the above are required
Other recommendations	–	LEAD patients should receive annual flu vaccinations	Body mass index in the range of 20–25 kg/m^2, waist circumference < 94 cm in males and < 80 in females

4.1.6. Summary of recommendations

At this time, no data from controlled, randomized clinical trials are available to suggest any benefits from any particular lifestyle modification dedicated to LEAD patients so as to reduce the mortality rate and incidence of CV events. Therefore, it is suggested that patients follow the recommendations for the entire high cardiovascular risk population. Convincing evidence is available to support the benefits of smoking cessation, increased physical activity, and improved diet. Guidelines of individual scientific associations differ slightly in their approach to individual interventions [36]. The summary of these guidelines is presented in Table 16.

4.2. Lipid-lowering treatment

4.2.1. Background

All LEAD patients are subject to the same principles of lipid-lowering treatment regardless of whether they receive medical therapy, are prepared for a surgical or endovascular procedure, or receive secondary prevention (following a procedure, a cardiovascular event, or amputation). Lipid-lowering treatment extends lifespan, reduces the risk of myocardial infarction and brain stroke, reduces the need for endovascular revascularization and the rate of amputations; as such, it is mandatory in all LEAD patients.

Table 17. Current (2018) SFSN PTK recommendations for risk classification in dyslipidemia patients and target LDL-C values including categories most prevalent in LEAD patients (in bold). The Pol-SCORE (modified EURO-SCORE) scale was also used in the proposed classification; however, the scale is used in primary prevention i.e. in patients who have not been diagnosed with LEAD

Risk category	Disease, risk factors or 10-year Pol-SCORE risk	Therapeutic target — LDL-C level
Extremely high	• Status post numerous cardiovascular events and/or revascularizations • Percutaneous stenting of main left coronary artery trunk and/or polyvascular coronary disease (comprehensive angioplasty in polyvascular coronary disease) • Generalized atherosclerosis — multiple vascular beds with additional risk factors • Progression of atherosclerotic cardiovascular disease in patients in whom LDL-C levels of < 55 mg/dL had been achieved and maintained steadily	< 35 mg/dL (< 0.9 mmol/L)
Very high	• Progression of atherosclerotic cardiovascular disease in patients in whom LDL-C levels of < 70 mg/dL (< 1.8 mmol/L) had been achieved and maintained steadily • Diagnosis of acute coronary syndrome, coronary, carotid, or peripheral artery disease • **Status post revascularization** • Pol-SCORE risk of > 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 males, < 65 ears in females) • Diagnosis of cardiovascular disease in diabetic patients or patients with stage 3/4 chronic kidney disease	< 55 mg/dL (< 1.4 mmol/L)
High	• ≥ 2 risk factors and Pol-SCORE risk of 10–20% • Diabetes or stage 3/4 chronic kidney disease with no other risk factors	< 70 mg/dL (< 1.8 mmol/L)
Moderate	• < 2 risk factors and Pol-SCORE risk of < 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

4.2.2. General recommendations

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

4.2.3. Target LDL-C values

The 2019 ESC guidelines as well as the SFSN PTK guidelines of the so-called 3rd Sopot Declaration require that all patients with LEAD and any additional risk factors should be classified to the highest risk group (extreme high risk group in the case of SFSN PTK classification) so as the **target serum LDL-C levels are below 35 mg/dL (< 0.9 mmol/L)**. Other LEAD patients with no additional risk factors and diagnosis of peripheral artery disease alone, are classified to the group of very high risk with **target LDL-C levels of below 55 mg/dL (< 1.4 mmol/L**). The typical target — LDL-C levels of below 70 mg/dL (< 1.8 mmol/L), as recommended in Europe after 2016, should be considered historical and inconsistent with current knowledge in the case of LEAD patients. Risk classes and target LDL-C values as proposed in 2018 by the SFSN PTK are presented in Table 17.

The new European Society of Cardiology guidelines announced in September 2019 reflect the values proposed in the Polish document. Table 18 compares target LDL-C values according to the old and the new ESC recommendations and the SFSN PTK recommendations.

Table 19 presents the 2019 ESC guidelines on the use of lipid-lowering agents in patients with LEAD and coronary artery disease.

4.2.4. The proposed management algorithm

- With regard to non-pharmacological management, attention should be paid to regular physical activity,

Table 18. Guidelines of the European Society of Cardiology (ESC 2016) and the Cardiovascular Pharmacotherapy Section of the Polish Society of Cardiology(SFSN PTK 2018), and ESC (2019)

Risk category	ESC 2016	SFSN PTK 2018	ESC September 2019
Extremely high		< 35 mg/dL (< 0.9 mmol/L)	Individuals with second cardiovascular event within 2 years from the first cardiovascular event: < 40 mg/dL (< 1 mmol/L)
Very high	LDL-C < 70 mg/dL (< 1.8 mmol/L)	LDL-C < 55 mg/dL (< 1.4 mmol/L)	LDL-C < 55 mg/dL (< 1.4 mmol/L)
High	< 100 mg/dL (< 2.6 mmol/L)	< 70 mg/dL (< 1.8 mmol/L)	< 70 mg/dL (< 1.8 mmol/L)
Moderate	< 115 mg/dL (< 3.0 mmol/L)	< 100 mg/dL (< 2.6 mmol/L)	< 100 mg/dL (< 2.6 mmol/L)
Low	< 115 mg/dL (< 3.0 mmol/L)	< 115 mg/dL (< 3.0 mmol/L)	< 115 mg/dL (< 3.0 mmol/L)

LDL-C — low-density lipoprotein cholesterol

Table 19. 2019 European Society of Cardiology recommendations on the use of lipid-lowering drugs in patients with lower extremity artery disease (LEAD) and coronary artery disease

Recommendation	Recommendation class	Level of evidence
In LEAD patients, lipid-lowering therapy with a maximum dose of statin or ezetinibe combined with PCSK9 inhibitor (if needed) is recommended to reduce cardiovascular risk	I	A

body weight control, Mediterranean diet, restricted dietary intake of sugar, animal fats and salt, abstinence from smoking, reduced consumption of fruit and vegetables, products containing unsaturated fatty acids, fish, nuts, and low-fat dairy products.

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

4.3. Anticoagulant and anti-platelet drugs

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

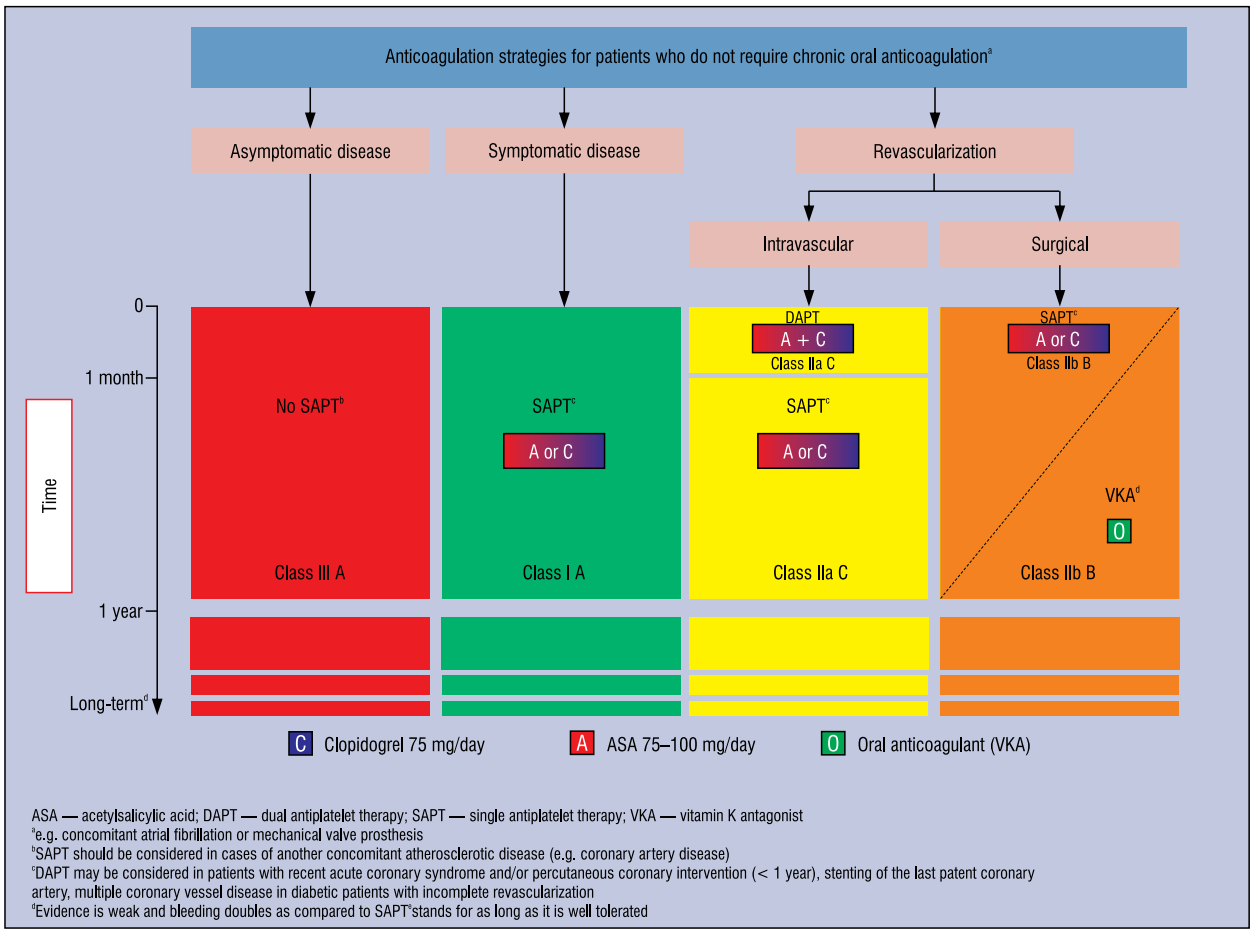


Figure 13. Anti-platelet treatment in LEAD patients not requiring anticoagulant treatment as per 2017 ESC guidelines. COMPASS! study results were not taken into consideration in the presented guidelines

in the entire LEAD spectrum (asymptomatic LEAD, intermittent claudication, and CLTI).

Presented below are the individual strategies of treatment using these drugs (Figs. 13, 14; Tables 20, 21):

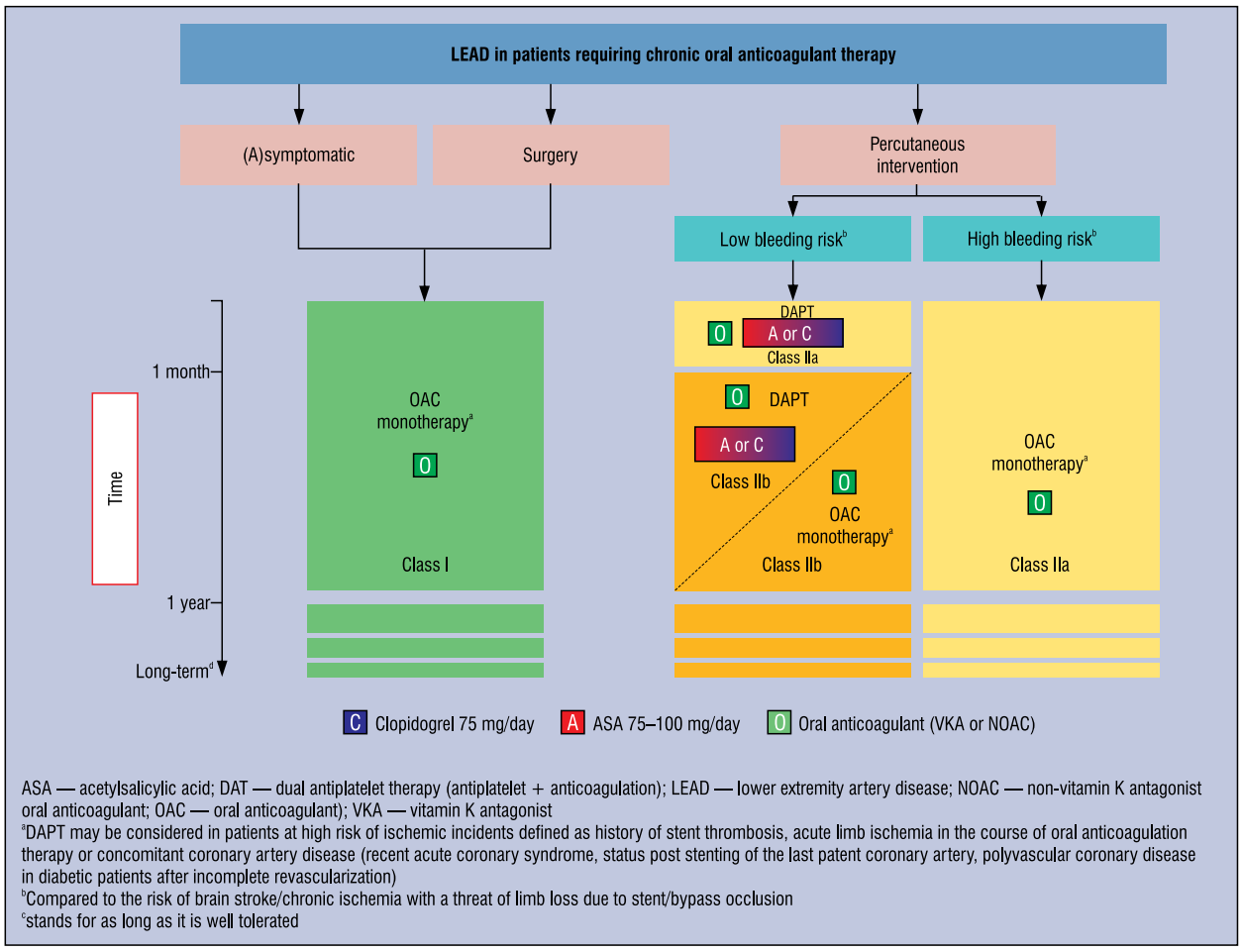
- single antiplatelet therapy (SAPT);
- dual antiplatelet therapy (DAPT) or antiplatelet-anticoagulant treatment with low vascular doses of novel anticoagulants;
- antiplatelet-anticoagulant treatment following lower extremity arterial bypass surgeries;
- antiplatelet-anticoagulant treatment following endovascular treatment of lower extremity artery disease;
- treatment of patients with lower extremity artery disease and concomitant coronary artery disease;
- antiplatelet-anticoagulant treatment in patients with lower extremity artery disease requiring long-term anticoagulation treatment.

4.3.1. Single antiplatelet therapy

Single antiplatelet therapy may be provided using acetylsalicylic acid (ASA) or clopidogrel. In LEAD patients, it is recommended only when clinical symptoms are present or after a revascularization procedure has been performed. As unambiguously demonstrated by the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, clopidogrel rather than ASA is the preferred antiplatelet drug in LEAD patients. Treatment optimization and addition of sulodexide may be considered.

4.3.2. Dual antiplatelet therapy or antiplatelet--anticoagulant treatment with low vascular doses of novel anticoagulants

Do date, no data are available regarding potential superiority of DAPT (including clopidogrel) over ASA alone in terms or reducing the incidence of CV events



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

Figure 14. Anticoagulant and anti-platelet therapy in LEAD patients requiring oral anticoagulant treatment as per 2017 ESC guidelines. COMPASS! study results were not taken into consideration in the presented guidelines

Table 20. Recommendations for anti-platelet and anticoagulation therapy in patients with peripheral artery diseases as per 2017 ESC guidelines. COMPASS! study results were not taken into consideration in the presented guidelines

Recommendations	Recommendation class	Level of evidence
In patients with symptomatic carotid stenosis, long-term SAPT is recommended	I	A
Long-term SAPT is recommended in all patients who have undergone revascularization	I	C
SAPT is recommended after infra-inguinal bypass surgery	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over ASA	IIb	B
Vitamin K antagonist may be considered after infra-inguinal autologous vein bypass	IIb	B
DAPT (ASA and clopidogrel) should be considered for at least one month following infra-inguinal stent implantation	IIa	C
DAPT (ASA and clopidogrel) may be considered following infrapopliteal stenting with man-made materials	IIb	B
Due to the lack of proven benefits, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic lower extremity artery disease	III	A

ASA — acetylsalicylic acid; DAPT — dual antiplatelet therapy; SAPT — single antiplatelet therapy

Table 21. Recommendations regarding anticoagulant and anti-platelet therapy in LEAD patients requiring oral anticoagulant treatment as per 2017 ESC guidelines. COMPASS! study results were not taken into consideration in the presented guidelines

Recommendations	Recommendation class	Level of evidence
OAC in patients with PAD and AF:		
• recommended if CHA_2DS_2-VASc score > 2	I	A
• should be considered in all remaining patients	IIa	B
In patients with PAD and indication for OAC use (e.g. AF or mechanical valve prosthesis), OAC monotherapy should be considered	IIa	B
Following endovascular revascularization, ASA or clopidogrel in combination with OAC should be considered for at least one month if the risk of bleeding is low compared to the risk of sent/bypass occlusion	IIa	C
Following endovascular revascularization, OAC monotherapy should be considered if the risk of bleeding is high compared to the risk of sent/bypass occlusion	IIa	C
Combination of OAC with one anti-platelet agent may be considered for more than one month in patients at high risk of ischemia or in patients with other strong indications for long-term SAPT	IIb	C

AF — atrial fibrillation; ASA — acetylsalicylic acid; OAC — oral anticoagulant; PAD — peripheral artery disease; SAPT — single antiplatelet therapy

in LEAD patients. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance Trial (CHARISMA) study, DAPT in LEAD patients reduced the incidence of myocardial infarctions, while presenting with a neutral effect on all other vascular incidents at the price of increased incidence of moderate, severe, or fatal bleedings.

In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS), a regimen consisting of 100 mg of ASA combined with rivaroxaban 2 × 2,5 mg in a subgroup of 7470 patients with peripheral artery disease (4129 patients with symptomatic LEAD, 1919 patients with carotid artery stenosis and 1422 patients with coronary artery disease and asymptomatic LEAD as diagnosed from the ABI value), when compared to ASA alone, was characterized by a significant decrease in the relative risk of: brain strokes by 42%, cardiovascular deaths by 22%, myocardial infarctions, brain strokes, and cardiovascular deaths combined by 24%, death for any reason by 18%, major amputations by 70%, all amputations for vascular reasons 60%, acute or chronic limb ischemia by 46%.

Since 2018, the therapeutic regimen ASA 100 mg + rivaroxaban 2 × 2,5 mg has been registered for the indication of: "prevention of thrombotic events due to atherosclerosis in adult patients with coronary artery disease or symptomatic peripheral artery disease at high risk of ischemic incidents". This indication is also included in the 2019 European guidelines for the management of chronic coronary syndromes. In cases of severe bleeding, SAPT may be considered (clopidogrel being the preferred agent) with treatment optimization and addition of sulodexide.

4.3.3. Antiplatelet-anticoagulant treatment following lower extremity arterial bypass surgeries

Clopidogrel regimen or the COMPASS study regimen may be used depending on the risk of bleeding at operator's discretion. When SAPT is provided, addition of sulodexide should be taken into consideration.

4.3.4. Antiplatelet-anticoagulant treatment following endovascular treatment of lower extremity artery disease

Currently, DAPT is recommended for at least one month following an endovascular intervention regardless of the stent type (non-coated metal stet or drug-eluting stent). Dual antiplatelet therapy is frequently continued after infrapopliteal artery stenting, albeit no evidence is available to support this management strategy. Efficacy of anticoagulant treatment was examined prospectively following percutaneous infra-inguinal revascularization. No improvement in vessel patency was observed while the incidence of bleedings increased significantly.

Long-term treatment may follow the COMPASS study regimen or, in cases of high bleeding risk, consist in SAPT (clopidogrel) with optimization and addition of sulodexide.

4.3.5. Management of LEAD patients with concomitant coronary artery disease

The COMPASS study regimen appears to be the optimum management strategy in these patients. In cases of high bleeding risk, single anti-platelet therapies (clopidogrel being preferred) with the addition of sulodexide should be taken into consideration.

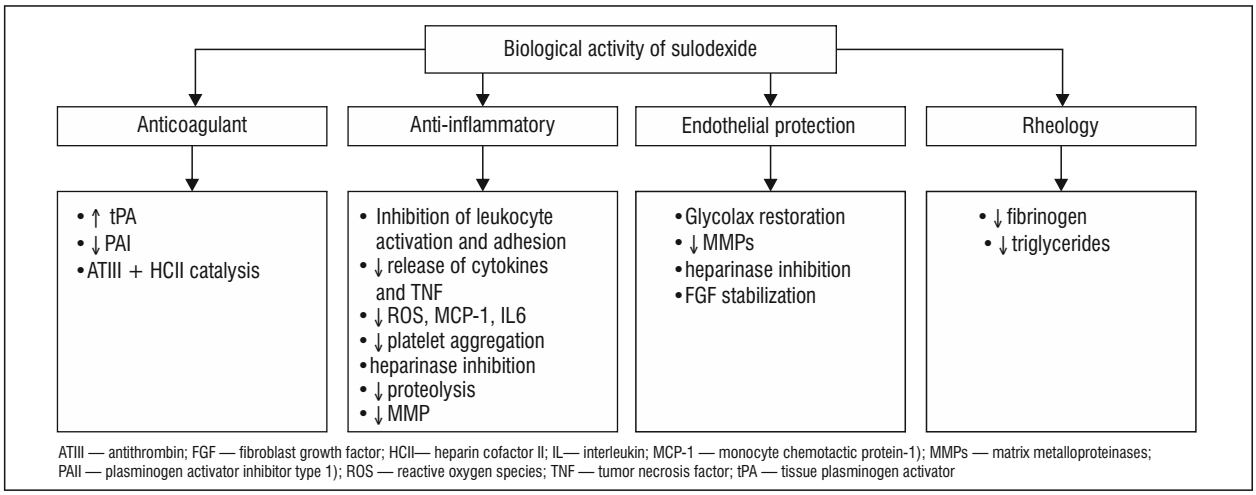


Figure 15. Biological activity of sulodexide

4.3.6 Management of LEAD patients requiring long-term anticoagulation treatment

In LEAD patients requiring long-term anticoagulation treatment, antiplatelet therapy is not required; instead, optimum doses of novel anticoagulants should be administered in monotherapy if indicated. The treatment may be continued for life or, in cases of very high bleeding risk, changed to sulodexide therapy.

The regimen for anti-platelet therapy in LEAD patients not requiring anticoagulant treatment as per 2017 ESC guidelines is presented in Figure 13 while the regimen for anticoagulant and anti-platelet therapy in LEAD patients requiring oral anticoagulant treatment as per 2017 ESC guidelines is presented in Figure 14.

4.4. Vascular pleiotropic treatment

4.4.1. Background

For many years, pharmacotherapy aimed at the reduction of ischemia-related symptoms was considered one of the most important aspects of LEAD patients, its main objective being the reduction of symptoms and the improvement in the quality of life. Today, the vascular pleiotropic treatment in LEAD patients is aimed at stabilization of atherosclerotic plaque and at the improvement in prognosis by reducing the cardiovascular risk rather than at the reduction of symptoms alone.

4.4.2. Vascular pleiotropic medication used to date

Numerous groups of agents were analyzed in terms of their vascular pleiotropic and protective character. Studies are available to show that some antihypertensive drugs (e.g. verapamil), statins, antiplatelet drugs and prostanoids (prostaglandins I2 and E1) have some beneficial impact on the walking distance and limb function. Drugs most extensively studied in this indication include cilostazol, naftidrofuryl, pentoxiphylline, buflomedyl, carnitine, and propionyl-L-carnitine. The beneficial impact of the aforementioned substances is usually mild to moderate and highly variable depending on the type of the study. No evidence was provided for these agents to significantly alter the outcome prognosis.

4.4.2.1. Cilostazol

- Cilostazol is a type III phosphodiesterase inhibitor registered for the treatment of intermittent claudication. Clinical studies demonstrated that,
- cilostazol increased mean platelet volume (MPV) and pain-free walking distance (PFWD) as compared to placebo [70, 73]. The beneficial impact of cilostazol on the walking distance is ambiguous. As revealed in one of meta-analyses, cilostazol at the dose of 100 mg two times a day increased the MWD by the average of 76% as compared to 20% in the placebo group. Another analysis suggested that the mean improvement attributed to cilostazol was as low as 25% [74].
- Numerous contraindications of cilostazol include congestive heart failure, history of clinically significant ventricular arrhythmia, unstable angina pectoris, myocardial infarction within last 6 months, coronary intervention within last 6 months, severe renal insufficiency, and concomitant use of at least 2 other antiplatelet or anticoagulant drugs.
- Cilostazol may reduce arterial blood pressure or cause cardiac arrhythmias.
- Common adverse effects include headache and gastrointestinal disorders.
- Cilostazol presents with antiplatelet activity and therefore should be used in caution when combined

with other anticoagulants and antiplatelet drugs commonly used in LEAD patients.
- Due to the above limitations, cilostazol is not preferred for widespread use in the treatment of lead patients.

4.4.2.2. Sulodexide

Sulodexide is a purified mix of glucosaminoglycans from porcine intestinal mucosa containing fast-moving heparin (80%) and dermatan sulfate (20%).

New knowledge from basic research as well as new data from clinical trials and everyday practice are indicative of the growing importance of drugs targeting the inflammatory response, endothelial dysfunction and the associated changes within the extracellular matrix as well as modulating the coagulability of blood (Fig. 15). Therefore, the interest in the use of sulodexide has also been increasing recently.

Results of clinical studies demonstrated that the activity of sulodexide is multidirectional and includes an effect on the hemostasis system, a reduction in thrombin generation, a profibrinolytic effect, and inhibition of pro-coagulation microparticle generation. It also has a documented effect on normalization of blood viscosity and lipid levels [75–80].

- Sulodexide exerts a protective effect on vascular endothelium. Following oral administration, it exerts a multitude of biological effects such as protection of endothelial structure and function, regulation of interactions between blood cells and endothelium, and prevention of vascular inflammation and proliferative lesions [75, 81].
- Clinical efficacy of sulodexide was documented in numerous vascular disorders, including alleviation of chronic venous disease symptoms, acceleration of lower limb venous ulcers, treatment of venous thromboembolism, intermittent claudication in PAD patients, or prevention or cardiovascular events after myocardial infarction and in diabetic nephropathy.
- Sulodexide is recommended in various indications: pursuant to the 2019 ESC guidelines for the management of pulmonary embolism [82] and the 2017 Polish Consensus guidelines for the management of venous thromboembolism [83], it is recommended as an alternative anticoagulant in long-term prevention of thrombosis due to its high safety profile. Pursuant to the most recent recommendations published in International Angiology [84], sulodexide is one of the highest-recommended drugs for the treatment of lower limb venous ulcers.
- Six-month sulodexide treatment administered to patients with intermittent claudication significantly reduced their PFWD — 65% compared to the baseline, and increased MWD by 33% compared to placebo; the effect was independent on the patients' diabetes status [85].

A meta-analysis of 19 studies in 849 patients with peripheral atherosclerosis confirmed the positive impact of sulodexide consisting in MWD being increased by 36% compared to placebo. Sulodexide was found to have a significant impact on the reduction in the levels of triglycerides (average of −28%) and fibrinogen (−13%), the reduction in plasma and serum viscosity, and the increase in HDL-C levels (+24.4%) [86].

- Oral sulodexide is characterized by high safety profile in long-term treatment — it does not interact with most medications, does not increase the risk of bleeding, and is well tolerated.
- Notably, the benefits of sulodexide therapy may be significant due to its multidirectional efficacy and high safety profile, particularly in LEAD patients with comorbidities.

4.4.3. Statins

- Much evidence is available to support the claim that statins reduce the risk of cardiovascular events and cardiovascular mortality in LEAD patients.
- As shown in small randomized trials, patients who receive statins may slightly improve their PFWD or PFWT (pain-free walking time), suggesting an additional vasoprotective effect of these drugs independent of their lipid lowering effect.
- Currently, statins are recommended in patients undergoing endovascular interventions as they reduce the incidence of postoperative cardiovascular events.
- Intensive statin therapy is associated with significant benefits combined with few adverse effects, and therefore, not only the beneficial impact of statins on the blood vessels being particularly important in LEAD patients but also their cardiovascular risk-lowering effects should be taken into consideration. Thus, statins are currently recommended in all LEAD patients regardless of their cholesterol levels and dyslipidemia status.

Walking distance elongation may be used as a measure when comparing the efficiency of vascular drugs. An example of such comparison is presented in Figure 16.

4.5. Antihypertensive treatment

4.5.1. Background

All LEAD patients are subject to the same principles of antihypertensive treatment regardless of whether they receive medical therapy, are prepared for a surgical or endovascular procedure, or receive secondary preven-

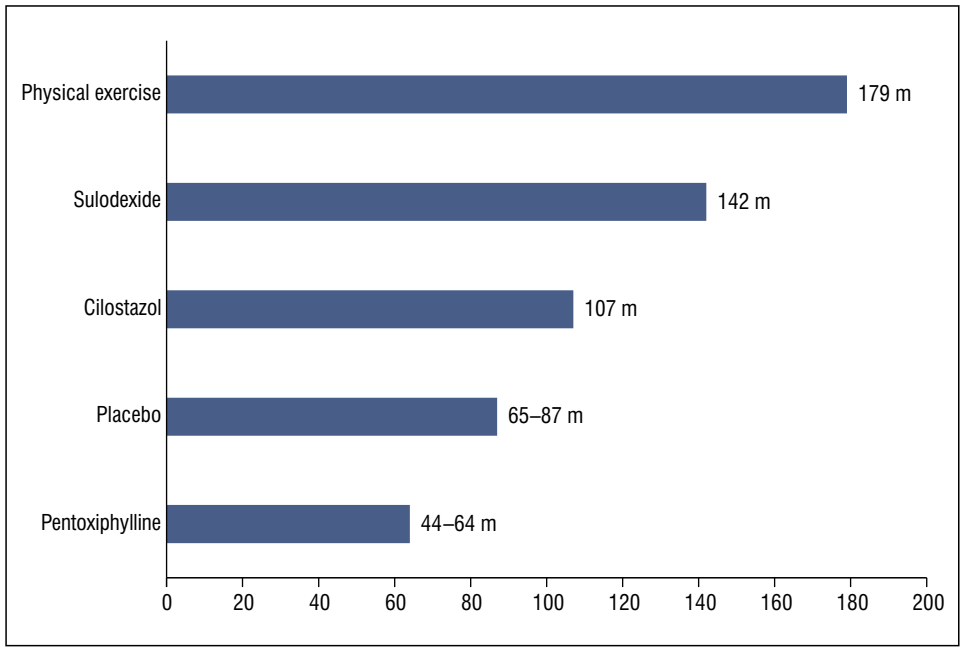


Figure 16. The effect of vascular drugs on the walking distance

Table 22. Blood pressure (BP) values for the diagnosis of arterial hypertension in treatment-naïve patients

Measurement type	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
O BPM	≥ 140	and/or	≥ 90
A BPM			
daytime (or when awake)	≥ 135	and/or	≥ 85
nighttime (or when asleep)	≥ 120	and/or	≥ 70
24-hour	≥ 130	and/or	≥ 80
H BPM (average)	≥ 135	and/or	≥ 85

A — ambulatory; BPM — blood pressure monitoring; H — home; O — office

tion (following a procedure, a cardiovascular event, or amputation). Antihypertensive treatment significantly reduces the risk of brain stroke, myocardial infarction, chronic renal failure, vascular complications and diabetes. In the long term, it reduces the mortality and risk of dementia; as such, it is mandatory in all LEAD patients.

4.5.2. General recommendations

All LEAD patients should have their arterial pressure measured at every office visit; in cases of difficulties with achieving the target values or discrepancies between office and home-based measurements, a 24-hour ambulatory blood pressure monitoring (24-ABPM) test should be performed . Due to the possibility of concomitant atherosclerotic lesions being present within small vessels such as retinal vessels, the 24-ABPM test should be performed once per year in all LEAD patients to assess pressure control and circadian pressure profile (risk of excessive nocturnal pressure drops, particularly in patients with concomitant glaucoma). Diagnosis of arterial hypertension in treatment-naïve patients consists in values above the reference range being confirmed in office, 24-hour ambulatory or home-based measurements as illustrated in Table 22.

4.5.3. Target arterial blood pressure values

Pursuant to the 2019 PTNT guidelines and 2018 ESC/ESH guidelines, target blood pressure values in patients diagnosed with arterial hypertension are those of **below 140/90 mm Hg**. However, **in most patients, greater blood pressure reduction to values below 130/80 mm Hg should be pursued provided the treatment is tolerated well**. In all patients with arterial hypertension, **diastolic blood pressures of 70–79 mm**

Table 23. General European algorithm for the treatment of arterial hypertension — starting from 2018 applicable also to patients with concomitant peripheral artery disease

Algorithm for most patients with arterial hypertension	
Treatment initiation	ACEi or sartan + calcium antagonist or diuretic
Step 2	ACEi or sartan + calcium antagonist and diuretic
Step 3	Refractory hypertension: add aldosterone antagonist or loop diuretic or alpha-blocker or beta-blocker treatment
Beta-blocker treatment — add earlier in cases of heart failure, status post myocardial infarction, atrial fibrillation, young females planning to become pregnant	

ACEi — angiotensin converting enzyme inhibitor

Hg should be aimed for. Target systolic blood pressure values depend on additional factors: as a rule, in patients below the age of 65, **systolic blood pressure should be in the range of 120–129 mm Hg**, whereas in patients with chronic renal disease or **patients after the age of 65, systolic pressure should be in the range of 130–139 mm Hg**. For patients in their 9th and 10th decade of life, particularly those poorly tolerating the treatment and presenting with frailty syndrome, systolic pressure range of 140–149 mm Hg is acceptable. Importantly, the new guidelines are the first to include therapeutic targets regarding heart rate (< 80 bpm) in patients with arterial hypertension; in patients with concomitant ischemic heart disease and/or heart failure, the heart rate range should be even lower (< 70 bpm).

4.5.4. Principles for non-pharmacological and pharmacological management (Table 23)

- With regard to non-pharmacological management, attention should be paid to regular physical activity, body weight control, Mediterranean diet, restricted dietary intake of sugar, animal fats and salt (< 5 g/d), abstinence from smoking, reduced consumption of fruit and vegetables, products containing unsaturated fatty acids, fish, nuts, and low-fat dairy products, as in the case of dyslipidemia.
- Alcohol consumption should be limited to a maximum of 14 units in males and 8 units in females (distributed over a week, not accumulated; patients should follow the Mediterranean style of alcohol intake, keeping in mind the cardioprotective effects of small quantities of alcohol, e.g. red wine; one alcohol unit corresponds to ca. 125 mL of red wine).
- **As a rule, pharmacological treatment starts with two antihypertensive drugs (preferably as a single pill combination [SPC])**; in the new guidelines, monotherapy of arterial hypertension is reserved only for patients with mild arterial hypertension (systolic pressure of 140–149 mm Hg) without other risk factors and for patients above the age of 80 and presenting with frailty syndrome; as a general rule, all other patients should start their treatment from 2 medications at once.
- According to the guidelines, **first-line single-pill combination** consists of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor antagonist (sartan) and a diuretic; **in practice, this means a possibility of using one out of four SPCs: ACEi + calcium antagonist** or **ACEi + diuretic** or **sartan + calcium antagonist** or **sartan + diuretic**. All 4 types of SPCs are available and broadly included in reimbursement lists in Poland.
- If the above SPC fails to achieve the target blood pressure value, **the second step consists in a third antihypertensive agent being added so that the patient receives a combination of: ACEi + calcium antagonist + diuretic** or **sartan + calcium antagonist + diuretic**. Both types of triple-agent SPCs are also available in Poland.
- If the above treatment again fails to achieve the target blood pressure values, new drugs are added to the regimen according to the algorithm in Table 22. One should keep in mind that the beta-adrenolytic agent may be added at any stage to control the heart rate, as a coronary drug used in heart failure or to control ventricular rate in atrial fibrillation.
- In LEAD patients, calcium antagonists from the group of dihydropyridine derivatives especially those not leading to peripheral edema (lercanidipine) as well as broader use of novel cardioselective yet strongly vasodilating beta-blockers (nebivolol) are particularly justified along with renin-angiotensin axis inhibitors (ACEi).
- With regard to other supportive antihypertensive agents, experts also suggest the use of superior, newer drugs with additional pleiotropic mechanisms and lower adverse effect profiles (e.g. eplerenone instead of spironolactone, torasemide instead of furosemide).
- Notably, "hybrid SPCs" combining e.g. 2 antihypertensive agents and a statin, were introduced to the

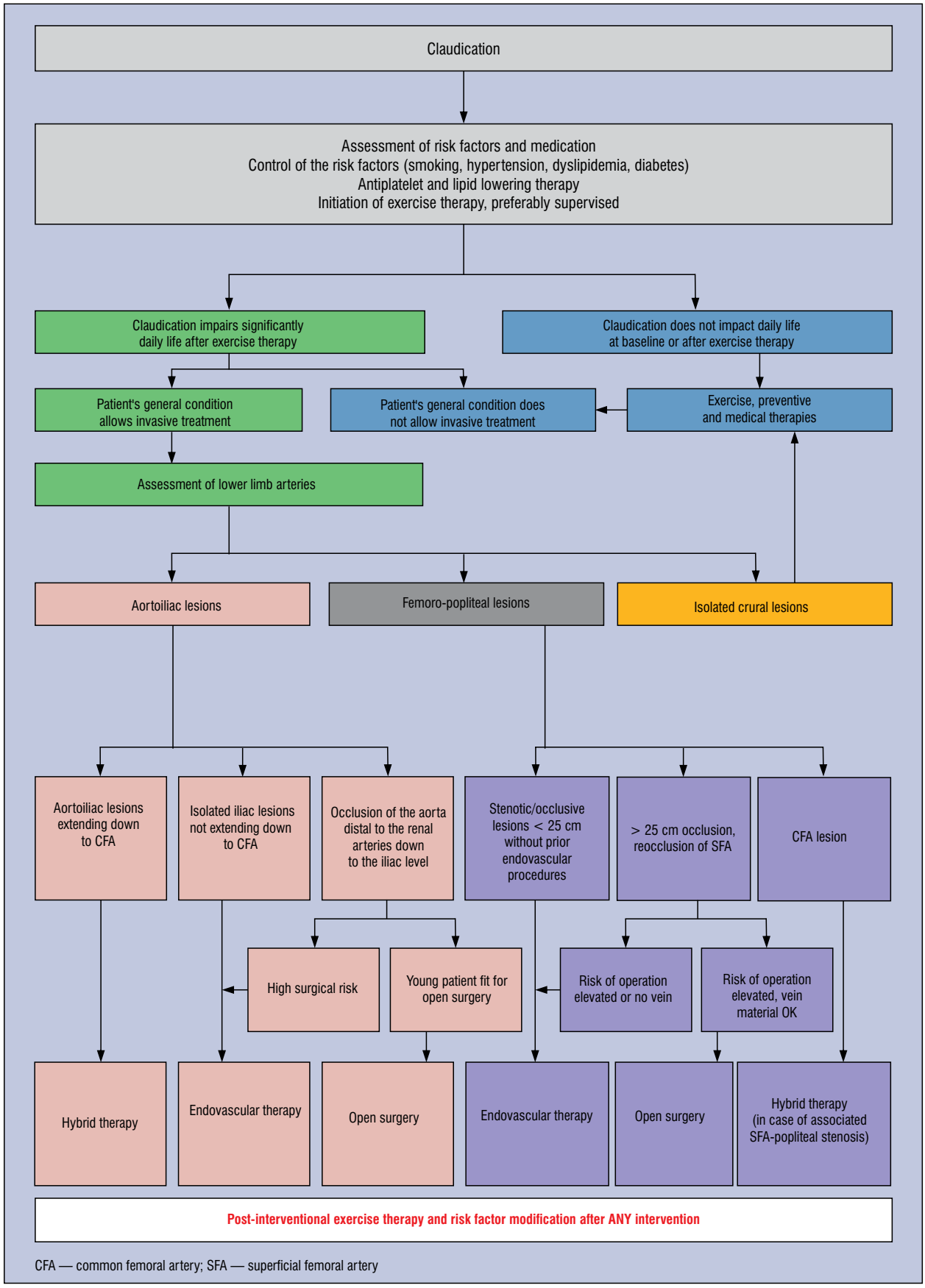


Figure 17. Management of patients with LEAD

market to simplify pharmacotherapeutic regimens Experts recommend that these new products are used whenever possible.

5. Standards for the management, care, follow-up, and recommended investigations

5.1. LEAD patients not qualified for surgery

5.1.1. Background

Due to coexisting risk factors, multimorbidity and advanced stage of atherosclerosis, clinical presentation LEAD patients is frequently complex and requires multidirectional diagnostics and treatment approaches. Multidisciplinary team involvement facilitates optimum approach to the diagnostics and treatment of LEAD patients, preventing unnecessary amputations. LEAD treatment team may consist of a primary care physician, general medicine specialist, diabetologist, endocrinologist, hypertension and lipids specialist, endovascular interventionist, vascular surgeon, orthopedist, neurologist, nurse, podiatrist, wound treatment specialist, smoking cessation specialist, and others. Each patient presents with a unique combination of symptoms, concomitant diseases and vascular risks, necessitating an individualized approach. Moreover, concomitant diseases may progress in patients with the development of new symptoms and pathophysiological lesions. Therefore, early initiation of the diagnostic process and appropriate consideration being paid to all patient data increase the chances of appropriate diagnosis and efficient treatment to prevent unnecessary amputations and increase patient's quality of life as well as survival [36].

5.1.2. Management outline

A general outline for diagnostic and therapeutic management of LEAD patients may be summarized as follows (Fig. 17):

5.1.3. Further diagnostics in patients diagnosed with LEAD

- The first stage of management should consist in appropriately early diagnostics. LEAD screening should be performed in adults above the age of 50 with risk factors such as high cholesterol levels, arterial hypertension, diabetes, smoking, obesity, family history of atherosclerosis, LEAD, or claudication, neuropathic leg pain or non-healing wounds or infection sites within the limb. In addition, screening should be performed in all patients above 70, regardless of the status of symptoms.
- Claudication is observed in about 60% of LEAD patients while other symptoms may be present in some patients with no pain discomfort. Likewise, critical limb ischemia may develop in patients with previous history of milder LEAD symptoms, but constitutes the first manifestation of the disease in 5–10% of patients. In patients with critical limb ischemia, the mortality rate within the first year after the incident may be as high as 20%, warranting emergency diagnostics and treatment.
- About 40–60% of LEAD patients have concomitant coronary artery disease of cerebrovascular disease, which makes it necessary to perform cardiological screening in all patients diagnosed with :EAD (Fig. 18).

5.1.4. Continued treatment following the diagnosis of LEAD

After the diagnosis, therapeutic management of LEAD patients consists of two aspects. The first aspect consist in addressing the symptoms and risks associated with lesion locations. The other aspects consists in addressing the higher risk of any cardiovascular incident in LEAD patients.

- Optimum medical treatment consists in the control of cardiovascular risk factors and includes optimum pharmacotherapy and optimum non-pharmacological strategies such as smoking cessation, healthy diet, body weight reduction, and regular exercise.
- Pharmacotherapy involves the use of antihypertensive, lipid-lowering and anticoagulant drugs. In patients with diabetes, optimum blood glucose control is recommended as per the general guidelines. Aspects of pharmacological and non-pharmacological treatment of LEAD patients have been presented in detail in other chapters and will therefore not be repeated.
- In all LEAD patients, perhaps most importantly in patients not qualified for procedural treatment, intensive pharmacotherapy and non-pharmacological treatment is required along with rigorous control of cardiovascular risk factors and compliance with ESC guidelines as outlined in Table 24.

According to current 2019 ESC guidelines as well as SFSN PTK recommendation summarized in the 3rd Sopot Declaration, all patients with LEAD and additional risk factors are classified as highest cardiovascular risk patients. According to current knowledge, target serum LDL-C levels in this group should be lower than 35 mg/dL (< 0.9 mmol/L). In case of LEAD patients without other risk factors, target LDL-C should be lower than 55 mg/dL (< 1.4 mmol/L). As mentioned before, traditional target LDL-C levels of less than 70 mg/dL (< 1.8 mmol/L) as recommended in Europe after 2016, are considered outdated. Therefore, as mentioned in Table 24, intensive antihypertensive treatment should be provided to all LEAD patients.

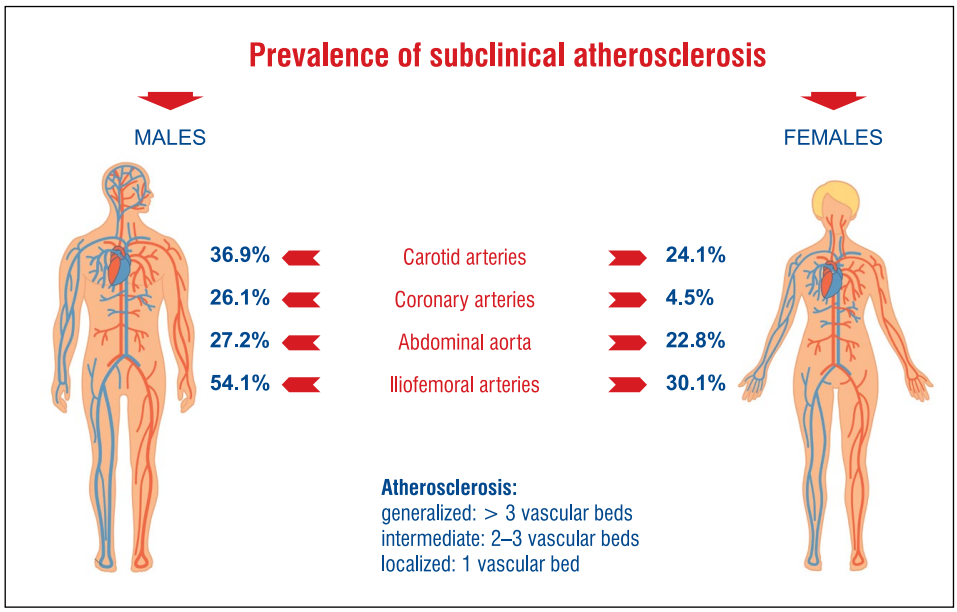


Figure 18. The prevalence of subclinical atherosclerosis depending on the location of the lesions

Table 24. Optimum non-procedural treatment of patients with lower extremity artery disease (LEAD) according to the European Society of Cardiology

Recommendations	Recommendation class	Level of evidence
Cessation of smoking is recommended to all LEAD patients	I	B
Healthy diet and physical activity are recommended to all LEAD patients	I	C
Statins are recommended in all LEAD patients	I	A
Strict blood glucose control is recommended to LEAD patients with diabetes	I	C
Antiplatelet treatment is recommended to all patients with symptomatic LEAD	I	C
Target blood pressure of < 140/90 mm Hg is recommended to patients with LEAD and arterial hypertension	I	A
ACEi or ARBs should be considered as first line of treatment in patients with LEAD and arterial hypertension	IIA	B

ACEi — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker

5.2. LEAD patients after revascularization surgeries

5.2.1. Background

Continued management to control cardiovascular risk factors, improve distant prognosis and reduce the risk of atherosclerosis progression and subsequent revascularization is very important in LEAD patients, particularly in the post-operative period.

Just as in other atherosclerotic conditions, the first element of comprehensive patient management consists in cardiovascular risk assessment. Notably, management according to the ESC guidelines differs slightly from that proposed by the 3rd Sopot Declaration [87, 88]. Consequently, some discrepancies may be observed depending on the adopted guidelines with regard to the target values recommended for risk factor control.

5.2.2. Cardiovascular risk assessment

According to Sopot Declaration, PAD patients are classified to the very high risk category or to the extreme risk category in the case of concomitant diabetes, stage 3/4 chronic kidney disease, heterozygous familial hypercholesterolemia, history of premature atherosclerotic disease (age < 55 in males and < 65 in females) as well as in patients who experienced PAD progression despite LDL-C levels having dropped below 70 mg/dL [88].

Table 25. Blood pressure control in patients after revascularization due to lower extremity artery disease

	PTNT 2019	ESH/ESC 2018 [89]
Target systolic pressure	Final therapeutic target: • patient < 65 years → < 130 and > 120 mm Hg • patient 65–80 years → < 140 and > 130 mm Hg • Patient > 80 years → < 150 and > 130 mm Hg	Patient 18–65 years → target 130 mm Hg or less if tolerated, not < 120 mm Hg Patient 65–79 years → target 130–139 mm Hg if tolerated Patient > 80 years → target 130–139 mm Hg if tolerated
Target diastolic pressure	< 80 mm Hg	70–79 mm Hg

ESC — European Society of Cardiology; ESH — European Society of Hypertension; PTNT — Polish Society of Hypertension

Table 26. Blood glucose control in patients with concomitant diabetes after revascularization due to lower extremity artery disease

	PTD 2019	ESC 2019 [90]
Target HbA_{1c} levels in patients with concomitant diabetes	HbA_{1c} < 6.5%: at stable blood glucose levels and minimized number of hypoglycemic episodes	HbA_{1c} < 7.0% or < 53 mmol/mol

ESC — European Society of Cardiology; HbA_1c — glycated hemoglobin; PTD — Polish Diabetes Association

Table 27. LDL-C level control in patients after revascularization due to lower extremity artery disease

	2018 Sopot Declaration	ESC 2019 [91]
Target LDL-C level	Extremely high risk (see body text) < 35 mg/dL (< 0.9 mmol/L)	In most patients, reduction in LDL-C levels by > 50% compared to baseline and target level of < 55 mg/dL (< 1.4 mmol/L)
	Very high risk (see body text) < 55 mg/dL (< 1.4 mmol/l)	Target values of < 40 mg/dL (< 1.0 mmol/L) may be considered in patients with diagnosed atherosclerosis who have experienced the second vascular incident within the period of 2 years while receiving maximum statin dose

ESC — European Society of Cardiology; LDL-C — low-density lipoprotein cholesterol

According to the ESC guidelines, all patients diagnosed with PAD are *a priori* classified as very high risk patients regardless of concomitant disease status [87]. Regardless of the adopted risk category, control of risk factors is required in all patients, including:

- **non-smoking** — no exposure to tobacco in any form;
- **proper diet** — food with low saturated fats content, rich in whole grain products, vegetables, fruit, and fish;
- **physical activity** — at least 150 minutes of moderate-intensity aerobic training per week (30 minutes 5 times a week) or 75 minutes of high-intensity aerobic training per week (15 minutes 5 times a weak) or a combination of the above.
- **body weight control** — body mass index maintained in the range of 20–25 kg/m^2, waist circumference < 94 cm in males and < 80 in females.

Further recommendations pertain to the control of arterial pressure, lipid levels, and blood glucose levels. Slight differences are observed between European and Polish guidelines as presented in Tables 25–27.

Besides the reduction of cardiovascular risk, there is another important aspect to LEAD patient management, namely prevention of future revascularizations. Recently, a meta-analysis was published which summarized the risk factors of rehospitalization following revascularization due to LEAD. These risk factors are also cardiovascular risk factors [92] and include:

- female gender;
- arterial hypertension;
- heart failure;
- chronic lung disease;
- diabetes;
- chronic renal insufficiency;
- dialysis therapy;
- nicotinism.

In addition, it should be kept in mind that efficient control of all the aforementioned risk factors is possible

only when pharmacotherapy recommended in LEAD patients is provided, including indispensable statins and additional medications supplementing the comprehensive treatment as discussed in other chapters.

5.3. LEAD patients after endovascular procedures

5.3.1. Post-interventional exercise therapy and risk factor modification

Patients with the diagnosis of lower limb ischemia and history of endovascular procedures are in the high health hazard group and should be included in an active counseling system. The TASC II guidelines include a recommendation regarding clinical follow-up programs for patients after endovascular procedures. It is recommended that patients are included in a clinical follow-up program lasting up to 2 years and consisting of regular follow-up visits at 6-month intervals. Visits may include an interview and vascular examination. Attention should also be paid to any comorbidities: ischemic heart disease, arterial hypertension, atrial fibrillation, deep vein thrombosis, history of pulmonary embolism, or type I or II diabetes mellitus. The premises of such a patient management system included identification of factors promoting vessel or stent restenosis, by-pass occlusion and their potential repair before patency loss. In 2005, studies were published with results questioning the need and the sense of post-procedural patient follow-up due to high costs of follow-up examinations compared to clinical benefits.

Currently, TASC II guidelines lack recommendations regarding management of patients following endovascular procedures. Numerous reports were published regarding the monitoring of patients after endovascular procedures. Authors from the Charing Cross Hospital proposed follow-up examinations on Day 1 and Month 3, 6, 9, and 12 after the procedure. Examination should include medical interview, ABI measurement, and Doppler ultrasound. In 2004, data were published from a program for the monitoring of patients with critical lower limb ischemia, after by-pass graft implantation, and after endovascular procedures. The program included follow-up visits at 6 weeks, 3, 6, and 9 months, and 1 year after the procedure. The visit consisted in ABI measurements at rest and after physical effort as well as ultrasound scan of the entire length of the vessel being repaired. Such monitoring facilitated early detection and treatment of restenosis. Ultrasound-detected stenosis of 50–76% with ABI drop of more than 0.15 and worsening of clinical status were considered indications for repeated intervention. According to the conclusions from the study, a monitoring program consisting of frequent follow-up visits combined with US scans and ABI measurements is required to maintain patency of revascularized vessels in this group of patients. In addition to statins and antiplatelet agents, controlled physical exercise should be used. On the other hand, benefits of vasoactive agents are somewhat dubious.

5.3.2. Antiplatelet-anticoagulant treatment following endovascular treatment of lower extremity artery disease

Currently, DAPT is recommended for at least one month following an intervention regardless of the stent type (non-coated metal stet or drug-eluting stent). In a randomized clinical study Zilver PTX comparing drug-eluting stents with non-coated metal stents, the study protocol required DAPT being administered for 2 months. In the IN.PACT SFA study, one half of patients received DAPT after one year. Dual antiplatelet therapy is frequently continued after infrapopliteal artery stenting, albeit no evidence is available to support this management strategy. Efficacy of anticoagulant treatment was examined prospectively following percutaneous infra-inguinal revascularization. No improvement in vessel patency was observed while the incidence of bleedings increased significantly.

At this time, no data from clinical studies are available to assess benefits of DAPT compared to SAPT following subclavian, visceral, and renal artery stenting. At most centers, clopidogrel (75 mg) is prescribed in combination with a small dose of ASA, usually for 1–3 months; in some cases, this period is extended to 1 year. An observation study revealed a trend towards a lower rate of secondary procedures due to failed revascularization when primary stenting was performed during DAPT.

The management of LEAD patients consists of two main elements: treatment aimed at reducing global cardiovascular risk and treatment addressing the symptoms and risks associated with lesions being located within the lower limbs; the latter is aimed at reducing limb-related symptoms and/or at saving the threatened limb. The recommended management aimed at reducing global cardiovascular risks, consisting of non-pharmacological methods as well as pharmacotherapy, is the same in all LEAD patients regardless of the area within the vascular system in which symptoms caused by atherosclerotic lesions are being manifested. Treatment addressing local lesions within the lower limbs is specific for LEAD patients.

5.3.3. Non-pharmacological methods

Pursuant to the 2017 ESC guidelines for the management of LEAD patients, the following measures are recommended in all patients:

1. cessation of smoking (recommendation class I B);
2. healthy diet and physical activity (recommendation class I C).

Non-pharmacological prevention strategies may also have a beneficial effect on the incidence of cardiovascular events within the limbs. The highest benefits in terms of symptom resolution and cardiovascular risk reduction are obtained from combination of the recommended methods; for example, cessation of smoking alone has a small impact on walking distance whereas the most noticeable improvement in the walking distance is observed for smoking cessation combined with cardio workout. Failing to quit smoking worsens the natural history of LEAD in patients with intermittent claudication and is associated with elevated risk of amputation.

Follow-up Doppler ultrasound examinations in patients following revascularization of stenting of peripheral arteries are performed for the following three reasons: 1) to monitor the quality of procedural treatment (restoration of patency, presence of persistent stenoses, assessment of hemodynamic outcomes of the procedure); 2) to detect potential restenoses; and 3) to evaluate the progression of atherosclerotic lesions in the remaining vessel segments.

Following endovascular procedures, both with and without stent deployment, deposits pressed into the vessel walls can be observed, forming persistent stenoses. Stenoses of less than 30% are not considered worrisome. Following subendothelial patency restoration, parts of the vessel wall in the transverse cross-section may be thinned and lacking the intima. The remaining parts of the wall are thickened by pressed atherosclerotic deposits. In a significant majority of this type of procedures (restricted to subintimal angioplasty alone), persistent stenoses in the range of 30–50% should be expected. However, important information from post-angioplasty examinations is provided not only by the assessment of persistent stenoses at the repair site but also by the assessment of hemodynamically significant stenoses upstream and downstream of the treated vessel segment and the assessment of restenoses within the repaired area in long-term follow-up. In the follow-up US scans, the implanted stent should be fully deployed, with straight wall contours and the flow-coding color completely filling the stent lumen. Due to the reduced compliance of vessel walls within the stented segment, flow velocities are usually higher than in native arteries. Following pathologies should be ruled out or confirmed and described in the course of the examination:

- in-stent stenosis caused the stent being compressed by deposits pressed into the vessel wall or by intimal hyperplasia within the stent lumen.
- stent fracture;
- stenosis upstream of the proximal or downstream of the distal end of the stent;
- obstruction.

Ultrasound examination is also important for the diagnostics of local vascular access complications, including in the assessment of hematomas, pseudoaneurysms, or arteriovenous fistulas.

When abnormalities are detected in revascularized vessel segments, their character, location, extent and degree of stenosis (obstruction) should be reported).

When a hemodynamically significant flow impairment or obstruction is detected, the arterial system of the entire limb should be examined and the location of collateral circulation flows should be identified.

5.4. LEAD patients with atrial fibrillation

Atrial fibrillation is common in LEAD patients and is associated with poorer treatment outcomes compared to non-AF patients. Although little data are available on regarding the choice of particular anticoagulant treatments in LEAD patients and indications for oral anticoagulant therapy, the first step consists in reevaluation of indications for the latter. Oral anticoagulant treatment should be continued only id explicitly indicated (e.g. paroxysmal, persistent, or permanent AF combine with CHA_2DS_2-VASc score of > 2 [congestive heart failure, arterial hypertension, age > 75 years {2 points}, diabetes, brain stroke {2 points.}, vascular disease, age 65–74 years, female gender]), mechanical valve prosthesis or pulmonary embolism. Notably, LEAD corresponds to 1 point in the CHA_2DS_2-VASc score and may impact the indications for use of oral anticoagulants (OACs). In a post-hoc analysis of data from Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study, a significant interaction was observed in relation to severe and other clinically significant bleedings as the risk of these events differed significantly between LEAD patients (n = 839) treated with rivaroxaban and and patients treated with warfarin (HR 1.40; 95% CI 1.06–1.86) on non-LEAD subjects (HR 1/03; 95% CI 0.95–1.11; P = 0.037). Further studies are needed.

The duration of combination treatment should be as short as possible (1 month), depending on clinical indications and bleeding risk. Addition of antiplatelet treatment may depend on concomitant coronary artery disease or the need for endovascular revascularization due to LEAD. In such cases, TAPT (e.g. ASA, clopidogrel and anticoagulant) is discouraged with the exception of stents being implanted in infrapopliteal vessels or complex lesions associated with very high risk of thrombosis. The proposed algorithm of management including LEAD treatment and bleeding risk control is

presented in Figure 14. Proton pump inhibitor is recommended for stomach protection; the intensity of OAC administration should be monitored cautiously against the target international normalized ratio values (INR) of 2.0–2.5 in patients receiving a vitamin K antagonist (VKA) with the exception of patients with mechanical mitral valve prosthesis. In patients receiving non-vitamin K antagonist oral anticoagulants (NOACs) combined with antiplatelet drugs, the dose should correspond to the lowest dose assessed in registration studies as pertaining to brain stroke prevention.

5.4.1. Combined antiplatelet and anticoagulant treatment

Conventional anticoagulant treatment is of no special importance in patients with symptomatic LEAD and no other indications for such treatment, such as e.g. Atrial fibrillation or venous thromboembolism. The efficacy of warfarin or acenocoumarol (with target INR values in the range of 2–3) combined with antiplatelet therapy compared to antiplatelet therapy alone in PAD patients was assessed in the Warfarin Antiplatelet Vascular Evaluation (WAVE) study to reveal that the combined antiplatelet and anticoagulant treatment was not superior in terms of major adverse cardiac event (MACE) prevention while being associated with a more than threefold increase in the incidence of life-threatening hemorrhages.

Recently, the COMPASS study assessed the new strategy for combined antiplatelet and anticoagulant treatment consisting in ASA being combined with a small dose of a NOAC; the treatment was compared to ASA or NOAC alone in patients diagnosed with stable cardiovascular disease. Since the new possibilities of combines anticoagulation treatment suggested by the results of the COMPASS could not have been included in the latest ESC guidelines for the management of PAD patients as published in 2017, they will be discussed in more detail herein as they would potentially impact future practice of LEAD patient management.

5.4.2. The COMPASS study

In a large, multicenter, randomized COMPASS study, combination of ASA (100 mg/d) and a small dose of rivaroxaban (2.5 mg twice daily) was compared to rivaroxaban alone (5 mg twice daily) or ASA alone (100 mg/d) in more than 27,000 patients with stable coronary artery disease or PAD. The study was discontinued after mean observation time of 23 months due to the observed superiority of ASA and rivaroxaban combination which led to a significant reduction in the incidence of complex endpoint encompassing cardiovascular deaths, myocardial infarctions ad brain strokes as well as to a reduction in cardiovascular and all-cause mortality rates.

In a prospectively designed analysis of a subgroup of 7470 patients with PAD (LEAD or carotid artery disease) combination of ASA and rivaroxaban was found to be associated with a significantly lower incidence of the aforementioned complex endpoint as compared to ASA alone (risk being reduced by 28%) as well as a significantly lower incidence of major limb-related events, including amputation (risk being reduced by 46%). The risk of all amputations for cardiovascular reasons was reduced by 60% while the risk of major amputations was reduced by 70% compared to ASA monotherapy group. Median treatment time was 21 months. The study inclusion criteria for LEAD patients included history of percutaneous or surgical intervention, history of amputation or intermittent claudication in patients with objectively documented LEAD (ABI $<$ 0.9 or arterial stenosis of $>$ 50%). Major limb-related events were defined as acute ischemia and severe chronic ischemia requiring vascular intervention or amputation. The results obtained within the LEAD subgroup were the same as in the entire PAD group. Rivaroxaban monotherapy did not reduce the incidence of primary endpoint compared to ASA monotherapy while being associated with a lower incidence of major limb-related events and lower rate of amputations. Rivaroxaban, either in monotherapy or in combination with ASA, was associated with increased risk of major hemorrhages, mostly within the gastrointestinal tract; no fatal hemorrhages, intracranial bleedings or hemorrhages within the key organs were observed.

Results of a separate analysis on the incidence of major limb-related events in 6391 LEAD patients included in the COMPASS study was also published. Compared to ASA alone, combination of rivaroxaban and ASA was associated with a 43% reduction in the incidence of major limb-related events, 59% reduction in the rate of amputations, and 24% reduction in the rate of peripheral vascular interventions. The occurrence of a major limb-related event was associated with poor prognosis (annual risk of death of 8.3%, annual risk of amputation 20.5%) Rivaroxaban was associated with increased risk of major hemorrhages, albeit not severe or fatal hemorrhages. As pointed out by the authors of the Editor's Comment, as absolute reduction of the risk of major limb-related incidents was more or less equal to the absolute increase in the risk of major hemorrhage, it might be difficult to assess the risk-to-benefit ratio for rivaroxaban-containing combination. The highest risk of major limb-related events was observed in patients with history of amputation or vascular intervention (3.8%); it was lower in patients with symptomatic LEAD and no history of amputation or vascular intervention (1.37%) and the lowest in asymptomatic LEAD patients (0.5%). Therefore, it appears that the risk-to-benefit ratio may

Table 28. Clinical categories of acute lower limb ischemia according to the Society for Vascular Surgery

Grade	Category	Dysesthesia	Motor deficit	Prognosis
I	Viable tissues	Absent	Absent	No immediate threat
IIA	Marginal threat	Absent or minimum (toes)	Absent	Can be saved by immediate treatment
IIB	Immediate threat	Extending beyond toes	Mild/moderate	Can be saved by immediate revascularization
III	Irreversible damage	Intense, numbness	Intense, paralysis (stiffness)	Severe tissue loss, permanent neural damage imminent

be highest in patients with history of amputation or vascular intervention and lowest in asymptomatic LEAD patients. Considering the overall reduction in the risk of MACEs in the COMPASS study, it was also concluded that inclusion of rivaroxaban in the treatment regimen would be most beneficial to patients with concomitant coronary artery disease, particularly patients with a history of myocardial infarction.

5.5. Management of acute ischemia

Acute limb ischemia (ALI) develops as the result of the inflow of blood and nutrients to metabolically active tissues such as muscles, skin, or nerves, being stopped in a sudden manner [19]. In contrast to chronic ischemia which may be associated with the development of collateral circulation due to its duration, acute ischemia is characterized by lack of collateral circulation to compensate the for loss of perfusion. Extended periods of ischemia may pose a threat not only to the limb, but to the patient's life as well. Hypoperfusion of the limb is associated with systemic acid-base balance disorders leasing to disturbed cardiovascular and renal function. Efficient reperfusion might increase these disturbances by the release of highly toxic reactive oxygen species. Thus, early diagnosis and initiation of optimum therapeutic management are crucial for possibly best treatment outcomes.

The incidence of complications and deaths in patients with acute ischemia is high. Despite emergency revascularization using thrombolytics or a surgical procedure, limb amputation is required in 10–15% of patients during hospitalization. About 15–20% of patients die within one year from episode, frequently due to comorbidities which predisposed them to acute limb ischemia [19, 93, 94].

A typical clinical presentation of acute limb ischemia is defined as 6P: pale, pulseless, painful, paralysed, paraesthetic and perishing with cold.

The most common causes of acute limb ischemia include arterial embolism or cardiac origin, atherosclerotic thrombosis, embolizing aneurysm, aortic dissection or arterial injury. Etiology of the disease, intensity and duration of symptoms, and the intensity of motor and sensory deficits in the limb are decisive for treatment planning. The time frame of 4–6 hours between the event and treatment is due to longer periods of ischemia not being tolerated by skeletal muscles.

After the diagnosis, 5000 IU of non-fractionated heparin should be administered unconditionally to prevent secondary thrombosis; analgesic treatment should also be delivered [19].

The role of heparin in preventing secondary progression of thrombosis was first described by Blaisdell in 1978. Maintenance of the patency of peripheral arteries, and particularly microcirculation, downstream of the obstruction site, is crucial for the overall treatment outcome [95].

Acute lower limb ischemia is treated by means of surgical or endovascular methods or by combinations of the two; hence, today's vascular surgery demands that specialist departments are equipped with hybrid operating rooms facilitating smooth transition between both modalities as needed. Duration of symptoms is of key importance for treatment planning. Pursuant to the SVS criteria, clinical categories of acute lower limb ischemia are defined along with time frames for the required revascularization procedure (Table 28).

In case of moderately intense symptoms of ischemia (grade I), general anticoagulation treatment and stabilization of patient's overall condition is usually required while the repair intervention may be carried out in an accelerated setting within 6–24 hours.

Patients diagnosed with borderline or direct threat of limb loss (grades IIA and IIB) should be operated within the "golden" 6 hours; among other factors, this is due to the high risk of ischemia progressing to grade III [96].

The decision regarding the treatment modality i grade IIA is largely dependent on the duration of symptoms. Local thrombolysis is more efficient when the duration of ischemia is shorter than 14 days. Surgical revascularization is recommended in individuals with contraindications to thrombolytic treatment, incomplete response to thrombolytic treatment, or disease duration of more than 14 days [97, 98].

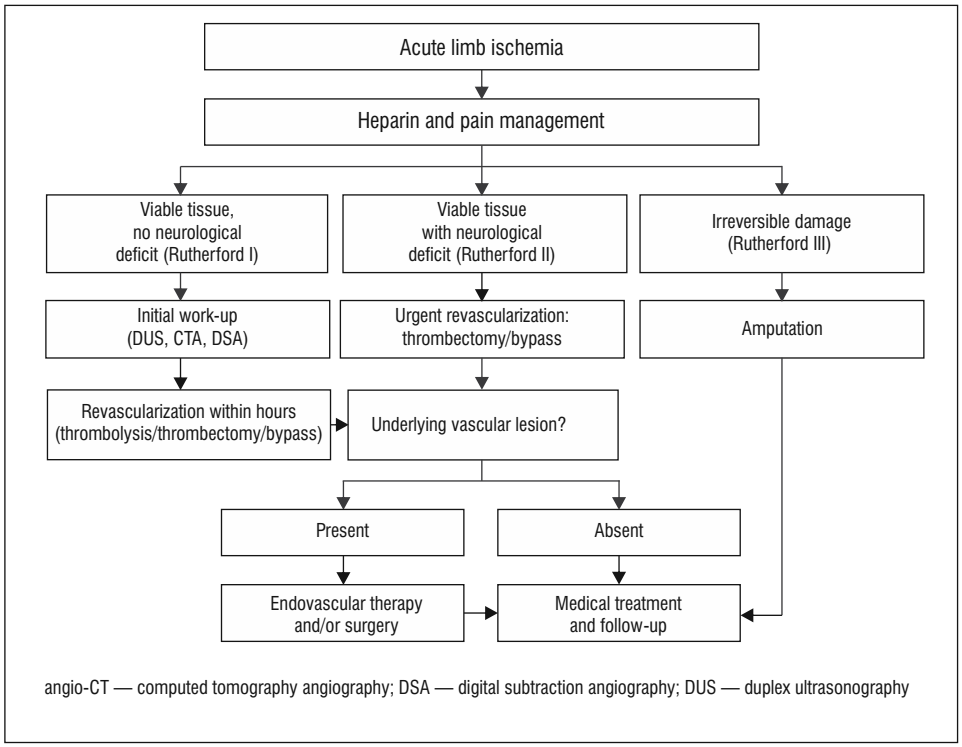


Figure 19. Algorithm for the Management of acute lower limb ischemia according to ECS and ESVS guidelines

In patients with grade I and IIA ischemia in whom the time of revascularization is not of the utmost importance, angiographic examination is recommended

as less invasive endovascular techniques such as aspiration thrombectomy or local thrombolysis can be performed in many cases with good clinical outcomes and recanalization rates of 75 to 92% [99–101].

Recombinant tissue plasminogen activator is the drug of choice at most centers offering local thrombolysis procedures. It is recommended to monitor the serum fibrinogen levels, as concentration lower than 2 g/dL is an indication for treatment discontinuation so as to avoid uncontrolled bleeding [102].

Complications following the thrombolysis are manifested as bleeding in 6–9% of cases, including as intracranial bleeding in less than 3% of cases. Main factors associated with increased risk of bleeding include the duration of treatment, age, low baseline thrombocyte level, and comorbid arterial hypertension [103, 104].

Emergency surgery is required in patients with acute limb ischemia classified as grade IIB (limb-threatening) [57]. In such cases, surgical rather than endovascular treatment is recommended; however, systems for mechanical or thrombolytic management as introduced in recent years open up new possibilities and prospects for wider use in the treatment of this group of patients.

In grade IIB ischemia, chances for limb saving still exist, but immediate surgery is required. If acute ischemia is due to an embolism, it should be removed by surgical means. In case of atherosclerotic arterial thrombosis, surgical thrombectomy is performed on intraoperatively located lesions; if needed, surgery may be supplemented with angioplasty, endarterectomy, or bypass grafting.

Revascularization of arteries with grade III ischemia is usually futile and may lead to opposite effects due to the high risk of organ dysfunction and death due to reperfusion [95]. In a significant majority of cases, emergency primary limb amputation is required [105].

Grade III ischemia is considered irreversible. However, if the duration of ischemia is not greater than 2 hours and if no muscle rigor is observed locally, revascularization success is still possible, albeit the possibility of post-operative subfascial tension quiring fasciotomy should be kept in mind [106].

5.5.1. Summary

The choice of the surgical technique depends on the etiology of acute limb ischemia; regardless of that, it should also ensure possibly fastest restoration of limb circulation. Final decision on the revascularization method should be made on case-by-case basis with the operating teams abilities and experience being taken into account. Prolonged ischemia is the most common cause of inefficient revascularization and limb amputation.

Figure 19 presents the algorithm for the management of acute lower limb ischemia according to the ESC/ESVS guidelines.

5.6. Peculiarity of care to amputation patients

5.6.1. Background

Evaluation of the amputation risk using the WIfI classification — the most severe form of LEAD is referred to as chronic limb threatening ischemia (CLTI. Wounds and infections should be taken into account along with ischemia (the new WIfI classification). The TASC classification has been removed from guidelines.

5.6.1.1. Minor amputation

In the case of CLTI, minor amputation (up to the forefoot level) is often required to remove necrotic tissues with minor consequences for patient's mobility. Revascularization is required prior to amputation for better wound healing. Determination of amputation range may be facilitated by $TcPO_2$ measurements within the foot and toe blood pressure measurements.

5.6.1.2. Major amputation

In patients with extensive necrosis or infected gangrene, as well as in immobile or severely comorbid patients, primary major amputation may be the optimum solution. Major amputation is the last resort of treatment aimed at prevention or suppression of generalized complications of irreversible lib ischemia; in some cases, improvement in patient's condition is possible with prosthesis and rehabilitation. In terminally ill patients, appropriate analgesic treatment and other maintenance therapy may also be provided.

Secondary amputation should be performed when revascularization has failed and reintervention is not possible or when the condition of the limb is deteriorating due to infection or necrosis despite the bypasses being patent and optimum treatment being delivered. In all cases, below-the-knee amputation should be preferred since conservation of the knee ensures better mobility after prosthesis fitting. Thigh-level amputation may be the best solution in bed-ridden patients.

5.6.2. Post-amputation patients — management and complications

Recovery after limb amputation

Limb amputation is performed as the last resort of treatment after all methods to save limb have failed. The recovery may take several months or more than a year depending on the type and extent of amputation and potential complications.

Informed consent of the patient is required for the procedure. In unconscious patients in direct life-threatening condition, the decision is made by the medical team.

5.6.2.2. Preparation for discharge

During post-operative rehabilitation including the strengthening of particular muscle groups and restoration of appropriate systemic competence levels, it is also important to educate patients on limitations caused by the procedure and available methods to eliminate these limitations using orthopedic equipment. Patient's family also plays an important role and should be instructed on the mode of care and the necessity of adapting patient's residence to their new needs.

5.6.2.3. Compression garments

After the surgery, stump swelling develops in patients as a normal consequence of the procedure. Compression garments may help reduce swelling and phantom pains. It is recommended that compression garments are worn all day long.

5.6.2.4. Discharge (several days to several weeks after the surgery

Once hospitalization is complete, patient should be referred to rehabilitation treatment. Patients should report for successive follow-up visits to monitor the wound healing process until it is completely healed. Patients should immediately report at their doctor's should any disturbing symptoms develop.

5.6.2.5. Prosthesis fitting (several months to more than one year after the surgery)

For most amputations, appropriate prostheses can be fitted to partially replace the function of the lost limb. The type of prosthesis may be adjusted to patient's needs and activity levels. A young and physically active patient would expect the prosthesis to largely replace the function of the amputated limb. Before fitting, the skin and the stump must be appropriately prepared (shaped) so that the patient will be able to take all advantage offered by the prosthesis.

5.6.2.6. Rehabilitation (immediately after the surgery for several months to more than a year)

Rehabilitation is an individual process aimed at possibly best return to normal activity. Appropriate physical therapy program and its goals should be agreed upon by the physical therapist and the patient.

Usually, rehabilitation starts a dozen or so hours after the procedure with several simple exercises performed in recumbent or sitting positions. Following amputation of the lower limb, patients are usually encouraged to use wheelchairs in the initial stage of rehabilitation. Also important is the mastering the technique of switching from the wheelchair onto a chair or bed and vice versa. As the wound heals and

the system recovers after the surgery, the range of exercises is broadened.

After wound healing has completed, prosthesis fitting may be started. Next, physiotherapist should train the patient in the use of the prosthesis.

Although rehabilitation may be a long and monotonous process, perseverance and commitment of both the patient and the therapist lead to very good outcomes, facilitating patient's return to physical or professional activity.

5.6.2.7. Hygiene

Stump skin should be kept clean to reduce the risk of injury or infection. Patients should wash their stump skin with soap and water at least once a day; after washing, skin should be delicately dried. The stump should not be immersed in water for longer periods as it would soften the skin making it more prone to abrasions and injuries. Moisturizing creams should be used on excessively drying skin. Some patients use special socks worn on the stump to reduce the risk of skin irritation.

The patient should monitor their limb daily and report at their doctors should any symptoms of infection such as redness, heat, skin tightness, purulent secretion from the wound or increasing swelling develop.

5.6.3. Care for the healthy limb

Protection of healthy limb is also important following amputation. If amputation was due e.g. To diabetes, the patient should be aware that the other limb is also at risk of complications potentially leading to amputation. Therefore, it is important to comply with physician's recommendations regarding the prevention of complications and risk reduction methods.

5.6.4. Amputation-related complications

As any procedure, amputation may be associated with risk of complications. An additional risk is also to delayed initiation of treatment.

Factors that determine the risk of complications include patient's age, comorbidities, or the type of amputation. The risk is increased in rescue amputations while being lower in scheduled procedures performed after proper patient preparation.

Amputation-related complications include cardiovascular complications, such as circulatory insufficiency, myocardial infarction, or vein thrombosis, delayed surgical wound healing, surgical wound infection, pneumonia, phantom pains, emotional problems.

In some cases, stump repair may also be required. Amputation is considered last resort treatment following the failure of all other treatment methods. However, for some patients, the amputation of a limb that was a source of pain and numerous limitations improves the overall quality of life and facilitates return to normal functioning.

5.6.5. Pain

Many patients experience stump pain or phantom pain after amputation. Phantom pain is perceived as pain within the amputated part of the limb. It may vary in intensity. Some patients report their phantom pains as short pain episodes while others experience strong and persistent pain.

Stump pains may also be caused by other factors such as abrasions caused by prosthesis or damage to the nerves in the course of amputation.

5.6.6. Phantom pain treatment

Phantom pain usually subsides with time; however, numerous methods are available to help reduce this pain and should be customized according to patient's needs.

Drugs used to reduce pain include non-steroidal anti-inflammatory drugs (NSAIDs),

- such as ibuprofen, anticonvulsants,
- such as carbamazepine or gabapentine, antidepressants, such as amitriptyline or nortriptyline, opioids, such as codeine or morphine, and steroid injections.

Several non-invasive techniques are also available to reduce pain, including cold or hot compresses, massage, electrostimulation, etc.

In some cases, additional surgery (e.g. neuroma removal) may be required to reduce pain.

5.7. Amputation wound management

Amputation wound management should vary, e.g. depending on the patient status and the condition of limb before the procedure. The presence and intensity of inflammation — both local and systemic (usually in diabetic patients [14] and immunosuppressed patients) — is of key importance.

In such patients, complete wound closure following short-term surgical bed drainage is not recommended; instead, exudate drainage should be left in place for a longer period, determined for a case-by-case basis, to monitor the wound and local antiseptic conditions. An important task for medical team managers (hospital managers, department/clinic heads, ward directors, ward nurses) consists in establishing a team responsible for wound healing in such patients. Teams should comprise of a surgeon (general, vascular, orthopedic), procedural nurse, rehabilitation therapist and orthopedic technician, diabetologist for diabetic patients, clinical dietitian, psychiatrist and psychologist, and a social worker.

The line-up of a multidisciplinary team involved in the treatment of arterial ulcers is presented in Figure 20.

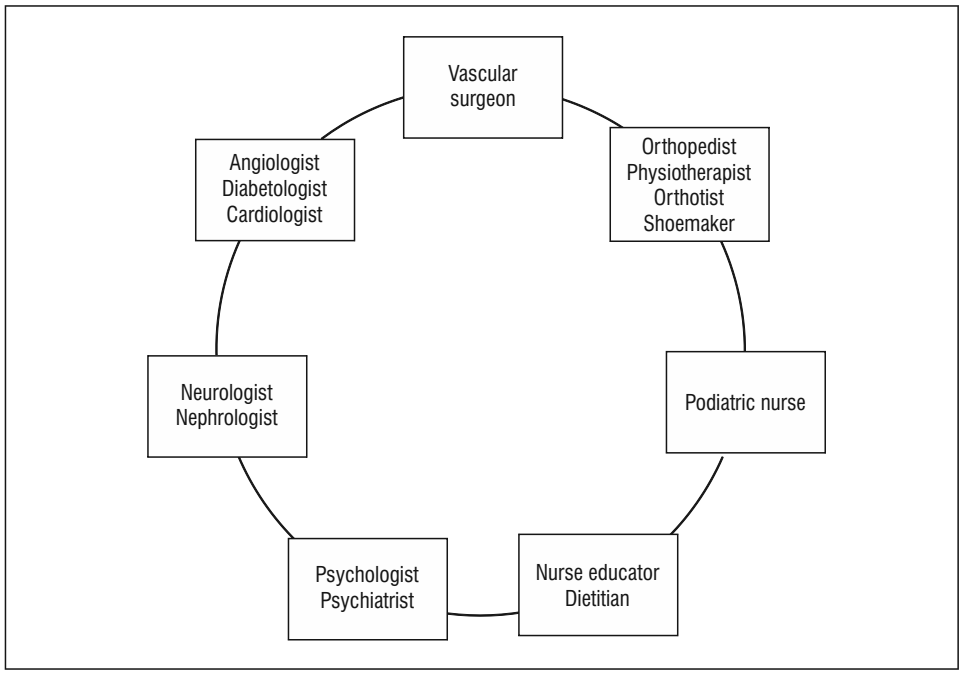


Figure 20. Multidisciplinary team involved in the treatment of arterial ulcers and in the management of post-amputation patients

The process of amputation wound healing consists of two stages:

I. Before surgical wound closure — the objective of the management team is to promote granulation within the resection site and prevent the infection of the surgical site [107]. Since most surgical wards are colonized with multidrug-resistant bacterial species, the main task of the patient management team should be to lower the risk of such colonization and consequential infection. To this end, following principles should be adhered to:
   a) wound condition assessments should be performed using gloves with compliance to asepticity and antisepticity principles;
   b) if possible, dressings should be changed in dressing rooms rather than in patient rooms;
   c) when placing patient in recumbent or semi-recumbent position, amputation stump should be elevated so as to minimize swelling;
   d) after the procedure bed sore prevention and patient rehabilitation should be initiated to help the patient regain their independence and to stimulate wound healing processes. Attention should also be paid to pain conditions including differentiation of pain origin (phantom pain, wound infection, bed sore in the stump);
   e) patients should receive appropriate nutrition compliant with wound healing principles;
   f) any symptoms of suppuration (elevation and redness of wound edges, purulent effusion, stump pain) require immediate revision of wound condition.

II. The second stage of wound healing consists in complete wound closure and preparation of the stump for the prosthesis to be fitted. At this stage, sutures should be removed (usually after 14-21 days) and temporarily replaced with steri-strips (ca. 5–10 days). Until the wound is closed, edges should be rinsed with an antiseptic agent or 0.9% NaCl if no signs of infection are present. While sutures remain in place, wound should be protected with sterile gauze pads; if inflammation persists within the wound edges, active dressings should be used as appropriate to local conditions. Gauze pads or active dressings should be secured so as to shape the stump in a funnel-like shape for safe prosthesis placement. Compression bandages are suitable for this purpose. Rigid compression bandages are used until the quantity of exudate/transudate is reduced. Soft compression bandages are used to reduce swelling at later stage of the wound healing process. Due to their structure and sensations they may cause (pain symptoms developing upon prolonged use), bandages should be changed even several times a day.

Principles (a–e) as listed for the first stage of the wound healing process also apply at this stage. At this stage, manual procedures to prepare the stump for prosthesis fitting (stump circulation-stimulating massages) become particularly important.

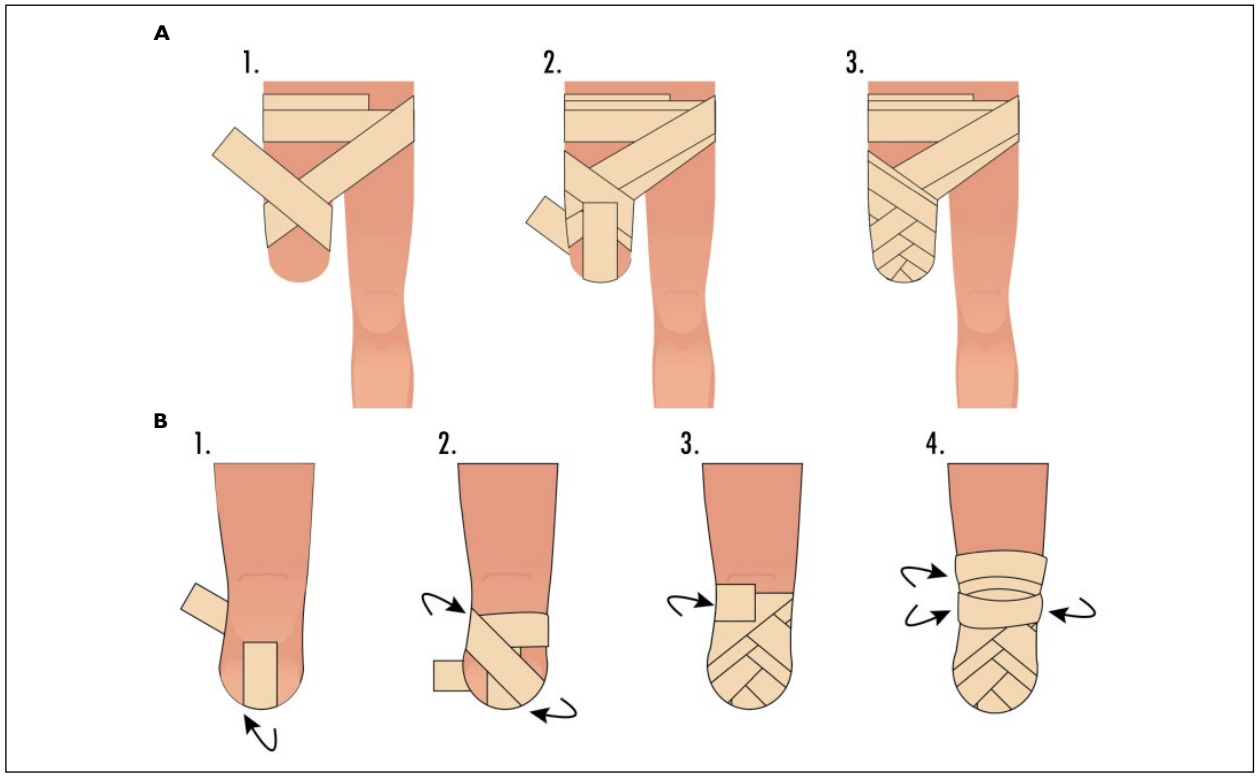


Figure 21. Principles for wrapping an elastic bandage on post-amputation stump: A — amputation above the knee; B — amputation below the knee. Adapted from https://www.amputee-coalition. org/wp-content/uploads/2015/08/Care-of-Your-Wounds-After--Amputation-Surgery.pdf

Principles for the placement of elastic bandages on above-the-knee and below-the-knee stumps are presented in Figure 21 A, B.

5.7.1. Wound management in patients with arterial ischemia

5.7.1.1. Systemic management of patients with wounds of ischemic origin

Firstly, the management of patients with wounds of ischemic origin should be aimed at determination of the extent of ischemic lesions and possibility of revascularization of arteries supplying blood to the wound area [108]. The baseline characteristics of ischemic lesions may vary since changes within the vascular bed may be due not only to the typical natural history of atherosclerosis as associated with age or smoking, but also to specific factors associated with long course of various comorbidities such as diabetes or vasculitis. For this reason, besides looking for ways to improve arterial blood supply, it is noteworthy to check whether ischemic lesions are not exacerbated by inappropriate or insufficient treatment of primary diseases. An example may be provided by high blood glucose levels being maintained and increasing plasma osmolarity which is particularly important during revascularization, particularly within the small arterial vessel area [109, 110].

Since most wounds in patients with signs of arterial ischemia are located within the shanks and feet, the diagnostic and therapeutic management should be immediate. Any delay in appropriate management increases not only the risk of losing the lower limb or a part thereof, but also the risk of complications due to the presence of devitalized tissue, including septic shock or acute coronary syndrome induction. The risk of such potential complications should be discussed with patients and their families prior to the treatment. Details of revascularization procedures also require consultation, as their effects are sometimes different than the expected improvement in limb blood supply (e.g. the blue toe syndrome). Sometimes, the team of vascular surgeons or interventional radiologists may refrain from performing the revascularization procedure. This is frequently the case in patients with signs of end-stage renal insufficiency, quite commonly at the stage of hemodialysis treatment. Primary life-saving amputation is performed when circulation cannot be improved and signs of critical limb ischemia are observed.

The success of the treatment also depends on the maintenance of tissue perfusion independent of revascularization. This may be achieved by means of:

- optimization of patient hydration (initially parenteral, if no contraindications are present); overall intake of about 1500–2000 mL of liquids/day or 30 mL/kg body weight; separate rules apply for patients with end-stage chronic renal insufficiency, severe heart failure, patients with fever or vomiting patients;
- resolution of pain (systemic pharmacotherapy in line with the analgesic ladder; NSAIDs should be avoided; local pharmacotherapy, e.g. lidocaine patches);
- supplementation with necessary nutrients (e.g. administration of special nutrient blends) [1 11];
- improvement of tissue oxygenation (administration of oxygen via nasal prongs or oxygen mask; avoiding excessive tissue by maintaining the body temperature of ca. 38°C, particularly within the lower limbs; maintenance of body position facilitating blood being supplied to necrotic tissues;
- hyperbaric oxygen [HBO] in case revascularization is impossible or its outcomes are insufficient);
- smoking cessation anti-tobacco treatment).

If signs of wound infection are observed, antibiotic therapy should be initiated as determined on a case-by-case basis (parenteral vs. oral) [112]. Short-term antibiotic therapy is also indicated in patients with neuropathic/ischemic ulcers without signs of infection (e.g. in diabetic patients, in whom signs of infection may not always be present due to immunosuppression). This is particularly important in the periprocedural period, including before and after revascularization. Studies revealed that patients subjected to short-term parenteral antibiotic therapy presented with lower rates of major and minor amputations. There are no indications for long-term antibiotic therapy in patients with arterial ulcers. Lack of improvement following antibiotic therapy indicates the necessity to identify the causes of this condition; a possible cause is the presence of non-removed, wet necrotic lesions (cf. point 2 in the principles for local management of wounds with signs of ischemia).

With regard to systemic treatment, optimization of treatment of diseases promoting delayed wound healing should be taken into account, e.g. by administration of loop diuretics to patients with edema due to heart failure. Metabolic control in diabetic patients is similarly important, as is normalization of blood pressure in hypertensive patients or lowering the patient's lipid profile [113]. If amputation is required, psychological and psychiatric care is required; pharmacotherapy of phantom pains should also be delivered. Independently, antiplatelet and anticoagulation therapy are of significant importance and have been discussed separately in section 4.3.

Motor rehabilitation should be offered at every stage of the treatment, also in cases when resection procedures are required. The principle of avoiding direct burden to the wound region applies.

5.7.2. Local management of wounds with signs of ischemia

5.7.2.1. General principles

In each case when a wound is of ischemic origin, potential for revascularization should be analyzed prior to any local treatment.

If dry necrotic tissue is present within the sound, it should not be removed; they may be left for autoamputation while being monitored for signs of superinfection. Paradoxically, dry necrosis may sometimes be transformed into wet necrosis following a revascularization procedure. If signs of wet necrosis are observed within the patient's wound, the basic rule consists in the removal of infected tissues.

Notably, bed sores are also wounds due to local ischemia, and therefore the prevention of bed sores is listed among the measures dedicated particularly for patients with signs of impaired arterial circulation and/or diabetes. Local methods, such as rings placed under the heels of special sponge dressings shaped to fit to the heel or the lumbar region are recommended. The risk of such lesions is very high during long surgeries, such as aortocoronary bypass grafting procedures. If bed sore develops in the heel region in a patient with atherosclerotic lesions within lower limb arteries. Systemic and local management principles should be followed as in the case of any other wound presenting with signs of ischemia.

5.7.2.2. Specific principles

Principles for local management in patients with wounds originating from impaired arterial perfusion depend on the current wound condition. Four clinical cases may be distinguished [114], as follows:

1. Arterial ulcer with signs of dry necrosis — no possibility of revascularization or no improvement following revascularization:
   - the wound consists in the necrosis of superficial skin layers (eschar) or skin along with the deeper tissue;
   - removal of necrotic tissue and placement of dressings maintaining moist wound environment are contraindicated;
   - the wound should be kept in conditions preventing moist wound environment; rinsing the wound with physiological saline should be avoided; antiseptic agents facilitating the maintenance of dry wound environment (e.g. povidone iodine) may

be used and wound may be protected using dry sterile gauze pads or dry dressing and non-compressing bandage (bandage must not be tied using bow knots etc.);
- skin around the wound should be hydrated with a moisturizing/oiling ointment, such as cholesterol ointment;
- if signs of infection develop below the dry necrotic tissue, methods for elimination thereof should be considered.

II. Arterial ulcer with signs of wet necrosis — no possibility of revascularization or no improvement following revascularization:
- If possible, the layer of wet necrotic tissue should be removed without the use of surgical instruments — dissemination
- of necrotic foci should be prevented by the maintenance of dry conditions; surgical resection of necrotic tissue should be performed if required;
- antiseptic agents facilitating the maintenance of dry wound environment (e.g. povidone iodine) should be used;
- if wet wound environment persists, absorbent dressing may be used, for example a dressing with silver ions if signs of infection are present; finally, wound should be protected with non-compressing bandage (bandage must not be tied using bow knots etc.);
- a moisturizing/oiling ointment, such as cholesterol ointment, should be applied to skin surrounding the wound.

III. Arterial ulcer with signs of dry necrosis — following successful revascularization:
- as in section I

IV. Arterial ulcer with signs of wet necrosis — following successful revascularization:
- in this case, necrotic tissue may be removed following revascularization procedure;
- In contrast to the previous types of wounds, moist wound environment should be maintained as per the TIME (tissue, infection, moisture, edge) strategy;
- a moisturizing/oiling ointment, such as cholesterol ointment, should be applied to skin surrounding the wound.

5.7.2.3. Additive methods in local treatment of wounds presenting with signs of necrosis [115]

Negative pressure wound therapy (NPWT) is an efficient method that may be used after blood supply is improved by means of revascularization procedures; however, periodic monitoring of wound condition should be performed (every 2–3 days) so that the treatment may be discontinued should the healing worsen.

Intermittent pneumatic compression (IPC) may be used after blood supply is improved by means of revascularization procedures; however, no data are available from studies assessing uniform indications for this method in patients with arterial circulation disorders.

Stem cell therapy — a potentially promising method, albeit no clinical evidence is available for its efficacy in this group of patients.

Gene therapy, for example vascular endothelial growth factor (VEGF) therapy — a potentially promising method, albeit no clinical evidence is available for its efficacy in this group of patients either.

Local oxygen therapy — albeit no clinical evidence is available for its efficacy in this group of patients.

Electrical stimulation of spinal cord — for reduction of pain.

5.7.3. Principles of care to patients with arterial ulcers

Despite clinical efficacy of revascularization procedures and the potential of the remaining methods, both systemic and local, patients with peripheral vessel diseases must remain under constant supervision of an interdisciplinary team consisting particularly of vascular and general surgeons, cardiologist, diabetologist, nephrologist, psychologist, and rehabilitation therapist. Podiatric procedures should be closely monitored by the treating physician i.e. the vascular surgeon or a diabetologist experienced the treatment of wounds in the case of diabetic patients.

Patients should be followed up for circulation efficiency following the revascularization procedure, as a minimum after 3, 6, and 12 months.

The development of new ulcers requires immediate control at a vascular surgery clinic so that the vascular system may be reassessed, potential revascularization may be undertaken, and further decisions may be made regarding continued systemic and local treatment.

6. An attempt at competence positioning — an algorithm for the referral of patients to primary care physicians, vascular surgeons, and other specialists

An algorithm for the referral of patients to primary care physicians, vascular surgeons, and other specialists is presented in Figure 22.

7. List of drugs most commonly used in lead patients, including dosage regimens

Medical treatment of LEAD patients is aimed at resolution of clinical symptoms (increasing the intermittent claudication distance) and at reduction of the risk of

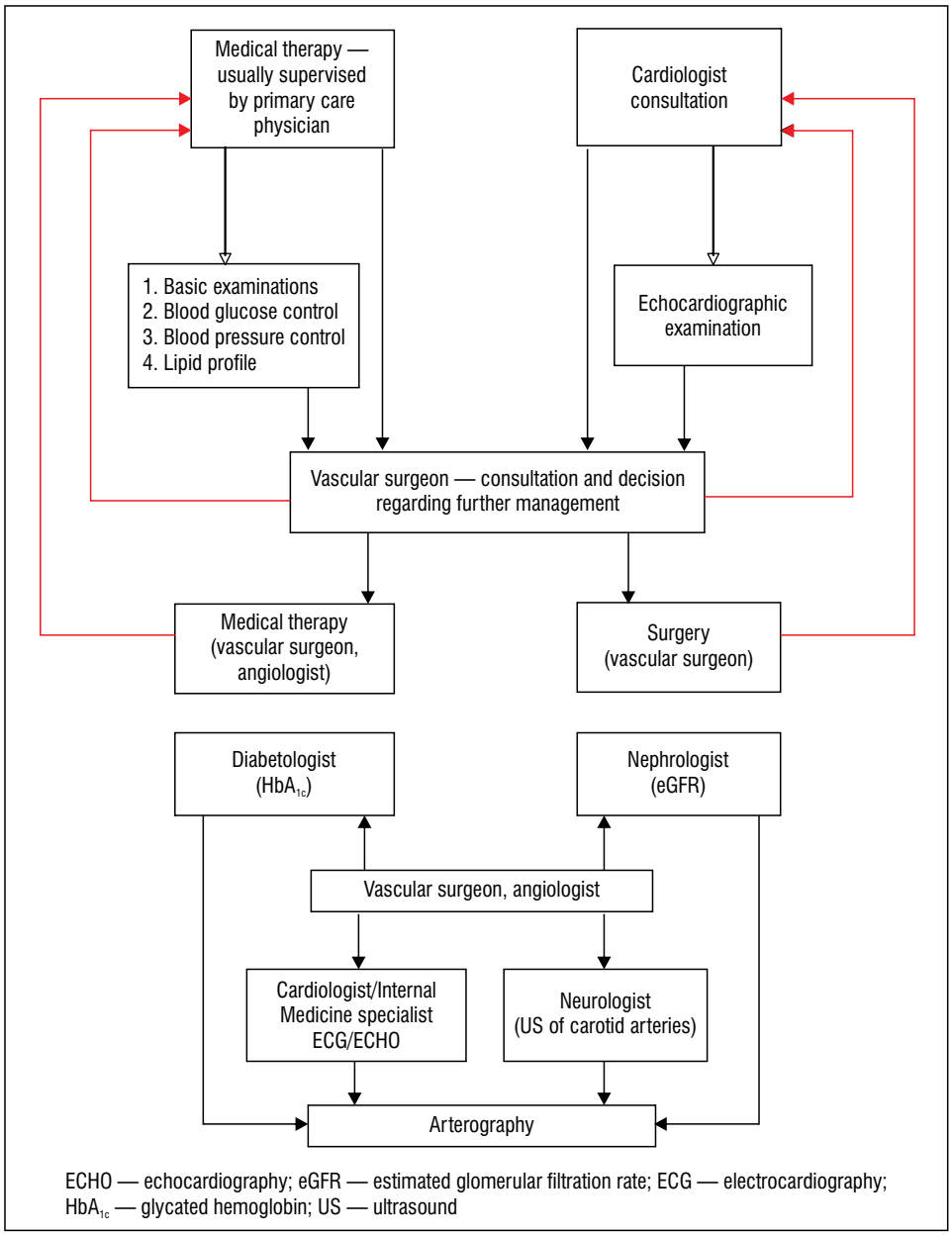


Figure 22. Algorithm for the referral of LEAD patients for further care

their progression and potential threat of limb loss. It is based on careful evaluation of risk factors, concomitant diseases, walking training and pharmacotherapy.

As per the 2017 ECS/ESVS guidelines, the role of medications is not exposed in the outcomes of the treatment of patients with intermittent claudication. Most common drugs used in the studies included cilostazol, naftidiofuryl, pentoxifylline, buflomedil, carnitine and propionyl-L-carnitine. However, objective documentation of treatment outcomes is limited. The positive impact on the walking distance, if any, is usually mild to moderate and is characterized by high inter-individual variability [74, 116–119].

7.1. Cilostazol (dosage: 100 mg 2 × day)

Cilostazol is a phosphodiesterase type 3 (PDE3) inhibitor. Inhibition of PDE3 increases the cAMP levels in vascular smooth muscles and platelets and inhibits aggregation of the latter.

MWD elongation was demonstrated in several clinical trials as compared to placebo or pentoxifylline. However, the effect on the MWD is highly variable. The recent analysis of Cochrane Collaboration database data revealed that the dose of 100 mg 2 times/day led to average elongation of MWD by 76% as compared to 20% in placebo groups. Another review suggested

that the mean improvement attributed to cilostazol was as low as 25% [74].

Cilostazol has an antiplatelet effect and therefore caution should be used when combining the drug with other antiplatelet drugs and anticoagulants. Interestingly, cilostazol reduced restenosis after endovascular treatment while increasing the incidence of hemorrhagic complications in randomized controlled trials [36].

Frequently reported adverse events included headache and diarrhea. Due to its mechanism of action, cilostazol may reduce arterial blood pressure and cause cardiac arrhythmias.

Cilostazol should be taken 30 minutes before breakfast and 30 minutes before the evening meal. When taken with meals, cilostazol was found to reach higher maximum plasma concentrations, which may lead to increased incidence of adverse events [120].

When administered to 23 patients with CLTI, cilostazol afforded a significant clinical improvement in 5 patients. Only one major amputation was required in the study group over the average follow-up period of 11.8 months [121].

Main contraindications include: congestive heart failure, hemorrhagic stroke/unstable angina pectoris/myocardial infarction/coronary intervention within last 6 months, history of significant ventricular arrhythmia, simultaneous use of at least 2 other anticoagulant agents (anti-platelet drugs or anticoagulants), severe renal dysfunction (creatinine clearance < 25 mL/min).

7.2. Naftidrofuryl (dosage: 200 mg 3 × day)

Naftidrofuryl is a strong antagonist of 5-hydroxytryptamine type 2 receptors in smooth muscle cells, affording reduced erythrocyte and platelet aggregation. The effect is observed in both cerebral and peripheral circulation. Naftidrofuryl has strong spasmolytic properties.

Its efficacy has been confirmed in a meta-analysis of 5 studies [118] ad in a Cochrane database survey. The walking distance increased significantly by 26% compared to placebo [122].

Patients' quality of life has also improved after naftidrofuryl treatment [123].

The most common adverse effects consist in mild gastrointestinal disorders. Naftidrofuryl used to be very popular in Poland in the 1980s; currently, it is not registered. It is still available in Western Europe.

7.3. Antiplatelet drugs

Antiplatelet drugs are of great importance for the treatment of LEAD patients. They are used in prevention of thrombotic events in the course of myocardial infarction, brain stroke, and peripheral artery disease. In LEAD patients, efficacy was documented for ASA used at doses of 75–325 mg per day, ticlopidine at doses of 250 mg bid and clopidogrel at the dose of 75 mg qd [124].

On the basis of randomized clinical studies, long-term antiplatelet therapy (ASA or clopidogrel) is recommended in patients with symptomatic chronic lower limb ischemia.

In case of patients with asymptomatic PAD, administration of ASA is not warranted. Also, dual antiplatelet therapy is not recommended in LEAD patients in the absence of other indications (e.g. presence of drug-eluting stent) due to the increased risk of bleeding and the lack of evidence regarding the benefits of DAPT [125–127].

Studies on other antiplatelet drugs (clopidogrel, ticagrelor, vorapaxar) revealed that despite additional benefits of their use, the elevated risk of bleeding or other adverse events lead to ASA being considered the drug of choice in patients with intermittent claudication [128–130].

7.4. Statins

Lipid-lowering agents are an important element of treatment in LEAD patients. By reducing the lipid levels, they not only slow down the disease progression, but also reduce the risk of potential cardiovascular complications. The pleiotropic effect of statins improves the function of vascular endothelium which is being impaired in the course of atherosclerosis . Among other factors, the pleiotropic effect consists in protection of vascular endothelium, stabilization of atherosclerotic plaque, anti-inflammatory activity and impact on the coagulation and fibrinolysis system.

The strength of statins depend on the product and dose.

As demonstrated in several studies, statins are effective in extending the walking distance. In patients treated with atorvastatin at the dose of 80 mg per day for 12 months, elongation of PFWD and reduction in the rate of cardiovascular episodes was observed [131].

Simvastatin used at the dose of 40 mg per day in short-term therapy of patients with intermittent claudication and comorbid hypercholesterolemia significantly increased the PFWD and ABI values [132].

However, no superiority of medical treatment (including statins) over supervised cardio workout or stenting has been demonstrated in the Claudication: Exercise vs. Endoluminal Revascularization (CLEVER) [133].

Large doses may increase the efficacy while also increasing the risk of adverse events such as gastrointestinal disorders, increased transaminase concentrations, myopathy, and, in extreme cases, rhabdomyolysis.

7.5. Pentoxiphylline (dosage: 400 mg 3 × day)

Pentoxiphylline is a xanthine derivative which, together with teophylline and caffeine, belongs to the group of non-selective phosphodiesterase blockers. Discovered in Germany in 1950, it was initially used as a drug improving microcirculation blood flow by means of reducing blood viscosity and thrombus formation potential. Multidirectional mechanism of action is highlighted for this agent, including the enhancement of intracellular adenosine-5'-triphosphate levels to reduce the outflux of potassium ions and increase phosphorylation of erythrocyte membrane proteins for membrane stabilization. As the consequence, deformability of erythrocytes is increased to facilitate their "squeezing" along tiny microcirculation vessels for better tissue oxygenation. Compared to naftidrofuryl and cilostazol, pentoxiphylline is characterized by lower efficacy of MWD elongation as it is increased by 60% for naftidrofuryl, 25% for cilostazol and 11% for pentoxiphylline and PFWD elongation as it is increased by 49%, 13%, and 9%, respectively [74].

Today, pentoxiphylline is used less commonly as more efficient drugs are available.

7.6. Sulodexide (dosage: 2 capsules [500 LSU] 2 × day)

Sulodexide is a blend of glucosaminoglycans containing fast-moving heparin (80%) and dermatan sulfate (20%). Sulodexide is characterized by strong, multidirectional effect including anticoagulation, profibrinolytic, anti-inflammatory, plasma lipid-lowering and vascular endothelium-protecting effects, particularly in hyperglycemic conditions [134]. Sulodexide inhibits activation and aggregation of platelets and reduces oxidative stress in leukocytes [135]. It inhibits the *in vitro* release of metalloproteinase-9 and reduces its activity in blood [75]. Anti-inflammatory effect is determined by the reduction in blood cytokine levels, including those of interleukin 6, transforming growth factor β1, and VEGF [136, 137].

Coccheri et al. [85] demonstrated that a six-month sulodexide treatment in patients with intermittent claudication significantly increased the pain-free walking distance by 76% compared to the baseline and by 33% compared to placebo (elongation by 142.3 ± 15.8 m; $P < 0.001$). The effect was independent on concomitant diabetes. A meta-analysis of 19 studies in 849 patients with peripheral atherosclerosis confirmed the earlier findings [86]. Sulodexide was found to have a significant impact on the reduction in the levels of triglycerides (average of −28%) and fibrinogen (−13%), the reduction in plasma and serum viscosity, and the increase in HDL-C levels (+24.4%). At the same time, PFWD elongation (36% compared to placebo) was observed.

7.7. Prostanoids — prostaglandins E1 and I2 (dosage 1 × 80 μg/day in slow intravenous infusion for 20 days)

Prostanoids are considered a treatment option for patients with critical limb ischemia not qualifying for revascularization; however, their efficacy in this indication is somewhat ambiguous.

As revealed by a Cochrane analysis published in 2018, although the results of studies published to date had suggested a significant pain-reducing effect and faster healing of ulcers in patients with critical limb ischemia, no unambiguous evidence from large randomized studies was available to confirm these findings [138].

7.8. L-carnitine (dosage: 2 × 1 capsule)

L-carnitine is synthesized from amino acids (lysine and methionine) in the liver, kidneys and brain and is involved in the transport of free fatty acids. Large quantities of L-carnitine can be detected in skeletal muscle cells. A reduction in L-carnitine levels leads to reduced metabolic potential of muscle cells and thus to reduced muscle energy efficiency. Although L-carnitine supplementation may be justified, clinical studies failed to demonstrate any advantages of its use compared to other LEAD treatment methods [139].

7.9. L-arginine (dosage: 3 × 2 g [2 sachets]/day)

Beneficial effects of L-arginine were demonstrated in patients with hypercholesterolemia. L-arginine was shown to restore proper cholesterol metabolism [140], improve endothelial function and reduce concentrations of oxidative stress markers [141]. Promising results were also obtained in a group of patients with chronic lower limb ischemia [142, 143; however, it appears that besides for supplementation-related benefits, L-arginine has no greater importance in the treatment of LEAD [144].

7.10. Angiotensin converting enzyme inhibitors

Angiotensin I-converting enzyme inhibitors are one of the most important classes of drugs in use today, its range of indications growing constantly. Its attributed effects include not only antihypertensive but also antiproliferative, nephroprotective, and even anticoagulation activities.

In a randomized study to assess the efficacy of ramipril in patients with intermittent indications, the drug was demonstrated to be effective in increasing the walking distance, although the improvement was not correlated with an ABI increase [145].

In a new meta-analysis of four studies remaining after two ramipril studies had been discontinued, no improvement in the walking distance was observed. Ramipril may be used in the treatment of LEAD in patients with concomitant arterial hypertension [146].

7.11. Gingko biloba (dosage: 2 × 1 capsule)

Gingko biloba has been used in natural medicine for thousands of years and is an important ingredient in traditional Chinese medicine. Gingko biloba presents with antioxidative and anti-aggregation effects. In a Cochrane Database systemic review encompassing a total of 11 studies in 477 patients, no clinically significant efficacy was demonstrated compare to placebo in patients with intermittent claudication [147].

7.12. Padma 28 (dosage: 2–4 capsules/day)

Data are available to suggest short-term efficacy of Padma 28 in increasing the walking distance; however, long-term results remain unknown and the quality of evidence is methodologically poor. Evidence on publication bias was also presented for these reports. Therefore, no sufficient evidence is available to recommend Padma 28 in routine LEAD treatment [148].

References:

1. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001; 286(11): 1317–1324, doi: 10.1001/jama.286.11.1317, indexed in Pubmed: 11560536.
2. Fowkes FG, Aboyans V, Fowkes FJI, et al. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol. 2017; 14(3): 156–170, doi: 10.1038/nrcardio.2016.179, indexed in Pubmed: 27853158.
3. Diehm C, Schuster A, Allenberg J, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis. 2004; 172(1): 95–105, doi: 10.1016/s0021-9150(03)00204-1.
4. Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007; 45 Suppl S: S5–67, doi: 10.1016/j.jvs.2006.12.037, indexed in Pubmed: 17223489.
5. Hooi JD, Kester AD, Stoffers HE, et al. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. Am J Epidemiol. 2001; 153(7): 666–672, doi: 10.1093/aje/153.7.666, indexed in Pubmed: 11282794.
6. Sampson UKA, Norman PE, Fowkes FG, et al. Global and regional burden of aortic dissection and aneurysms: mortality trends in 21 world regions, 1990 to 2010. Glob Heart. 2014; 9(1): 171–180.e10, doi: 10.1016/j.gheart.2013.12.010, indexed in Pubmed: 25432126.
7. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015; 116(9): 1509–1526, doi: 10.1161/CIRCRESAHA.116.303849, indexed in Pubmed: 25908725.
8. Joosten MM, Pai JK, Bertoia ML, et al. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. JAMA. 2012; 308(16): 1660–1667, doi: 10.1001/jama.2012.13415, indexed in Pubmed: 23093164.
9. Garg PK, Biggs ML, Carnethon M, et al. Metabolic syndrome and risk of incident peripheral artery disease: the cardiovascular health study. Hypertension. 2014; 63(2): 413–419, doi: 10.1161/HYPERTENSIONAHA.113.01925, indexed in Pubmed: 24191289.
10. Jude EB, Oyibo SO, Chalmers N, et al. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care. 2001; 24(8): 1433—1437, doi: 10.2337/diacare.24.8.1433, indexed in Pubmed: 11473082.
11. Emdin CA, Anderson SG, Callender T, et al. Usual blood pressure, peripheral arterial disease, and vascular risk: cohort study of 4.2 million adults. BMJ. 2015; 351: h4865, doi: 10.1136/bmj.h4865, indexed in Pubmed: 26419648.
12. Howard DPJ, Banerjee A, Fairhead JF, et al. Oxford Vascular Study. Population-Based Study of Incidence, Risk Factors, Outcome, and Prognosis of Ischemic Peripheral Arterial Events: Implications for Prevention. Circulation. 2015; 132(19): 1805–1815, doi: 10.1161/CIRCULATIONAHA.115.016424, indexed in Pubmed: 26350058.
13. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation. 1993; 88(3): 837–845, doi: 10.1161/01.cir.88.3.837, indexed in Pubmed: 8353913.
14. Meijer WT, Grobbee DE, Hunink MG, et al. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med. 2000; 160(19): 2934–2938, doi: 10.1001/archinte.160.19.2934, indexed in Pubmed: 11041900.
15. Allison MA, Criqui MH, McClelland RL, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2006; 48(6): 1190—1197, doi: 10.1016/j.jacc.2006.05.049, indexed in Pubmed: 16979004.
16. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA. 2001; 285(19): 2481–2485, doi: 10.1001/jama.285.19.2481, indexed in Pubmed: 11368701.
17. Laschkolnig A, Kollerits B, Lamina C, et al. Lipoprotein (a) concentrations, apolipoprotein (a) phenotypes, and peripheral arterial disease in three independent cohorts. Cardiovasc Res. 2014; 103(1): 28–36, doi: 10.1093/cvr/cvu107, indexed in Pubmed: 24760552.
18. Aboyans V, Criqui MH, Denenberg JO, et al. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation. 2006; 113(22): 2623–2629, doi: 10.1161/CIRCULATIONAHA.105.608679, indexed in Pubmed: 16735675.
19. Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007; 33 Suppl 1: S1–75, doi: 10.1016/j.ejvs.2006.09.024, indexed in Pubmed: 17140820.
20. Nowak KL, Rossman MJ, Chonchol M, et al. Strategies for achieving healthy vascular aging. Hypertension. 2018; 71(3): 389–402, doi: 10.1161/HYPERTENSIONAHA.117.10439, indexed in Pubmed: 29311256.

21. Zhu C, Yu Yi, Montani JP, et al. Arginase-I enhances vascular endothelial inflammation and senescence through eNOS-uncoupling. BMC Res Notes. 2017; 10(1): 82, doi: 10.1186/s13104-017-2399-x, indexed in Pubmed: 28153047.
22. Voghel G, Thorin-Trescases N, Farhat N, et al. Chronic treatment with N-acetyl-cystein delays cellular senescence in endothelial cells isolated from a subgroup of atherosclerotic patients. Mech Ageing Dev. 2008; 129(5): 261–270, doi: 10.1016/j.mad.2008.01.004, indexed in Pubmed: 18302967.
23. Yi B, Nguyen MC, Won MH, et al. Arginase Inhibitor 2,3,5,4'-Tetrahydroxystilbene-2-O-β-D-Glucoside Activates Endothelial Nitric Oxide Synthase and Improves Vascular Function. Planta Med. 2017; 83(3-04): 210–216, doi: 10.1055/s-0042-111014, indexed in Pubmed: 27392245.
24. Tsuboi T, Maeda M, Hayashi T. Administration of L-arginine plus L-citrulline or L-citrulline alone successfully retarded endothelial senescence. PLoS One. 2018; 13(2): e0192252, doi: 10.1371/journal.pone.0192252, indexed in Pubmed: 29415069.
25. Sosińska-Zawierucha P, Maćkowiak B, Staniszewski R, et al. Sulodexide slows down the senescence of aortic endothelial cells exposed to serum from patients with peripheral artery diseases. Cell Physiol Biochem. 2018; 45(6): 2225–2232, doi: 10.1159/000488167, indexed in Pubmed: 29587258.
26. Li T, Liu X, Zhao Z, et al. Sulodexide recovers endothelial function through reconstructing glycocalyx in the balloon-injury rat carotid artery model. Oncotarget. 2017; 8(53): 91350–91361, doi: 10.18632/oncotarget.20518, indexed in Pubmed: 29207649.
27. Ciszewicz M, Polubinska A, Antoniewicz A, et al. Sulodexide suppresses inflammation in human endothelial cells and prevents glucose cytotoxicity. Transl Res. 2009; 153(3): 118–123, doi: 10.1016/j.trsl.2008.12.007, indexed in Pubmed: 19218094.
28. Hassanshahi A, Hassanshahi M, Khabbazi S, et al. Adipose-derived stem cells for wound healing. J Cell Physiol. 2019; 234(6): 7903–7914, doi: 10.1002/jcp.27922, indexed in Pubmed: 30515810.
29. Fowkes FGR, Murray GD, Butcher I, et al. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008; 300(2): 197–208, doi: 10.1001/jama.300.2.197, indexed in Pubmed: 18612117.
30. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation. 1996; 94(11): 3026–3049, doi: 10.1161/01.cir.94.11.3026, indexed in Pubmed: 8941154.
31. Fowkes FGR, Murray GD, Butcher I, et al. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008; 300(2): 197–208, doi: 10.1001/jama.300.2.197, indexed in Pubmed: 18612117.
32. Hirsch AT, Haskal ZJ, Hertzer NR, et al. American Association for Vascular Surgery, Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, ACC/AHA Task Force on Practice Guidelines, American Association of Cardiovascular and Pulmonary Rehabilitation, National Heart, Lung, and Blood Institute, Society for Vascular Nursing, TransAtlantic Inter-Society Consensus, Vascular Disease Foundation. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol. 2006; 47(6): 1239–1312, doi: 10.1016/j.jacc.2005.10.009, indexed in Pubmed: 16545667.
33. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017; 69(11): e71–e7e126, doi: 10.1016/j.jacc.2016.11.007, indexed in Pubmed: 27851992.
34. Khan NA, Rahim SA, Anand SS, et al. Does the clinical examination predict lower extremity peripheral arterial disease? JAMA. 2006; 295(5): 536–546, doi: 10.1001/jama.295.5.536, indexed in Pubmed: 16449619.
35. Da Silva A, Widmer L. Occlusive peripheral artery disease. Early diagnosis, incidence, course, significance. Bern, Stuttgart, Wien: Hans Huber Verlag; 1980: 1–97.
36. Aboyans V, Ricco JB, Bartelink MLEL, et al. ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018; 39(9): 763–816, doi: 10.1093/eurheartj/ehx095, indexed in Pubmed: 28886620.
37. Perk J, De Backer G, Gohlke H, et al. European Association for Cardiovascular Prevention & Rehabilitation (EACPR), ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012; 33(13): 1635–1701, doi: 10.1093/eurheartj/ehs092, indexed in Pubmed: 22555213.
38. Pan Zw, Lu Yj, Yang Bf. MicroRNAs: a novel class of potential therapeutic targets for cardiovascular diseases. Acta Pharmacol Sin. 2010; 31(1): 1–9, doi: 10.1038/aps.2009.175, indexed in Pubmed: 19966833.
39. Fic P, Kowalczuk K, Grabarska A, et al. MicroRNA — a new diagnostic tool in coronary artery disease and myocardial infarction. Postepy Hig Med Dosw (Online). 2014; 68: 410–418, doi: 10.5604/17322693.1100348, indexed in Pubmed: 24864093.

40. Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg. 2007; 33 Suppl 1: S1–75, doi: 10.1016/j.ejvs.2006.09.024, indexed in Pubmed: 17140820.
41. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (Updating the 2005 Guideline). Journal of the American College of Cardiology. 2011;58(19):2020-45. doi: 10.1016/j.jacc.2011.08.023.
42. Tendera M, Aboyans V, Bartelink ML, et al. European Stroke Organisation, ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011; 32(22): 2851–2906, doi: 10.1093/eurheartj/ehr211, indexed in Pubmed: 21873417.
43. Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Society for Vascular Surgery. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg. 2015; 61(3 Suppl): 2S–41S, doi: 10.1016/j.jvs.2014.12.009, indexed in Pubmed: 25638515.
44. Halliday A, Bax JJ. The 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg. 2018; 55(3): 301–302, doi: 10.1016/j.ejvs.2018.03.004, indexed in Pubmed: 29579461.
45. Zheng ZJ, Sharrett AR, Chambless LE, et al. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis. 1997; 131(1): 115–125, doi: 10.1016/s0021-9150(97)06089-9, indexed in Pubmed: 9180252.
46. Vriens B, D'Abate F, Ozdemir BA, et al. Members of the National Foot Care Audit Steering Group, American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care. 2003; 26(12): 3333–3341, doi: 10.2337/diacare.26.12.3333, indexed in Pubmed: 14633825.
47. Writing Group M, Writing Committee M, Accf/Aha Task Force M. 2011 ACCF/AHA Focused Update of the Guideline for the Management of patients with peripheral artery disease (Updating the 2005 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;124(18): 2020–2045. doi: 10.1161/CIR.0b013e31822e80c3, indexed in Pubmed: 21959305.
48. Tehan PE, Santos D, Chuter VH. A systematic review of the sensitivity and specificity of the toe-brachial index for detecting peripheral artery disease. Vasc Med. 2016; 21(4): 382–389, doi: 10.1177/1358863X16645854, indexed in Pubmed: 27165712.
49. Christensen CLP. Core curriculum for vascular nursing: an official publication of the society for vascular nursing (SVN). Philadelphia, Lippincott Williams & Wilkins 2014.
50. Rose S. Noninvasive vascular laboratory for evaluation of peripheral arterial occlusive disease: part II — clinical applications: chronic, usually atherosclerotic, lower extremity ischemia. J Vasc Interv Radiol. 2000; 11(10): 1257–1275, doi: 10.1016/s1051-0443(07)61300-1.
51. Nicolaï SPA, Kruidenier LM, Rouwet EV, et al. The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. J Vasc Surg. 2009; 50(1): 89–94, doi: 10.1016/j.jvs.2008.12.073, indexed in Pubmed: 19563956.
52. Aly S, Sommerville K, Adiseshiah M, et al. Comparison of duplex imaging and arteriography in the evaluation of lower limb arteries. Br J Surg. 1998; 85(8): 1099–1102, doi: 10.1046/j.1365-2168.1998.00786.x, indexed in Pubmed: 9718005.
53. Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US — a meta-analysis. Radiology. 2000; 216(1): 67–77, doi: 10.1148/radiology.216.1.r00jl0367, indexed in Pubmed: 10887229.
54. Li Z, Zheng Z, Ding J, et al. Contrast-enhanced ultrasonography for monitoring arterial inflammation in takayasu arteritis. J Rheumatol. 2019; 46(6): 616–622, doi: 10.3899/jrheum.180701, indexed in Pubmed: 30824642.
55. Ouwendijk R, Kock MC, van Dijk LC, et al. Vessel wall calcifications at multi-detector row CT angiography in patients with peripheral arterial disease: effect on clinical utility and clinical predictors. Radiology. 2006; 241(2): 603–608, doi: 10.1148/radiol.2412050781, indexed in Pubmed: 16966479.
56. Langenberger H, Schillinger M, Plank C, et al. Agreement of duplex ultrasonography vs. computed tomography angiography for evaluation of native and in-stent SFA re-stenosis — findings from a randomized controlled trial. Eur J Radiol. 2012; 81(9): 2265–2269, doi: 10.1016/j.ejrad.2011.05.035, indexed in Pubmed: 21703792.
57. Met R, Bipat S, Legemate DA, et al. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. JAMA. 2009; 301(4): 415–424, doi: 10.1001/jama.301.4.415, indexed in Pubmed: 19176443.
58. Collins R, Burch J, Cranny G, et al. A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease. Health Technol Assess. 2007; 11(20): III–IV, XI, indexed in Pubmed: 17462170.
59. Stegemann E, Sansone R, Heiss C. Carbon dioxide angiography is a standard technique to supplement iodinated contrast angiography and can be a feasible alternative. Angiology. 2016; 67(10): 974, doi: 10.1177/0003319716660014, indexed in Pubmed: 27436493.
60. Jawahar D, Rachamalla HR, Rafalowski A, et al. Pulse oximetry in the evaluation of peripheral vascular disease. Angiology. 1997; 48(8): 721–724, doi: 10.1177/000331979704800808, indexed in Pubmed: 9269142.
61. Comerota AJ, Throm RC, Kelly P, et al. Tissue (muscle) oxygen saturation (StO_2): a new measure of symptomatic lower-extremity arterial disease. J Vasc Surg. 2003; 38(4): 724–729, doi: 10.1016/s0741-5214(03)01032-2, indexed in Pubmed: 14560221.

62. Cassar K, Coull R, Bachoo P, et al. Management of secondary risk factors in patients with intermittent claudication. Eur J Vasc Endovasc Surg. 2003; 26(3): 262–266, indexed in Pubmed: 14509888.
63. McDermott MM, Mehta S, Ahn H, et al. Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease. J Gen Intern Med. 1997; 12(4): 209–215, doi: 10.1046/j.1525-1497.1997.012004209.x, indexed in Pubmed: 9127224.
64. Fowkes FG, Housley E, Riemersma RA, et al. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992; 135(4): 331–340, doi: 10.1093/oxfordjournals.aje.a116294, indexed in Pubmed: 1550087.
65. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc. 1985; 33(1): 13–18, doi: 10.1111/j.1532-5415.1985.tb02853.x, indexed in Pubmed: 3965550.
66. Törnwall ME, Virtamo J, Haukka JK, et al. Prospective study of diet, lifestyle, and intermittent claudication in male smokers. Am J Epidemiol. 2000; 151(9): 892–901, doi: 10.1093/oxfordjournals.aje.a010293, indexed in Pubmed: 10791562.
67. Wiseman S, Powell J, Greenhalgh R, et al. The influence of smoking and plasma factors on prosthetic graft patency. Eur J Vasc Surg. 1990; 4(1): 57–61, indexed in Pubmed: 2182344.
68. Housley E, Leng GC, Donnan PT, et al. Physical activity and risk of peripheral arterial disease in the general population: Edinburgh Artery Study. J Epidemiol Community Health. 1993; 47(6): 475–480, doi: 10.1136/jech.47.6.475, indexed in Pubmed: 8120503.
69. Piepoli MF, Davos C, Francis DP, et al. ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). BMJ. 2004; 328(7433): 189, doi: 10.1136/bmj.37938.645220.EE, indexed in Pubmed: 14729656.
70. Regensteiner JG, Ware JE, McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc. 2002; 50(12): 1939–1946, doi: 10.1046/j.1532-5415.2002.50604.x, indexed in Pubmed: 12473004.
71. Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet. 2002; 360(9344): 1455–1461, doi: 10.1016/S0140-6736(02)11472-3, indexed in Pubmed: 12433513.
72. Trichopoulou A, Costacou T, Bamia C, et al. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003; 348(26): 2599–2608, doi: 10.1056/NEJMoa025039, indexed in Pubmed: 12826634.
73. Thompson PD, Zimet R, Forbes WP, et al. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol. 2002; 90(12): 1314–1319, doi: 10.1016/s0002-9149(02)02869-2, indexed in Pubmed: 12480040.
74. Stevens JW, Simpson E, Harnan S, et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. Br J Surg. 2012; 99(12): 1630–1638, doi: 10.1002/bjs.8895, indexed in Pubmed: 23034699.
75. Mannello F, Medda V, Ligi D, et al. Glycosaminoglycan sulodexide inhibition of MMP-9 gelatinase secretion and activity: possible pharmacological role against collagen degradation in vascular chronic diseases. Curr Vasc Pharmacology. 2013; 11(3): 354–365, doi: 10.2174/15701611113110300010.
76. Mannello F, Raffetto JD. Matrix metalloproteinase activity and glycosaminoglycans in chronic venous disease: the linkage among cell biology, pathology and translational research. Am J Transl Res. 2011; 3(2): 149–158. Epub 2011/03/19. PubMed PMID: 21416057; PubMed Central PMCID: PMCPMC3056561.
77. Mattana P, Mannello F, Ferrari P, et al. Vascular pathologies and inflammation: The anti-inflammatory properties of sulodexide. Italian Journal of Vascular and Endovascular Surgery. 2012; 19: 1–7.
78. Połubińska A, Staniszewski R, Baum E, et al. Sulodexide modifies intravascular homeostasis what affects function of the endothelium. Adv Med Sci. 2013; 58(2): 304–310, doi: 10.2478/ams-2013-0016, indexed in Pubmed: 24421218.
79. Sosińska P, Baum E, Maćkowiak B, et al. Sulodexide reduces the proinflammatory effect of serum from patients with peripheral artery disease in human arterial endothelial cells. Cell Physiol Biochem. 2016; 40(5): 1005–1012, doi: 10.1159/000453157, indexed in Pubmed: 27941341.
80. Suminska-Jasinska K, Polubinska A, Ciszewicz M, et al. Sulodexide reduces senescence-related changes in human endothelial cells. Med Sci Monit. 2011; 17(4): CR222–CR226, doi: 10.12659/msm.881719, indexed in Pubmed: 21455109.
81. Bręborowicz A. Sulodexide — mixture of glycosaminoglycans with the protective effect towards the vascular endothelium. Acta Angiologica. 2014; 20(3): 112–8.
82. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing G-J, Harjola V-P, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS) The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J. 2019.
83. Tomkowski W, Kuca P, Urbanek T, et al. Żylna choroba zakrzepowo-zatorowa — wytyczne profilaktyki, diagnostyki i terapii Konsensus Polski 2017. Acta Angiologica. 2017; 23(2): 73–113.
84. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol. 2018; 37(3): 181–254, doi: 10.23736/S0392-9590.18.03999-8, indexed in Pubmed: 29871479.
85. Coccheri S, Scondotto G, Agnelli G, et al. Arterial Arm of the Suavis (Sulodexide Arterial Venous Italian Study) group. Sulodexide in the treatment of intermittent claudication. Results of a randomized, double-blind, multicentre, placebo-controlled study. Eur Heart J. 2002; 23(13): 1057–1065, doi: 10.1053/euhj.2001.3033, indexed in Pubmed: 12093059.

86. Gaddi A, Galetti C, Illuminati B, et al. Meta-analysis of some results of clinical trials on sulodexide therapy in peripheral occlusive arterial disease. J Int Med Res. 1996; 24(5): 389–406, doi: 10.1177/030006059602400501, indexed in Pubmed: 8895043.
87. Piepoli MF, Hoes AW, Agewall S, et al. ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37(29): 2315–2381, doi: 10.1093/eurheartj/ehw106, indexed in Pubmed: 27222591.
88. Szymański FM ea. Recommendation for the management of dyslipidemia in Poland — Third Declaration of Sopot. Interdisciplinary Expert Position Statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy. Choroby Serca i Naczyń. 2018; 15(4): 199–210.
89. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39(33): 3021–3104.
90. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASDThe Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). Eur Heart J. 2019.
91. Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019 [Epub ahead of print], doi: 10.1093/eurheartj/ehz455, indexed in Pubmed: 31504418.
92. Smith SL, Matthews EO, Moxon JV, et al. A systematic review and meta-analysis of risk factors for and incidence of 30-day readmission after revascularization for peripheral artery disease. J Vasc Surg. 2019; 70(3): 996–1006.e7, doi: 10.1016/j.jvs.2019.01.079, indexed in Pubmed: 31445653.
93. Eliason JL, Wainess RM, Proctor MC, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Ann Surg. 2003; 238(3): 382–389; discussion 389, doi: 10.1097/01.sla.0000086663.49670.d1, indexed in Pubmed: 14501504.
94. Earnshaw JJ, Whitman B, Foy C. National Audit of Thrombolysis for Acute Leg Ischemia (NATALI): clinical factors associated with early outcome. J Vasc Surg. 2004; 39(5): 1018–1025, doi: 10.1016/j.jvs.2004.01.019, indexed in Pubmed: 15111854.
95. Blaisdell FW, Steele M, Allen RE. Management of acute lower extremity arterial ischemia due to embolism and thrombosis. Surgery. 1978; 84(6): 822–834, indexed in Pubmed: 715701.
96. Rutherford RB. Clinical staging of acute limb ischemia as the basis for choice of revascularization method: when and how to intervene. Semin Vasc Surg. 2009; 22(1): 5–9, doi: 10.1053/j.semvascsurg.2008.12.003, indexed in Pubmed: 19298929.
97. van den Berg JC. Thrombolysis for acute arterial occlusion. J Vasc Surg. 2010; 52(2): 512–515, doi: 10.1016/j.jvs.2010.01.080, indexed in Pubmed: 20434297.
98. Comerota AJ, Gravett MH. Do randomized trials of thrombolysis versus open revascularization still apply to current management: what has changed? Semin Vasc Surg. 2009; 22(1): 41–46, doi: 10.1053/j.semvascsurg.2009.01.003, indexed in Pubmed: 19298935.
99. Sarac TP, Hilleman D, Arko FR, et al. Clinical and economic evaluation of the trellis thrombectomy device for arterial occlusions: preliminary analysis. J Vasc Surg. 2004; 39(3): 556–559, doi: 10.1016/j.jvs.2003.10.061, indexed in Pubmed: 14981448.
100. Rogers JH, Laird JR. Overview of new technologies for lower extremity revascularization. Circulation. 2007; 116(18): 2072–2085, doi: 10.1161/CIRCULATIONAHA.107.715433, indexed in Pubmed: 17967988.
101. Henke PK. Contemporary management of acute limb ischemia: factors associated with amputation and in-hospital mortality. Semin Vasc Surg. 2009; 22(1): 34–40, doi: 10.1053/j.semvascsurg.2009.01.002, indexed in Pubmed: 19298934.
102. Lee K, Istl A, Dubois L, et al. Fibrinogen level and bleeding risk during catheter-directed thrombolysis using tissue plasminogen activator. Vasc Endovascular Surg. 2015; 49(7): 175–179, doi: 10.1177/1538574415611234, indexed in Pubmed: 26462979.
103. Kuoppala M, Åkeson J, Svensson P, et al. Risk factors for haemorrhage during local intra-arterial thrombolysis for lower limb ischaemia. J Thromb Thrombolysis. 2011; 31(2): 226–232, doi: 10.1007/s11239-010-0520-2, indexed in Pubmed: 20848161.
104. Agle SC, McNally MM, Powell CS, et al. The association of periprocedural hypertension and adverse outcomes in patients undergoing catheter-directed thrombolysis. Ann Vasc Surg. 2010; 24(5): 609–614, doi: 10.1016/j.avsg.2009.12.011, indexed in Pubmed: 20413257.
105. Patel NH, Krishnamurthy VN, Kim S, et al. CIRSE and SIR Standards of Practice Committees. Quality improvement guidelines for percutaneous management of acute lower-extremity ischemia. J Vasc Interv Radiol. 2013; 24(1): 3–15, doi: 10.1016/j.jvir.2012.09.026, indexed in Pubmed: 23273693.
106. O'Connell JB, Quiñones-Baldrich WJ. Proper evaluation and management of acute embolic versus thrombotic limb ischemia. Semin Vasc Surg. 2009; 22(1): 10–16, doi: 10.1053/j.semvascsurg.2008.12.004, indexed in Pubmed: 19298930.
107. Edlich RF, Rodeheaver G, Thacker J, Edgerton M. Fundamentals of Wound Management in Surgery, Technical Factors In Wound Management. South Plainfield, NJ: Chirurgecom. 1977; 22.
108. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017; 69(11): e71–e7e126, doi: 10.1016/j.jacc.2016.11.007, indexed in Pubmed: 27851992.
109. Weir GR, Smart H, van Marle J, et al. Arterial disease ulcers, part 2: treatment. Adv Skin Wound Care. 2014; 27(10): 462–476; quiz 476, doi: 10.1097/01.ASW.0000453881.34345.08, indexed in Pubmed: 25225993.
110. Weir GR, Smart H, van Marle J, et al. Arterial disease ulcers, part 1: clinical diagnosis and investigation. Adv Skin Wound Care. 2014; 27(9): 421–8; quiz 429, doi: 10.1097/01.ASW.0000453095.19109.5c, indexed in Pubmed: 25133344.

111. Arnold M, Barbul A. Nutrition and wound healing. Plast Reconstr Surg. 2006; 117(7 Suppl): 42S–58S, doi: 10.1097/01.prs.0000225432.17501.6c, indexed in Pubmed: 16799374.
112. Kummer O, Widmer MK, Plüss S, et al. Does infection affect amputation rate in chronic critical leg ischemia? Vasa. 2003; 32(1): 18–21, doi: 10.1024/0301-1526.32.1.18, indexed in Pubmed: 12677760.
113. Morcos R, Louka B, Tseng A, et al. The evolving treatment of peripheral arterial disease through guideline-directed recommendations. J Clin Med. 2018; 7(1), doi: 10.3390/jcm7010009, indexed in Pubmed: 29315259.
114. Committee BCPNSaW. Guideline:Assessmeet and Treatment of Lower Leg Ulcers (Arterial, Venous &Mixed) in Adults. 2014.
115. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the treatment of arterial insufficiency ulcers. Wound Repair Regen. 2006; 14(6): 693–710, doi: 10.1111/j.1524-475X.2006.00177.x, indexed in Pubmed: 17199834.
116. Robless P, Mikhailidis DP, Stansby GP, et al. Cilostazol for peripheral arterial disease. Cochrane Database Syst Rev. 2007(1): CD003748, doi: 10.1002/14651858.CD003748.pub2, indexed in Pubmed: 17253494.
117. Momsen AH, Jensen MB, Norager CB, et al. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. Eur J Vasc Endovasc Surg. 2009; 38(4): 463–474, doi: 10.1016/j.ejvs.2009.06.002, indexed in Pubmed: 19586783.
118. Bedenis R, Stewart M, Cleanthis M, et al. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014(10): CD003748, doi: 10.1002/14651858.CD003748.pub4, indexed in Pubmed: 25358850.
119. Salhiyyah K, Senanayake E, Abdel-Hadi M, et al. Pentoxifylline for intermittent claudication. Cochrane Database Syst Rev. 2012; 1: CD005262, doi: 10.1002/14651858.CD005262.pub2, indexed in Pubmed: 22258961.
120. Lee D, Lim LA, Jang SB, et al. Pharmacokinetic comparison of sustained- and immediate-release oral formulations of cilostazol in healthy Korean subjects: a randomized, open-label, 3-part, sequential, 2-period, crossover, single-dose, food-effect, and multiple-dose study. Clin Ther. 2011; 33(12): 2038–2053, doi: 10.1016/j.clinthera.2011.10.024, indexed in Pubmed: 22129569.
121. Shalhoub J, Davies AH, Franklin IJ. Cilostazol may improve outcome in critical limb ischemia. Int Angiol. 2009; 28(5): 363–366, indexed in Pubmed: 19935589.
122. de Backer TLM, Vander Stichele R, Lehert P, et al. Naftidrofuryl for intermittent claudication. Cochrane Database Syst Rev. 2012; 12: CD001368, doi: 10.1002/14651858.CD001368.pub4, indexed in Pubmed: 23235580.
123. Spengel F, Clément D, Boccalon H, et al. Findings of the Naftidrofuryl in Quality of Life (NIQOL) European study program. Int Angiol. 2002; 21(1): 20–27, indexed in Pubmed: 11941270.
124. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996; 348(9038): 1329–1339, doi: 10.1016/s0140-6736(96)09457-3, indexed in Pubmed: 8918275.
125. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. The Lancet. 2018; 391(10117): 219–229.
126. Bhatt DL, Fox KAA, Hacke W, et al. CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006; 354(16): 1706–1717, doi: 10.1056/NEJMoa060989, indexed in Pubmed: 16531616.
127. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. New Eng J Med. 2017;377(14):1319-30. 2017.
128. Bonaca MP, Bhatt DL, Storey RF, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol. 2016; 67(23): 2719–2728, doi: 10.1016/j.jacc.2016.03.524, indexed in Pubmed: 27046162.
129. Cacoub PP, Bhatt DL, Steg PG, et al. CHARISMA Investigators. Patients with peripheral arterial disease in the CHARISMA trial. Eur Heart J. 2009; 30(2): 192–201, doi: 10.1093/eurheartj/ehn534, indexed in Pubmed: 19136484.
130. Patel MR, Becker RC, Wojdyla DM, et al. Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: Data from the PLATO Trial. Eur J Prev Cardiol. 2015; 22(6): 734–742, doi: 10.1177/2047487314533215, indexed in Pubmed: 24830710.
131. Mohler ER, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation. 2003; 108(12): 1481–1486, doi: 10.1161/01.CIR.0000090686.57897.F5, indexed in Pubmed: 12952839.
132. Mondillo S, Piercarlo B, Barbati R. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. ACC Curr J Rev. 2003;12(4):16. doi: 10.1016/s1062-1458(03)00264-2.
133. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. J Am Coll Cardiol. 2015; 65(10): 999–1009.
134. Tiozzo R, Cingi MR, Pietrangelo A, et al. Effect of heparin-like compounds on the in vitro proliferation and protein synthesis of various cell types. Arzneimittelforschung. 1989; 39(1): 15–20, indexed in Pubmed: 2719740.
135. Rajtar G, Marchi E, de Gaetano G, et al. Effects of glycosaminoglycans on platelet and leucocyte function: role of N-sulfation. Biochem Pharmacol. 1993; 46(5): 958–960, doi: 10.1016/0006-2952(93)90507-s, indexed in Pubmed: 8373448.
136. Borawski J, Dubowski M, Pawlak K, et al. Effect of sulodexide on plasma transforming growth factor-beta1 in healthy volunteers. Clin Appl Thromb Hemost. 2010; 16(1): 60– –65, doi: 10.1177/1076029608326170, indexed in Pubmed: 19117965.
137. Połubińska A, Staniszewski R, Baum E, et al. Sulodexide modifies intravascular homeostasis what affects function of the endothelium. Adv Med Sci. 2013; 58(2): 304–310, doi: 10.2478/ams-2013-0016, indexed in Pubmed: 24421218.
138. Vietto V, Franco JVa, Saenz V, et al. Prostanoids for critical limb ischaemia. Cochrane Database Syst Rev. 2018; 1: CD006544,

doi: 10.1002/14651858.CD006544.pub3, indexed in Pubmed: 29318581.

139. Hiatt WR, Regensteiner JG, Creager MA. Propionyl-L-carnitine improves exercise performance and functional status in patients with claudication. ACC Current Journal Review. 2001;10(6):32-3. doi: 10.1016/s1062-1458(01)00467-6. 2001.
140. Drexler H, Zeiher AM, Meinzer K, et al. Correction of endothelial dysfunction in coronary microcirculation of hypercholesterolaemic patients by L-arginine. Lancet. 1991; 338(8782-8783): 1546–1550, doi: 10.1016/0140-6736(91)92372-9, indexed in Pubmed: 1683971.
141. Kawano H, Motoyama T, Hirai N, et al. Endothelial dysfunction in hypercholesterolemia is improved by L-arginine administration: possible role of oxidative stress. Atherosclerosis. 2002; 161(2): 375–380, doi: 10.1016/s0021-9150(01)00671-2, indexed in Pubmed: 11888520.
142. Jabłecka A, Bogdański P, Balcer N, et al. The effect of oral L-arginine supplementation on fasting glucose, HbA_{1c}, nitric oxide and total antioxidant status in diabetic patients with atherosclerotic peripheral arterial disease of lower extremities. Eur Rev Med Pharmacol Sci. 2012; 16(3): 342–350, indexed in Pubmed: 22530351.
143. Jabłecka A, Checiński P, Krauss H, et al. The influence of two different doses of L-arginine oral supplementation on nitric oxide (NO) concentration and total antioxidant status (TAS) in atherosclerotic patients. Med Sci Monit. 2004; 10(1): CR29–CR32, indexed in Pubmed: 14704633.
144. Wilson A, Harada R, Nair N, et al. L-arginine supplementation in peripheral arterial disease. Circulation. 2007; 116(2): 188–195, doi: 10.1161/circulationaha.106.683656.
145. Shahin Y, Cockcroft JR, Chetter IC. Randomized clinical trial of angiotensin-converting enzyme inhibitor, ramipril, in patients with intermittent claudication. Br J Surg. 2013; 100(9): 1154–1163, doi: 10.1002/bjs.9198, indexed in Pubmed: 23842829.
146. Vlachopoulos C, Terentes-Printzios D, Aboyans V, et al. Angiotensin converting enzyme inhibitors and walking distance: Have we walked the whole distance? Atherosclerosis. 2016; 252: 199–200, doi: 10.1016/j.atherosclerosis.2016.08.001, indexed in Pubmed: 27543007.
147. Nicolaï SPA, Kruidenier LM, Bendermacher BLW, et al. Ginkgo biloba for intermittent claudication. Cochrane Database Syst Rev. 2009; 39(2): CD006888–158, doi: 10.1002/14651858.CD006888.pub2, indexed in Pubmed: 19370657.
148. Stewart M, Morling JR, Maxwell H, et al. Padma 28 for intermittent claudication. Cochrane Database Syst Rev. 2013; 3(7): CD007371, doi: 10.1002/14651858.CD007371.pub2, indexed in Pubmed: 23861015.