Review

Cutting-edge European guidelines for managing lower extremity peripheral arterial disease – Featuring selected insights on PAD management

A key highlight by the Young Academy of the European Society of Vascular Medicine (ESVM)

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Summary: The new guidelines for the management of peripheral arterial and aortic diseases (PAAD) from the European Society of Cardiology and endorsed by the European Society of Vascular Medicine (ESVM), emphasize on a comprehensive and multidisciplinary approach focusing on prevention, diagnosis, treatment, and follow-up of patients with a wide range of PAAD, including lower extremity peripheral arterial disease (PAD). The aim of this summary, focusing on PAD and coordinated by the Young Academy of ESVM, is to provide young angiologists with the fundamental principles of these guidelines and to assist them in navigating their everyday clinical practice. PAD diagnosis relies on objective evaluation of flow/oxygen reduction at rest, with arterial ultrasound as the first imaging modality to confirm the presence of arterial lesions. The main goals of PAD management are not only to improve functioning and prevent the occurrence of adverse events at the lower limb level, but

also to reduce the overall atherosclerotic burden and achieve the general well-being of patients. To this end, traditional and nontraditional cardiovascular risk factors need to be properly addressed through lifestyle changes and tailored drug therapies. For patients with exertional limb symptoms, supervised exercise training is recommended. Interventional treatment is indicated for limb salvage in patients with chronic limb threatening ischemia and may also be discussed in a multidisciplinary setting in less severe patients with persisting symptoms and reduced quality of life after a minimum period of optimal medical treatment including exercise therapy. For trainees or young specialists in Angiology/Vascular Medicine, these guidelines provide essential elements to improve patient management, encourage interdisciplinary collaboration, and ensure an integrated approach to vascular diseases.

Keywords: Peripheral arterial disease, guidelines, management, training

Introduction

Atherosclerotic lower extremity peripheral arterial disease (PAD) is a prevalent condition worldwide [1, 2]. Besides the presence of symptoms and impaired functioning at the limb level, PAD is a systemic condition resulting in high morbidity and mortality in affected patients [3, 4]. Therefore, proper management is essential to improve both functioning and quality of life (QoL) while reducing risks of major adverse cardiovascular (MACE) and limb events (MALE). Recently, the European Society of Cardiology (ESC) guidelines, endorsed by the European Society of Vascular Medicine (ESVM), for the management of peripheral arterial and aortic diseases (PAAD) have been released [5]. Such guidelines emphasize on a comprehensive and multidisciplinary approach focusing on prevention, diagnosis, treatment, and follow-up of patients with a wide range of PAAD, including PAD. It is essential for young professionals to learn the foundational principles from these guidelines and use them to navigate their everyday practice, ensuring they are well-equipped to provide optimal care for their patients.

This summary has been coordinated by the Young Academy of the ESVM. The purpose of this initiative is to contribute gathering young angiologists and trainees in the field of Angiology to advance Vascular Medicine in Europe. By fostering a network of vascular specialists, the ESVM aims to ensure that future healthcare providers can deliver comprehensive and effective care for vascular patients. Given the growing epidemiology of vascular diseases, including PAD, this effort is vital to address the impending health burden these conditions will represent in the coming years.

Mastering peripheral arterial disease care: Essential insights from the latest European Guidelines

Holistic view of peripheral arterial and aortic diseases

The latest ESC guidelines highlight that the aorta and peripheral arteries are not only interconnected but also integral parts of a unique vascular arterial system [5]. Conditions affecting one segment often have significant implications for the other, underscoring the need for a holistic approach to their management. Shared risk factors point out the importance of a comprehensive evaluation, avoiding the traditional fragmented approach. This integrated perspective aims to improve coordination and therapeutic outcomes for the patients with the full spectrum of PAAD, including PAD.

Key recommendations

- A holistic approach to managing vascular diseases, addressing the entire arterial system, is recommended.
- In particular, evaluation of the patient with PAD should be extended to the abdominal aorta and may also include additional peripheral arterial territories, such as the supra-aortic trunks.

Prevalence of peripheral arterial disease

PAD is a widespread condition with global impact. According to recent reports, at least 113 million people aged 40 and older might be affected by PAD, with about 42.6% living in low- or middle-income countries [1, 2]. Overall, PAD prevalence is approximately 1.52%, though it rises sharply with age, affecting 15–20% of people aged 70 years and older and up to 30% of those aged over 80 years. Between 1990 and 2019, the prevalence of PAD increased by 72%, outpacing global population growth by 45% [6].

Sex plays a role in PAD prevalence. In fact, women show a higher age-standardized prevalence of PAD. Among individuals aged 80–84 years, 18.03% of women have PAD compared with 10.56% of men [1]. However, years of life lost are estimated to be higher in males (i.e., 17.2 vs. 9.8 in females), suggesting greater premature mortality rates in the male sex [2].

The ankle-brachial index (ABI) is non-invasive, simple to perform, and has minimal risks, making it a suitable test for PAD screening. Although screening for PAD seems obvious due to its two to three times increased mortality, high prevalence in the elderly, ease of detection, and relatively harmless prevention, the evidence is sparse. Screening of men aged $\geq$65 years for PAD is likely to be both clinically effective and cost effective in a lifetime perspective [7].

As for other traditional atherosclerotic CV diseases, PAD prevalence increases with the number of CV risk factors (CVRFs) [8]. In fact, the impact of traditional CVRFs on

PAD risk has been found to be cumulative, with the greater the number of CVRFs, the higher the risk [9]. According to the latest Global Burden of Disease report, modifiable CVRFs were responsible for around 70% of the global PAD burden 2019 [1], which suggests there is still much to improve in the CV risk management in this clinical setting.

Key recommendations

- Screening for PAD using ABI calculation should be considered for individuals older than 65 years with CVRFs.
- While this approach must be evaluated on a case-by-case basis, further evidence is needed to assess the cost-effectiveness of systematic PAD screening in specific populations.

Peripheral arterial disease and cardiovascular risk

Atherosclerosis affects the entire arterial tree with plaques, becoming larger with time and narrowing the arterial lumen with reduced downstream blood flow to the limbs, leading to the diagnosis of PAD. From a local perspective, PAD reduces functionality and viability of the lower limbs, with an associated risk of disease progression. If left untreated, this condition can result in severe complications, including rest pain, non-healing ulcers, and even limb amputation [4, 10].

Although the risk of local complications is often misconceived as predominant in patients with PAD, the burden of MACE is equally relevant. In fact, damage to the arteries of the lower limbs in atherosclerosis reduces life expectancy and increases the risk of stroke and myocardial infarction [3, 11, 12, 13]. Compared to the general population, affected patients display poorer outcomes regardless of the presence of PAD-related symptoms [10]. Importantly, MALE occurrence drastically increases the risk of death and amputation [4]. Therefore, it is essential to adopt a proactive approach to managing CV risk factors and enact a global view of the patient.

Although several studies have shown that patients with polyvascular disease experience significantly worse clinical outcomes compared to those with single vascular site disease, the clinical benefit of systematic screening for asymptomatic coronary artery disease or cerebrovascular disease in patients with PAD has yet to be demonstrated [5]. However, patients should be actively questioned about symptoms suggestive of disease at other vascular sites and appropriately investigated.

Key recommendations

- Early detection of PAD clinical signs and symptoms and continuous patient education on the importance of timely care are recommended to effectively prevent serious complications both at the CV and limb level.

- In patients with PAD, MACE and MALE should be recognized as contributing to a shared health burden. Preventing these conditions should be prioritized as the main objective in patient care, regardless of whether the disease is symptomatic.

Presentation and categorization of peripheral arterial disease

Patients with PAD present with a wide range of clinical manifestations, from being entirely asymptomatic to exhibiting symptoms that may be either typical or atypical and usually resolving with rest [5, 14, 15].

The new ESC guidelines offer a structured and simplified approach to classify PAD, aiding in timely diagnosis and treatment [16]:

- *Asymptomatic PAD:* patients show no symptoms, but the underlying arterial disease is present. Attention should be given to cases of "masked PAD", where the absence of symptoms is due to reduced walking capacity from non-PAD causes, lack of motivation, or decreased pain sensitivity.
- *Symptomatic (effort-related) PAD:* patients experience intermittent claudication (IC) (pain, cramping, or fatigue in the legs) or atypical symptoms (such as burning, heaviness, leg weakness, numbness, or fatigue during walking without pain) effort related.
- *Chronic limb-threatening ischaemia (CLTI):* a severe form of PAD characterized by rest pain, non-healing wounds, or gangrene with a critical hemodynamic impairment (ankle pressure <50 mmHg, toe pressure <30 mmHg, and/or transcutaneous oxygen pressure (TcPO2) <30 mmHg).

Screening and diagnosis of peripheral arterial disease

PAD should be suspected in all patients with exertional limb symptoms, particularly in the elderly with CVRFs and other atherosclerotic CV diseases. However, sedentary lifestyle and several comorbidities could mask the occurrence of symptoms and make it difficult to suspect the disease [17]. Importantly, women often exhibit atypical or no symptoms, complicating diagnosis and management [18]. Clinical history and physical examination with skin inspection, vascular auscultation, and pulse palpation may support the clinical suspicion of PAD [5]. Determining walking impairment and functional status is mandatory. In case of limb wounds, amputation risk assessment should be systematically performed using the Wound, Ischaemia, and foot Infection (WIfI) classification.

The ABI is the recommended initial test for PAD screening and diagnosis. ABI is calculated as the ratio of the highest systolic blood pressure (SBP) at the ankle level to the SBP measured at the arm. Therefore, it allows a hemodynamic definition of the disease, independent of the extent

of atherosclerotic lesions and the presence of symptoms. A resting ABI ≤0.90 indicates a reduction of at least 10% in SBP at the ankle compared with the arm, assuming that SBP at the arm level is close to that at the aortoiliac bifurcation. This index has a sensitivity of 68–84% and specificity of 84–99% for diagnosing PAD [5, 17, 19, 20, 21]. Besides limb perfusion assessment, ABI serves as a surrogate marker for CV and all-cause mortality [22, 23]. Medial artery calcification, which primarily occurs in elderly patients and those with diabetes or chronic kidney disease, can falsely increase ankle pressure, thus affecting the accuracy of ABI. In this case, additional methods such as toe pressure measurement with toe-brachial index (TBI) calculation must be considered. TBI values ≤0.70 are usually considered diagnostic for PAD, with sensitivity and specificity ranging from 45% to 100% and 17% to 100%, respectively [24]. Notably, ABI can also be estimated from distal Doppler waveforms regardless of the presence of medial artery calcification, which might improve its diagnostic performance [25].

Imaging methods are required to obtain anatomical localization and define severity of arterial lesions. Doppler ultrasound (DUS) is the recommended first-line imaging modality to confirm PAD lesions. This technique has a sensitivity of 88% and specificity of 95% for detecting >50% stenosis [26]. DUS is a non-invasive and low-cost technique, yet operator-dependent and less accurate for defining distal lesions and in the presence of calcifications. Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are recommended as adjuvant imaging, particularly when planning interventional treatment in patients with aorto-iliac or multi-segmental/complex disease [5].

Key recommendations (Figure 1)

- The ABI calculation is recommended as the first-line test for PAD screening and diagnosis, using a cutoff of ≤0.90 as a diagnostic criterion.
- In case of incompressible ankle arteries (ABI >1.40), or in patients with diabetes or chronic kidney disease and normal ABI values, additional methods like the TBI calculation are recommended.
- DUS is recommended as the first-line imaging technique to confirm PAD lesions, whereas CTA or MRA are adjuvant methods for preparation of interventional procedures.
- Special consideration: tailored screening and management strategies for women are warranted, including systematic screening from age 65 and active inquiry about atypical symptoms.

Quality of life and functional assessment

Patients with PAD have reduced walking capacity and self-reported QoL, both mental and physical [27, 28, 29, 30]. They also exhibit decreased muscle strength and balance [31, 32], leading to a faster decline in functional abilities

in both symptomatic and asymptomatic patients. Reduced functional status is associated with lower QoL and predicts further mobility loss and increased CV mortality [33, 34].

Functional status and health related QoL can be assessed using patient reported outcome measures (PROMs) [35]. Several questionnaires are currently available to assess PROMs in patients with PAD [30, 36]. Generic, non-disease-specific measurement tools like the Short Form-36 (SF-36) evaluate the impact of general health, including not only PAD but also other comorbidities, on functioning, health status, and QoL of patients with chronic diseases [37]. The Walking Impairment Questionnaire (WIQ) is a PAD-specific PROMs questionnaire that evaluates symptom severity, walking distance and speed, and stair-climbing ability in affected patients. It is sensitive to changes over time and strongly correlates with functional limitations assessed by treadmill and 6-minute walk testing [38, 39]. The Vascular Quality of Life Questionnaire (VascuQoL) is another PAD-specific questionnaire that assesses health related QoL across the full spectrum of symptom severity, including social and emotional well-being [40].

Treadmill testing is the gold standard for assessing walking performance [41, 42]. Maximum walking and pain-free walking distances should be recorded. In addition, the 6-minute walk test should be performed for functional assessment [43, 44].

Key recommendation

- Comprehensive walking capacity assessment and self-reported QoL evaluation should be considered for all patients with PAD, whether symptomatic or asymptomatic.

Management of peripheral arterial disease

Patients with PAD face a significantly elevated risk of mortality and CV complications, including MACE and MALE, with the risk escalating as the number of additional arterial territories affected increases, including coronary arteries, supra-aortic trunks, and renal arteries [45, 46]. Therefore, clinicians must prioritize treatments addressing both CV and limb-specific risk factors, including pharmacological interventions and lifestyle changes. Particularly aggressive management strategies must be implemented in case of polyvascular disease, including proactive management of all modifiable risk factors through a combination of lifestyle modifications and drug therapy, as well as intensified antithrombotic treatment, which has been proven to achieve better outcomes without a corresponding increase in bleeding risk [47].

Treatment objectives for PAD include

- Preventing MACE and MALE.
- Improving QoL through symptom relief, enhanced mobility, and promotion of a healthy lifestyle.
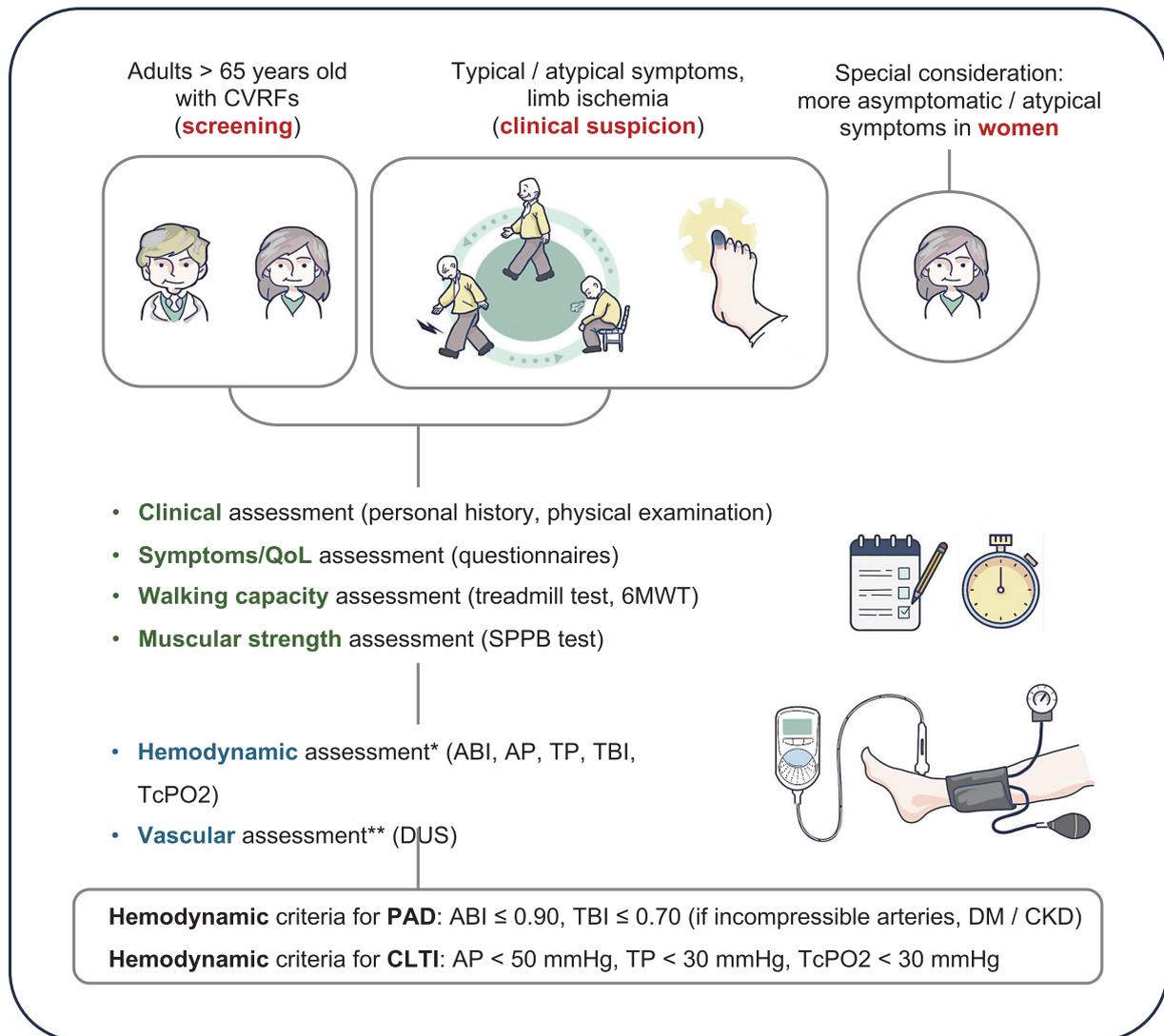
Figure 1. Screening and diagnosis of peripheral arterial disease. *Notes.* ABI: ankle-brachial index; AP: ankle pressure; CLTI: chronic limb-threatening ischemia; CVRFs: cardiovascular risk factors; DUS: doppler ultrasound; PAD: peripheral arterial disease; SPPB: short physical performance battery; TBI: toe-brachial index; TcPO2: transcutaneous oxygen pressure; TP: toe pressure; WIfI: Wound, Ischaemia, and foot Infection classification; 6MWT: 6-minute walk test. *Aim: confirmation of PAD and CLTI diagnosis. **Aim: confirmation of PAD lesions.

Key management components (Figure 2)

- *Lifestyle modifications:* recommended for all PAD patients. Regular physical activity (low- to moderate-intensity or high, if tolerated), a Mediterranean-style diet, and smoking cessation are essential for overall vascular health. Patient education is also crucial to enhance adherence to these interventions.
- *Lipid-lowering therapy:* recommended for all PAD patients. Use of high-intensity statin (i.e., Atorvastatin 40–80 mg or Rosuvastatin 20–40 mg) is mandatory regardless of baseline low-density lipoprotein cholesterol (LDL-C) levels, targeting LDL-C below 1.4 mmol/L (55 mg/dL) with a >50% reduction from baseline values. If the target is not achieved on maximally tolerated statins and ezetimibe, treatment with a proprotein convertase subtilisin/kexin type 9

inhibitor (PCSK9i) is recommended. For statin-intolerant patients who do not achieve LDL-C target with ezetimibe, it is recommended to add bempedoic acid alone or in combination with a PCSK9i.
- *Antihypertensive therapy:* recommended for patients with hypertension, targeting SBP between 120–129 mmHg, if tolerated. An individualized, more lenient goal should be considered in patients ≥85 years old, with clinically severe frailty, or limited life expectancy (<3 years). Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptors blockers (ARBs) should be considered as first-line antihypertensive therapy when treating hypertension. ACEIs/ARBs may be considered in all patients with PAD, regardless of BP levels, in the absence of contraindications. Further options should be discussed based on patient comorbidities and tolerance.
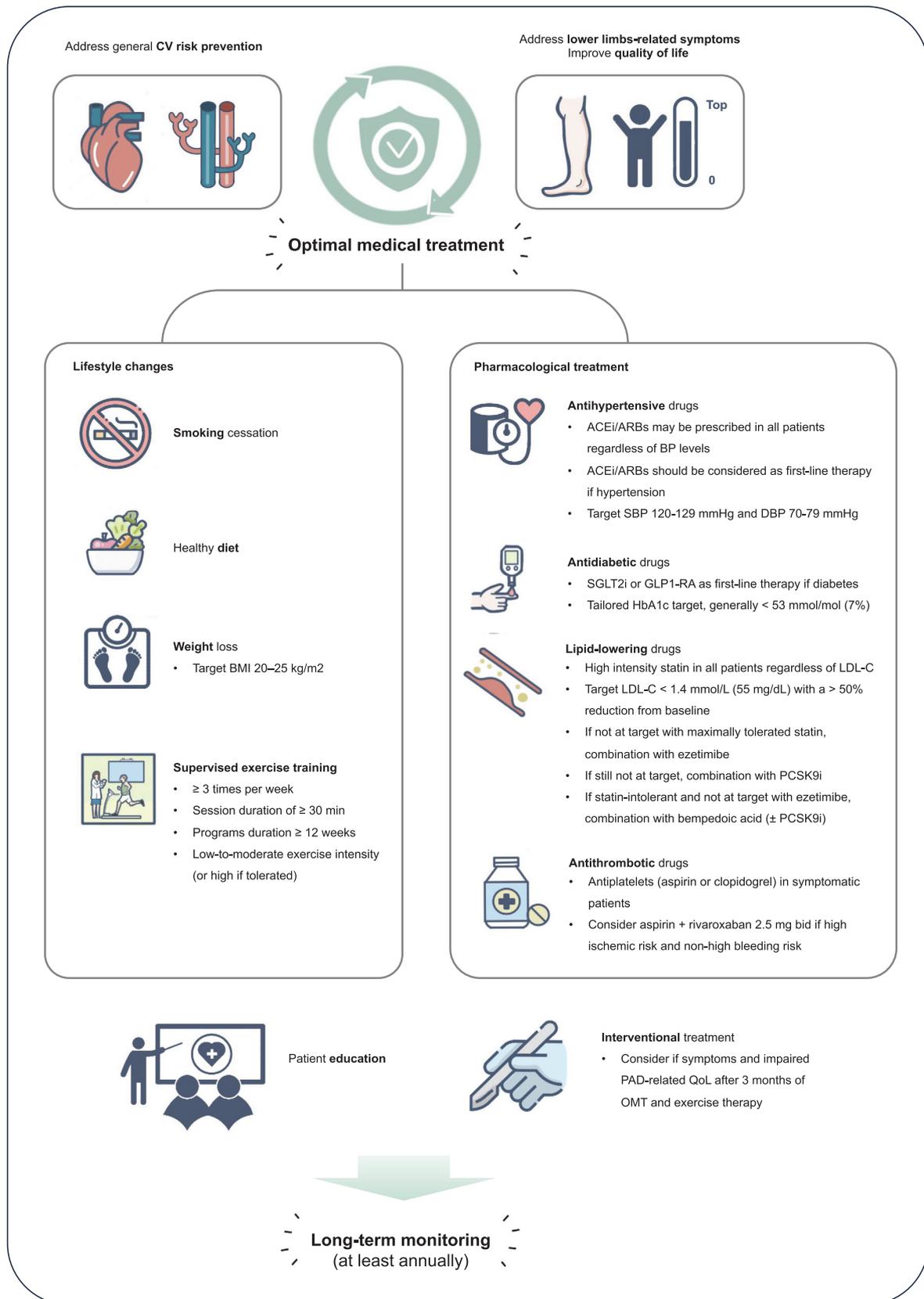
Figure 2. Management of peripheral arterial disease. *Notes.* ACEi: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptors blockers; BMI: body mass index; CV: cardiovascular; DBP: diastolic blood pressure; GLP-1 RA: glucagon-like peptide-1 receptor agonists; HbA1c: haemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; OMT: optimal medical therapy; PAD: peripheral arterial disease; QoL: quality of life; SBP: systolic blood pressure; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

Table I. Key recommendations for interventional treatment of symptomatic (effort-related) peripheral arterial disease (per arterial bed)*.

Arterial bed	Recommendation
Aorto-iliac arteries	• Either an endovascular or a surgical approach should be considered (according to the lesion morphology and patient risk)
Common iliac arteries	• Primary stenting should be considered
External iliac arteries	• Balloon angioplasty (more often with stenting) should be considered
Femoro-popliteal arteries	• Drug-eluting endovascular treatment should be considered as the first-choice strategy • An open surgical approach might be considered when an autologous vein is available in patients with low surgical risk and technical factors suggesting advantages over endovascular approaches
BTK arteries	• Treatment of isolated BKT lesions is not recommended • In highly selected patients with severe exertional limb symptoms in whom endovascular femoro-popliteal treatment is performed, treatment of BTK arteries might be considered in the same intervention if there is substantially impaired outflow

Notes. BKT: below-the-knee. *After a minimum period of optimal medical treatment including exercise therapy.

● *Antidiabetic therapy:* recommended with sodium-glucose co-transporter-2 inhibitors and/or glucagon-like peptide-1 receptor agonists with proven CV benefit are recommended in patients with type 2 diabetes and PAD to reduce CV events, independent of baseline or target HbA1c and concomitant glucose-lowering medication. Patients with diabetes and PAD should have an individualized HbA1c target according to comorbidities, diabetes duration, and life expectancy. To reduce microvascular complications, an HbA1c <53 mmol/mol (7%) is commonly recommended.

● *Antithrombotic therapy:* use of antiplatelet therapy (aspirin or clopidogrel) is recommended in symptomatic patients. It should be also considered on individual basis in patients with masked PAD, or with multi-level or severe asymptomatic disease. A combination of aspirin and rivaroxaban 2.5 mg bid should be considered in patients with PAD, high ischemic risk, and non-high bleeding risk, as well as in non-high bleeding risk patients following lower limb revascularization.

● *Supervised exercise training (SET):* recommended for symptomatic PAD patients to improve symptoms and functional capacity. Training frequency of at least three times per week, training session duration of at least 30 min, and training program duration of at least 12 weeks should be considered. In patients with CLTI, lower limb exercise training is not recommended, though upper limb exercise should be considered.

● *Interventional treatment:* in patients with symptomatic PAD and impaired PAD-related QoL after a 3-month period of optimal medical treatment and exercise therapy, revascularization options may be considered (summarized in Table I). The choice between open surgery and endovascular treatment depends on many aspects, such as anatomical lesion location, lesion morphology, and general patient condition. In case of endovascular revascularization, the choice of techniques and devices to be used should be performed according to standardized criteria [48, 49]. For limb salvage in patients with CLTI, revascularization is recommended following multidisciplinary evaluation.

● *Long-term monitoring:* PAD is a chronic disease requiring long-term angiological care. Regular follow-up, at least annually, is recommended to assess clinical and functional status, medication adherence, limb symptoms, and CV risk factors, with DUS evaluation if necessary.

Multidisciplinary care

Effective PAD management requires a multidisciplinary and interprofessional team approach, with referral networks ensuring that patients with complex cases receive specialized care in high volume centres [5]. Angiologists play a central role in the diagnostic workup, management, and follow-up of patients with PAD, as well as in coordinating the various specialists involved in the patient's care. Experts in different complementary fields play an important role in PAD patients management and these include radiologists, endocrinologists, nephrologists, and diabetologists. Given the relevance of SET for the care of patients with PAD, exercise therapists are crucial for proper management. Dieticians can also be helpful in providing guidance to patients. Due to the high risk of MACE, neurologists and cardiologists need to be involved in the multidisciplinary approach as well. In case of interventional treatment, in addition to interventional angiologists, vascular surgeons, and in some cases interventional radiologists play a significant role. Wound care nurses and podiatrists ensure optimal treatment of ischemic wounds in patients with CLTI. For patients with progressive aortic disease requiring surgery, cardiac surgeons, anaesthesiologists, and CV intensive care specialists are needed. Finally, the important role of general practitioners should not be underestimated, as they are integral part of the multidisciplinary approach to PAD patients. Early involvement of specialists outlined above can prevent disease progression, risk of MACE, and improves both QoL and survival of patients with PAD [5].
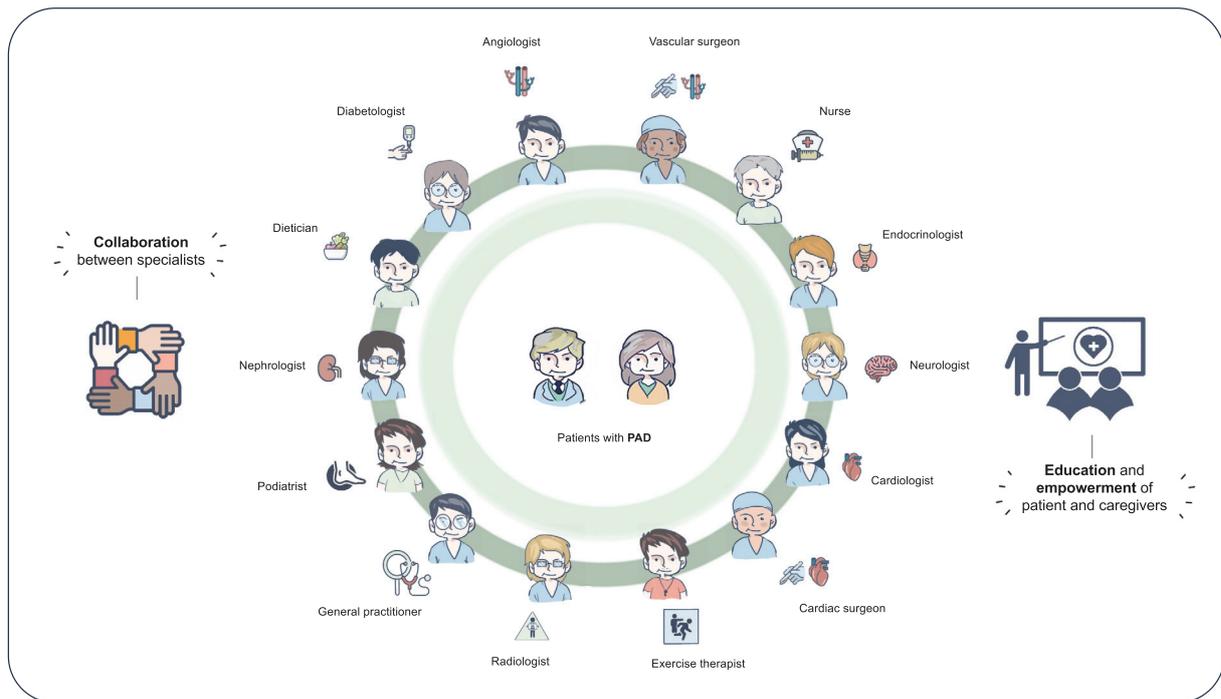
Figure 3. Multidisciplinary care of peripheral arterial disease. *Note.* PAD: peripheral arterial disease.

Key recommendations (Figure 3)

- Facilitate timely referrals to specialized centres for complex cases to ensure comprehensive care.

Patient and caregiver involvement

Educating and empowering patients and their caregivers about PAD management through tailored guidance is mandatory. Engaging them in treatment decisions fosters a supportive environment conducive to healing. Involving patients' families, friends, and support networks contributes significantly to sustaining and perpetuating lifestyle changes and maintaining treatment adherence in the long term [50].

Key recommendation

- Actively involve patients and caregivers in discussions about treatment, lifestyle changes, and the importance of follow-up care.

Conclusions

The 2024 ESC guidelines outline a unified, patient-centred strategy for managing PAD, highlighting the multidisciplinary nature of care and the pivotal role of angiologists as coordinators overseeing diagnosis, treatment, and follow-up. This approach aims to improve QoL and reduce the burden of PAD through optimized, collaborative management.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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