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Review Article

Peripheral arterial disease (PAD) – A challenging manifestation of atherosclerosis

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SUMMARY

The diagnosis of peripheral arterial disease (PAD) is not always evident as symptoms and signs may show great variation. As all grades of PAD are linked to both an increased risk for cardiovascular complications and adverse limb events, awareness of the condition and knowledge about diagnostic measures, prevention and treatment is crucial. This article presents in a condensed form information on PAD and its management.

1. Introduction

Peripheral arterial disease, PAD, usually caused by atherosclerosis, may imply engagement of any artery outside the heart and brain, but the term is most commonly used for lower limb disorder, e.g., asymptomatic lower limb PAD, intermittent claudication (IC) and chronic limb threatening ischemia (CLTI). Several clinical classifications exist, based either on symptoms or anatomy (Hardman et al., 2014). The Rutherford classification includes three stages for intermittent claudication (mild, moderate and severe) and further three for CLTI (rest pain, minor and major tissue loss) (Rutherford et al., 1997) whereas both the TASC and GLASS classifications are based on detailed vascular anatomy related to revascularisation options (Jaff et al., 2015; Conte et al., 2019a). PAD generally implies concomitant cardiovascular (CV) and/or cerebrovascular disorder and increased mortality. Patients with an ankle-brachial pressure index ≤0.9 (see below) are at a 3–6 times higher risk for death compared to subjects without PAD (Norgren et al., 2007). In a population-based study from the Netherlands, a certain reduction of mortality was observed between the periods 1998–2004 and 2005–2010, most likely as a result of improved prevention (van Haelst et al., 2018). Early diagnosis and risk factor modification as well as secondary prevention to reduce CV events are therefore of greatest importance. Treatment to improve function, and in case of CLTI to promote ulcer healing and increase limb salvage, should also be considered. It is evident that many patients do not receive correct advice and treatment, or appropriate measures are initiated later than desired (Song et al., 2019; Ramos et al., 2016). Impaired medication adherence is also a recognized challenge indicating a need for well-adjusted care amongst physicians (Brand et al., 2021). Detailed PAD guidelines have previously been published by cardiovascular and peripheral arterial communities, including the European Society of Cardiology (ESC) (Aboyans et al., 2017), the American Heart Association/American

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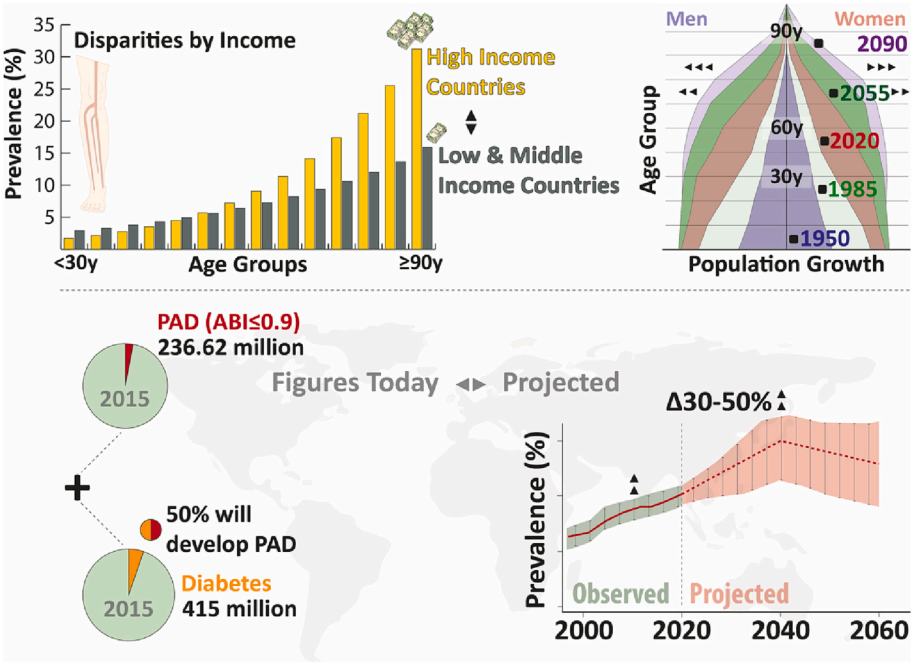

Fig. 1. Graphical illustration of the current trends in PAD epidemiology.

College of Cardiology (AHA/ACC) (Gerhard-Herman et al., 2017) and by a joint guideline committee (focusing on chronic limb-threatening ischemia) including the Society for Vascular Surgery (SVS), the European Society for Vascular Surgery (ESVS) and the World Federation of Vascular Societies (WFVS) (Conte et al., 2019a). There is also an even more recent Asia-Pacific Consensus Statement on the Management of Peripheral Artery Disease (Abola et al., 2020). While all the aforementioned guidance documents cover all relevant aspects of PAD in great detail, the authors of the current review have found it important to provide brief, practical and concise information on PAD in a more condensed form in order to reach a broader audience of physicians with the ultimate purpose to increase PAD awareness and improve preventive medicine and management of PAD patients at an early stage.

2. Epidemiology of lower extremity PAD: a global phenomenon

PAD has predominantly occurred in older individuals in high income countries (HICs) (Criqui and Aboyans, 2015). However, in recent years a global epidemiological transition has taken place so that many populations throughout the world are now affected (Fowkes et al., 2013). In HICs the prevalence of PAD (symptomatic and asymptomatic) reported in 2013 was similar in men and women and rose with age from 5% at 45 to 49 years to 18% at 85 to 89 years. In low- and middle-income countries (LMICs) a comparable pattern was found.

The numbers of PAD cases worldwide between the years 2000 and 2010 increased by a quarter to approximately 200 million in 2010. This increase was greater in LMICs (29%) than in HICs (13%) resulting in the highest numbers in 2010 occurring in Southeast Asia and Western Pacific Regions. This upward trend has persisted so that by 2015, 236 million were estimated to have the disease (Song et al., 2019).

The prevalence of only symptomatic PAD is more relevant to disease experienced in primary care. The prevalence of IC has been investigated widely using questionnaires in USA and Europe. A review in HICs found a prevalence of <1% at <50 years of age, increasing to 6% at age > 65 years (Norgren et al., 2007). IC is usually higher in men than in women but not universally so (Sigvant et al., 2007).

In recent years, it has been shown that "atypical" leg pain is frequent (McDermott et al., 2001). In the general population in the Netherlands, 1.6% were found to have classic IC whereas 5% had atypical symptoms (1.2% non-calf pain, 3.7% calf pain but not classic IC) (Stoffers et al., 1996). These findings have implications for the spectrum of patients in clinical practice that might be considered to have PAD.

Undoubtedly the growth of the world population especially at older ages has had a major influence on the rise in PAD, as has the increase in diabetes (Fowkes et al., 2017). Furthermore, the reduced mortality of patients following myocardial infarction and stroke may lead to more atherogenic individuals surviving long enough to be diagnosed with PAD.

A continuing increase in PAD is likely, by perhaps around 30–50% by the year 2045. Ongoing improvements may well occur in outcomes following acute CV events. Thus, appropriate diagnosis and management of PAD should be highly relevant for many years to come for physicians globally, including those working in primary care. Fig. 1 shows some key epidemiological features relevant to this predicted growth in PAD.

Main message: PAD is increasing worldwide, most obvious in low- and middle-income countries

3. Pathophysiology, risk factors and symptoms

PAD is usually caused by atherothrombotic occlusion or stenosis of the lower limb arteries (Narula et al., 2020). Rare causes include vasculitis, popliteal entrapment, artery endofibrosis and cystic adventitial disease (Golledge, 2022). In response to leg ischemia, a number of compensatory physiological processes are activated (Golledge, 2022). Collateral arteries remodel to provide increased leg blood supply (arteriogenesis) and new small arterial connections may also form (angiogenesis) (Krishna et al., 2015). The compensatory responses to ischemia are frequently inadequate to meet the demands of lower extremity muscles which undergo a range of pathological changes including atrophy, fibrosis and mitochondrial dysfunction, implicated in causing functional decline usually seen in most PAD patients (McDermott et al., 2020).

Established risk factors for PAD include smoking, diabetes, older age, dyslipidaemia, hypertension, obesity and chronic kidney disease (Golledge, 2022). Recent studies have identified higher prevalence of PAD in women compared to men in the age group 45–70 years (Golledge, 2022). PAD prevalence also varies by ethnicity and geographic locality,

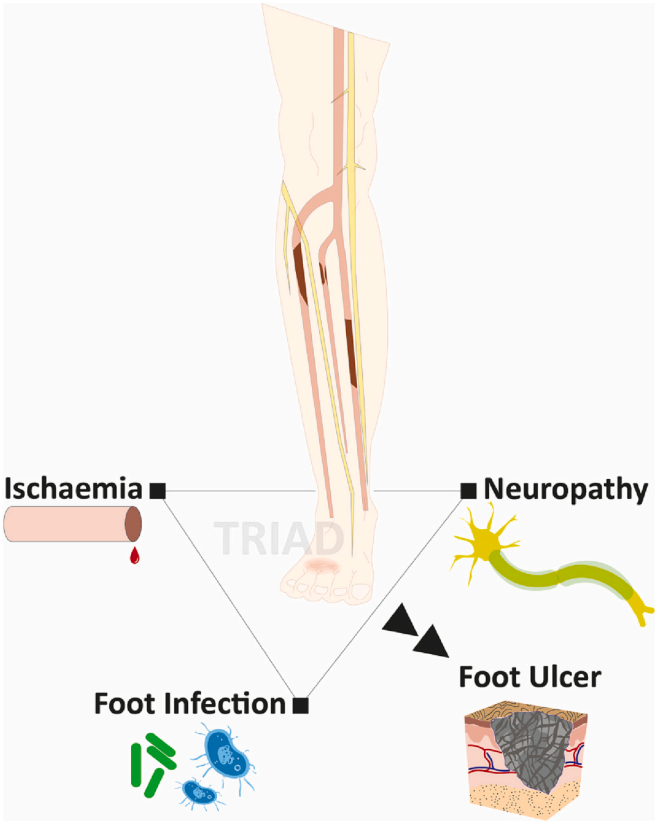

Fig. 2. Graphical illustration of the complex interplay between the principal risk factors for the development of diabetic foot problems.

with higher prevalence reported in Aboriginal and Torres Strait Islander Australians, African Americans and Hispanics (Fowkes et al., 2017; Allison et al., 2007; Singh et al., 2018). Genetic risk factors include prothrombotic mutations, such as factor V Leiden variant (Klarin et al., 2019).

The most recognized symptom of PAD is pain in the calf induced by walking and relieved by rest, known as intermittent claudication (IC) (Schorr and Treat-Jacobson, 2013). Patients may also suffer pain at other lower limb sites or be asymptomatic (McDermott et al., 2010; Hirsch et al., 2001). In one study 19% were asymptomatic, 49% had atypical symptoms and 32% had IC (McDermott et al., 2010). Atypical symptoms included leg pain unrelated to walking, numbness of the leg and paresthesia. The more advanced stage of PAD is CLTI, characterized by ischemic ulceration or gangrene of the lower limb, usually the foot, or ischemic rest pain. A previous study of a US Medicare population found that 15% of patients presenting with PAD had CLTI but this is likely a substantial over estimate of the community prevalence of CLTI (Nehler et al., 2014).

Patients with PAD are at high risk of major adverse CV events, such as myocardial infarction, stroke or CV death during follow-up. The risk of major amputation is low in people with ischemia which is not limb threatening (0.5–1.0% per year) but much higher in people with CLTI (5–10% per year) (Golledge, 2022).

Main message: PAD may present in a variety of ways, all associated with a high risk of CV events and thus control of modifiable risk factors is key in management

4. The diabetic foot – a challenge in PAD treatment

Diabetes, rapidly increasing in prevalence, affects around 6% of the Western European population. The complications of diabetes pose a large healthcare burden. Specifically, foot complications account for more admissions than any other complications in people with diabetes.

The lifetime risk of foot ulceration in people with diabetes is around 19–34%, and the presence of ulceration is associated with limb loss and premature mortality. Importantly, >80% of those who undergo amputation will have had a preceding foot ulcer where an opportunity for limb salvage was missed (Armstrong et al., 2017).

4.1. Aetiology

There is a complex interplay of risk factors in the development of foot complications in people with diabetes. These include PAD, peripheral neuropathy, foot deformity and a history of prior ulceration or minor foot amputation (Fig. 2). It has been estimated that most patients (45–60%) have a combination of neuropathy and PAD (neuroischaemic ulceration). The development of infection in those with ulceration frequently leads to emergency presentation (Prompers et al., 2007).

4.2. Peripheral artery disease in diabetes

PAD is four times more common in patients with diabetes and around half of patients with a diabetic foot ulcer have co-existing PAD. The distribution of disease is often more distal, especially in the crural vessels. They are often more calcified with longer occlusions. Importantly, patients with diabetes are less likely to form collaterals, an important explanation why the distal perfusion of the foot may be particularly impaired.

4.3. Microcirculation

The microcirculation is not directly affected by atherosclerosis, but diabetes affects the microcirculation in other ways. Vasomotor abnormalities occur which may reduce capillary flow in the skin. There is thickening of vascular endothelial cells, with associated increased permeability and platelet aggregation. These observations help to explain how wounds, which are healthy and bleeding at the time of surgery, can deteriorate and die back as the vessels in the microcirculation thrombose. Neuropathy also shunts blood away from the nutritive capillary bed.

4.4. Infection

Infection is often the final common pathway to acute presentation. The immune response of people with diabetes may be abnormal. Neutrophil phagocytosis is impaired, not only increasing the risk of infection but also potentially masking the clinical response. Only about one third of patients with a foot infection will be pyrexial and the white cell count may not be elevated despite extensive sepsis.

4.5. Wound healing

It is a common misconception that diabetes in itself causes delayed wound healing. There are numerous experimental studies that suggest this is not the case, however the co-existence of PAD and infection may impair wound healing.

4.6. Vascular assessment

Ankle-brachial pressure index (ABPI) may be artefactually raised in people with diabetes who may have calcified incompressible lower limb arteries. Toe pressures or toe-brachial index (TBI) are likely to be more meaningful due to relative sparing of the pedal arteries. Whilst ABPI and toe pressures give useful information regarding large vessel disease, transcutaneous oxygen pressure measurement ($TcpO_2$) gives additional information regarding the microcirculation. Normal perfusion assessments do not guarantee wound healing, but perfusion deficits identified by a $TcpO_2 < 25$ mmHg, toe pressure < 30 mmHg or ankle pressure <

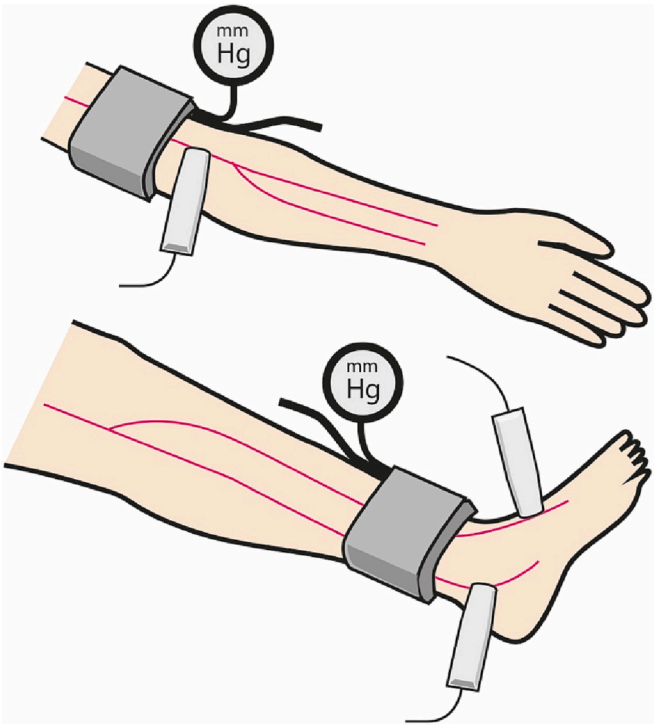

Fig. 3. Schematic illustration of the ankle-brachial pressure index (ABPI) measurement technique. The Doppler signal is identified in the posterior tibial and dorsal pedal arteries. Once the flow signal has been identified, the cuff is inflated until the flow signal disappears. The cuff is released slowly until the flow signal returns, which reflects the systolic ankle pressure. The systolic blood pressure in both arms is measured and by convention the ABPI is thereafter calculated by dividing the highest recorded ankle pressure with the highest recorded arm pressure. The PAD diagnosis is established by an ABPI measurement that falls outside the normal range (0.91–1.39) and both lower and higher (indicating severely calcified and less compressible arteries) values than this threshold verifies PAD. Values between 0.91 and 1.00 should be considered borderline.

50 mmHg increase the risk of wounds failing to heal and major amputation. These patients should be considered for further vascular imaging and revascularisation.

Main message: PAD is closely linked to diabetes mellitus, requiring careful management

5. Diagnostic procedures

The PAD diagnosis is usually established on clinical grounds by combining a comprehensive medical history including an assessment of the patient's lower limb symptoms and walking ability with a clinical vascular exam that includes ABPI measurements. Thus, neither objective walking tests nor medical imaging is universally required to establish the diagnosis, although such tests and investigations may further support the differential diagnostic process in patients where the cause of the lower limb symptoms remains unclear. Beyond a detailed assessment of lower limb symptoms and their impact on regular activities and health-related quality of life, the medical history should also cover CV risk factors (Santoro et al., 2018).

While CLTI symptoms are more obvious, less severe PAD stages may be challenging to distinguish from other highly prevalent diseases. The most important differential diagnosis that may mimic PAD symptoms are spinal stenosis and hip- and knee osteoarthritis, why referral to an orthopaedic specialist may be of value in cases where the PAD diagnosis is less convincing. While neurogenic claudication typically occurs with extension of the spine and is relieved with flexion, it may require sitting down or lying supine for full symptom relief. Osteoarthritis may cause lower extremity pain that occurs with exertion, but patient-reported walking distances remain more variable than in PAD, and the lower limb pain character is less specific. Both in spinal stenosis and in osteoarthritis the lower limb symptoms also resolve less quickly when compared with vascular claudication due to PAD. Earlier stages of PAD may also be masked by many other factors and conditions which can delay or interfere with diagnosis. Examples include sedentary lifestyle, lack of distinct symptoms due to coexisting neuropathy, co-morbidities that affect physical activity levels, or misinterpretation of atypical symptoms (Gardner et al., 2007; McDermott et al., 1999).

5.1. Clinical vascular examination and ankle-brachial pressure index (ABPI) measurement

Peripheral pulse examination should include the femoral, popliteal, posterior tibial, and dorsalis pedis pulses. Any palpable pulse abnormality should raise a suspicion of PAD. Clinical examination should also include lower limb and feet skin examination, to identify signs of chronic arterial impairment, skin discoloration or atrophy, absence of hair on toes and nail dystrophy. When CLTI is suspected, a proper assessment of foot status including ulcer/gangrene status and signs of foot infection should be included in the clinical examination (Kullo and Rooke, 2016).

The ABPI is the preferred bedside test for PAD screening and for establishing the diagnosis. The measurement is made in the supine position and by using a pen Doppler and a manual blood pressure cuff placed distally at the ankle level. The measurement technique and proper interpretation of measurement results are described in Fig. 3 (Aboyans et al., 2012).

5.2. Toe pressures and toe-brachial index

The assessment of the absolute toe pressure (TP) and the toe brachial index (TBI) are additional measuring methods that can establish PAD diagnosis in more challenging populations with inconclusive clinical and/or ABPI findings. The digital arteries are commonly spared from medial arterial calcification and thus TP/TBI is less prone than ABPI to measurement errors which is especially important in patients with diabetes mellitus. Systolic TP is about 20–40 mmHg lower than the corresponding ankle pressure and thus a TBI lower than 0.7 is considered abnormal (Hoyer et al., 2013).

5.3. Walking tests

The treadmill test is a useful diagnostic method that both can objectively determine IC severity and reveal stenotic or occlusive arterial lesions that remain undetected at rest. Especially in PAD patients with aortoiliac lesions, the resting ABPI could still fall within the normal range, as the eventual pressure drop over even a significant stenosis heavily depends on volume flow. An immediate post-exercise ABPI drop of at least 20% or an absolute ABPI pressure drop of 30 mmHg or more confirm PAD (Aboyans et al., 2012).

The six-minute walk test (6MWT) assesses the maximum walking distance covered during an indoor flat ground walking time of six minutes. The patient walks back and forth on a 30-m corridor distance and is allowed to stop when required. The patient reports the onset of lower limb pain and the corresponding covered distance is captured as the initial claudication distance while the total covered distance is being measured after six minutes (McDermott et al., 2014).

5.4. Medical imaging

Duplex ultrasonography (DUS) is a reasonable first imaging tool in patients where the PAD diagnosis has not been possible to establish with investigations described above. CT and MR angiographies as well as invasive digital subtraction angiography should be reserved for

Table 1
Summary of recommendations for prevention and medical treatment in PAD. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, GLP1-RA = glucagon-like peptide-1 receptor agonist, LDL = low-density lipoprotein, PCSK9 = proprotein convertase subtilisin/kexin type 9, SGLT2 = sodium-glucose co-transporter 2.

Risk factor	Target	Therapy and suggested therapeutic agents	References
Sedentary living	Regular exercise	Supervised exercise therapy	(Aboyans et al., 2018; Jansen et al., 2019)
Smoking	Total abstinence	Nicotine replacement therapy Bupropion Varenicline Cessation support programs	(Aboyans et al., 2018; Willigendael et al., 2004)
LDL-cholesterol	<1.4 mmol/l and reduction >50% from baseline	Statins Ezetimibe PCSK-9 inhibitors	(Ramos et al., 2016; Aboyans et al., 2018; Mach et al., 2020; Oyama et al., 2021)
Arterial hypertension	120–129/70–80 mmHg <65 years, 130–139/70–80 mmHg ≥65 years	ACEI or ARB CCB Thiazide diuretics	(Aboyans et al., 2018; Williams et al., 2018)
Platelet and coagulation activity (if symptomatic PAD or other atherosclerotic disease)		Single antiplatelet therapy with clopidogrel or aspirin. Combination of aspirin and low dose rivaroxaban.	(Committee, 1996; Katsanos et al., 2015; Anand et al., 2018; Bonaca et al., 2020; Belch et al., 2010)
Type 2 diabetes mellitus	HbA1c < 7.0% (<53 mmol/mol)	GLP1-RA SGLT2 inhibitors	(Cosentino et al., 2020; McGuire et al., 2021)

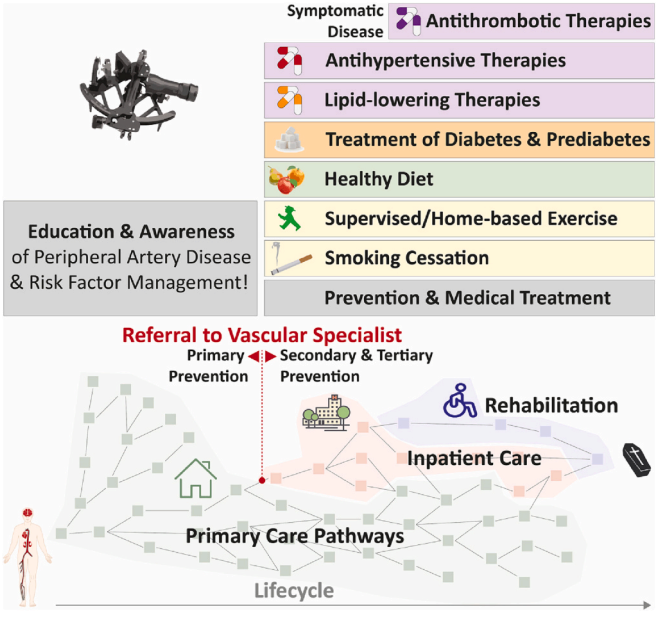

Fig. 4. Summary of recommended optimal medical management throughout the PAD patient life cycle.

revascularisation procedural planning.

Main message: PAD diagnosis requires clinical assessment and (at least) a haemodynamic assessment using the ankle-brachial pressure index

6. Prevention and medical treatment

PAD patients have widespread atherosclerosis and high rates of CV events, and a low ABPI is related to increased risk for CV events and mortality (Heald et al., 2006). Efficient treatment of atherosclerotic risk factors should therefore be offered to all PAD patients, as summarized in Table 1 and Fig. 4 (Aboyans et al., 2018).

6.1. Diet and exercise

A healthy diet rich in vegetables, fruit, and fish with low content of saturated fat as well as regular physical exercise are recommended (Aboyans et al., 2018; Mach et al., 2020; Adegbola et al., 2022; Jansen et al., 2019). If possible, exercise therapy should be supervised during three 30–45 min sessions per week to improve both walking distance and risk factor profile (Jansen et al., 2019).

6.2. Smoking cessation

Smoking cessation is strongly recommended with beneficial effects on disease progression (Willigendael et al., 2004). Nicotine replacement therapy, varenicline, bupropion, and formal cessation support programs can be used (Barua et al., 2018).

6.3. Lipid-lowering therapies

Increased total and low-density lipoprotein (LDL) cholesterol and triglyceride levels, and decreased levels of high-density lipoprotein are risk factors for PAD. Statin therapy is therefore warranted in PAD patients with or without symptoms, as risk reductions in major adverse CV events (MACE) and all-cause mortality have been documented in both groups (Ramos et al., 2016; Mach et al., 2020). An LDL goal of <1.4 mmol/L (55 mg/dL) and a LDL reduction of ≥50% from baseline is recommended (Mach et al., 2020), and follow-up is important to ensure that these targets are reached. In addition to effects upon CV mortality and morbidity, statins may improve walking distance in claudication, reduce amputation rates and improve graft patency. If targets are not reached with maximal tolerable statin doses complemented by ezetimibe and lifestyle change, combination with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may be considered (Mach et al., 2020). The addition of PCSK9 inhibitors to statins decreased acute arterial events across all vascular territories in patients with atherosclerotic CV disease including PAD (Oyama et al., 2021).

6.4. Antihypertensive treatment

Antihypertensive therapy reduces CV events and mortality, and guidelines (Williams et al., 2018) on blood pressure (BP) lowering are applicable in PAD. Treatment is recommended at BP ≥140/90 mmHg, and target BP, if tolerated, is 120–129/70–80 mmHg in patients <65 years, and 130–139/70–80 mmHg for patients >65 (Williams et al., 2018). Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are first-line therapy in hypertensive PAD patients as they reduce CV events in this group. Most patients require multiple drugs to achieve target BP, however, and calcium channel blockers and thiazide diuretics are recommended as first additions (Williams et al., 2018). If BP remains uncontrolled despite combination of these three drug classes, spironolactone should be considered. Beta-blockers do not affect walking capacity or adverse limb events but have not been evaluated in CLTI (Conte et al., 2019a; Conte et al., 2019b).

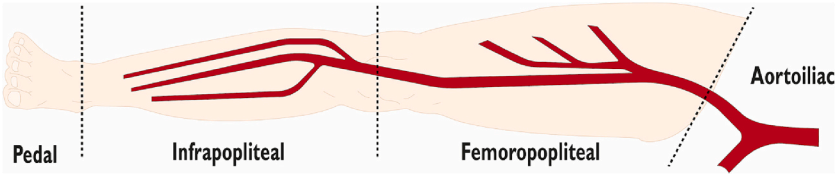

Fig. 5. Schematic illustration of the main lower limb revascularization arterial target segments.

6.5. Antithrombotic treatment – antiplatelet therapy

Antiplatelet treatment has no beneficial effects in asymptomatic PAD and is not recommended in PAD patients without leg symptoms or other symptomatic manifestations of atherosclerosis (Aboyans et al., 2018).

Antiplatelet therapy reduces vascular morbidity in symptomatic PAD. In the PAD subgroup of the CAPRIE trial (Committee, 1996), clopidogrel reduced both CV mortality and MACE compared to aspirin. A meta-analysis of 49 RCTs showed that neither aspirin, cilostazol, picotamide, ticagrelor, ticlopidine, or vorapaxar were superior to clopidogrel in PAD when benefits on both cardiovascular and limb outcomes and potential harm of treatment were taken into account (Katsanos et al., 2015). Single antiplatelet treatment with aspirin or clopidogrel is therefore recommended in symptomatic stable PAD (Aboyans et al., 2018).

6.6. Combined antiplatelet and anticoagulant (dual pathway) therapy

The combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg daily reduces both a composite of CV death, myocardial infarction, or stroke as well as rates of amputation and other major adverse limb events (MALE) in patients with either stable PAD or carotid artery disease compared to aspirin alone (Anand et al., 2018). CLTI guidelines (Conte et al., 2019a; Conte et al., 2019b) therefore advocate consideration of this combination in patients with stable PAD without high bleeding risk.

Evidence for double antiplatelet therapy (DAPT) after endovascular revascularization in lower limbs is lacking. Combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg daily is beneficial compared to aspirin alone after revascularization in PAD (Bonaca et al., 2020), whereas no additive beneficial effects of combining aspirin with clopidogrel were demonstrated after open peripheral bypass surgery, except for in patients with prosthetic grafts (Belch et al., 2010).

6.7. Antidiabetic therapy

Tight glucose control is beneficial (Cosentino et al., 2020) and recommended in all PAD patients with diabetes (Aboyans et al., 2018). Treatment targets are individual, but $HbA_{1c} < 7\%$ or < 53 mmol/mol is recommended to prevent atherosclerotic progression and other diabetic complications (Cosentino et al., 2020). In elderly patients, less rigorous targets might be accepted to reduce risk for hypoglycaemic episodes (Cosentino et al., 2020). Glucagon-like peptide-1 receptor agonists (GLP1-RA) liraglutide, dulaglutide, and semaglutide have positive effects on CV events compared to placebo in patients with type 2 diabetes (Cosentino et al., 2020), and liraglutide reduces amputation rate. Sodium-glucose co-transporter 2 (SGLT2) inhibitors empaglifozin, dapaglifozin, and canaglifozin also reduce CV outcomes and help reduce weight (Cosentino et al., 2020). A significantly increased rate of mainly minor amputations was reported with canaglifozin, but this finding was not confirmed in a meta-analysis (McGuire et al., 2021). GLP1-RA or SGLT2 inhibitors are recommended in patients with type 2 diabetes and concurrent PAD (Cosentino et al., 2020), but canaglifozin should be used with caution in CLTI patients with diabetes (Neal et al., 2017).

Main message: secondary prevention should always be part of the treatment of PAD patients. Risk factors are closely related to PAD, and require treatment

7. Treatment of IC symptoms

Patients suffering from IC benefit from exercise, preferably supervised, to increase pain-free and maximal walking distance. Usually, patients are advised to walk until maximal or moderate pain occurs, while recent data suggests that also pain-free walking may be of value (Seed et al., 2021).

Regarding drug treatment, the documentation is limited. A recent Cochrane Database Systematic Review (Brown et al., 2021) concluded that cilostazol and pentoxifyllin increase walking distance, but both are used with great variation between countries. Cilostazol also carries a risk for uncomfortable side effects. No recommendation regarding drug treatment of IC could therefore be provided (Aboyans et al., 2012).

Main message: exercise should always be part of the treatment of intermittent claudication

8. Lower limb revascularisation

Revascularisation is the term used to describe a wide range of open surgical (bypass, endarterectomy), endovascular (balloon angioplasty, stenting), and so-called hybrid procedures (which combine these open and endovascular techniques), that are used to increase the arterial blood supply to the legs and feet (Beckman et al., 2021).

Most patients who may benefit from revascularisation fall into three categories

- Chronic limb threatening ischaemia, CLTI
- Wounds and ulcers that are not primarily due to arterial insufficiency, but where reduced arterial blood flow prevents healing or limits treatment options, e.g. when restricted blood flow prevents safe use of compression therapy for chronic venous ulceration
- Intermittent claudication, IC

Arteries supplying the legs are divided into three segments (Fig. 5):

- Aorto-iliac (AI) - the aorta and common (CIA), external (EIA) and internal iliac (IIA) arteries; termed the arterial ‘inflow’ to the leg.
- Femoro-popliteal (FP) - the common (CFA), deep DFA (also known as profunda femoris artery, PFA) and superficial femoral arteries (SFA), and the popliteal artery (PA) at the level of the knee.
- Infra-popliteal (IP) -the tibio-peroneal trunk (TPT) and the three crural arteries -the anterior tibial (ATA), the posterior tibial (PTA) and peroneal (PerA) arteries, termed the arterial ‘outflow’.

All patients with tissue loss should be considered for revascularisation. It is very important that no CLTI patient be offered amputation without first being fully assessed by a vascular surgeon regarding their suitability for revascularisation.

The mainstay of treatment for the great majority of IC patients should be medical with advice on lifestyle choices and exercise. Revascularisation should only be considered if, despite having been successfully implemented for at least 6 months, non-interventional treatment has failed to satisfactorily improve the patient’s quality of life.

Much of the discussion around revascularisation for CLTI centres on

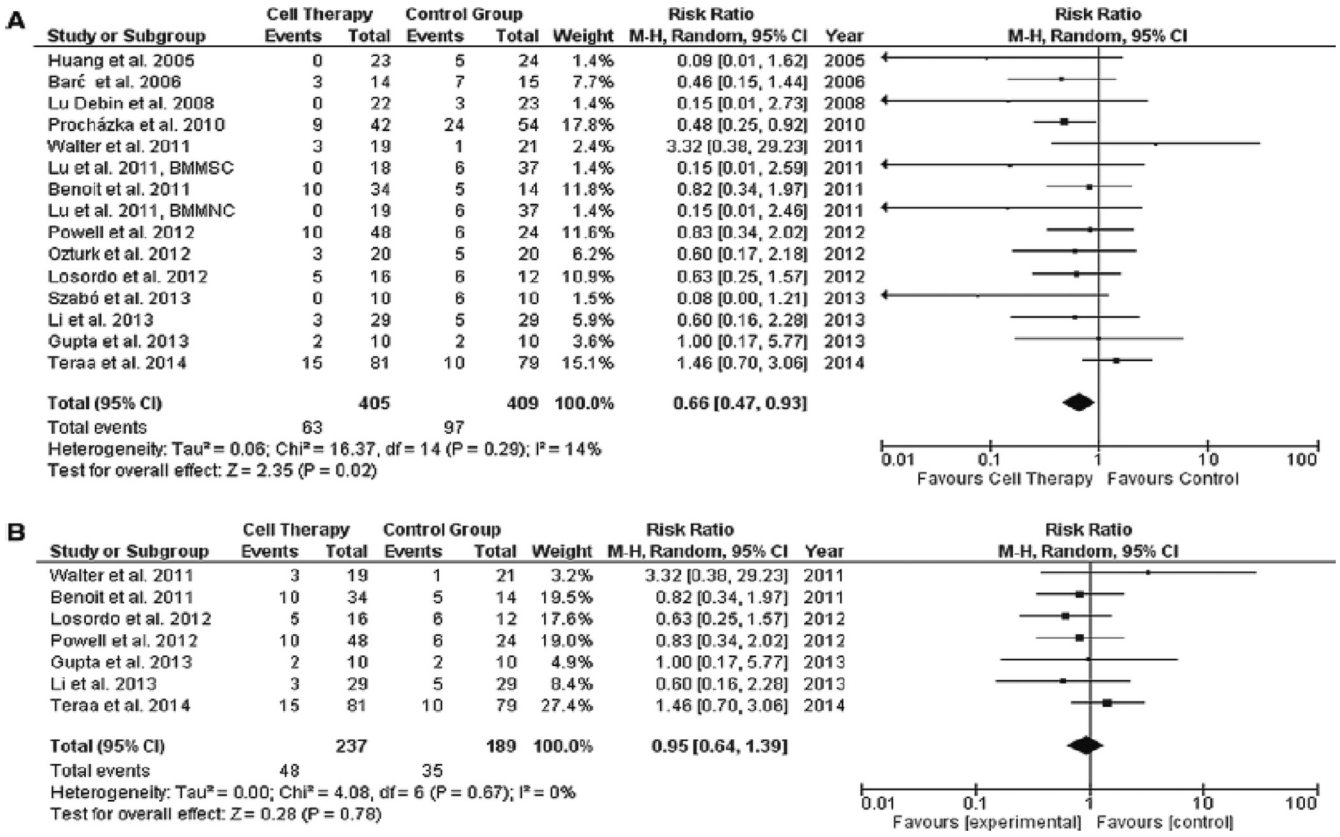

Fig. 6. Comparison of outcome of randomized clinical trials using autologous BMMNCs for angiogenesis in PAD: A: randomized trials versus B: randomized placebo-controlled trials (reprinted with permission from (Teraa et al., 2013a). No benefit, when randomized placebo-controlled trials were considered only.

whether to first offer a surgical, endovascular, or hybrid intervention (Conte et al., 2019a; Conte et al., 2019b). Endovascular procedures involve the use of a wide variety of different devices such as balloons (balloon angioplasty, BA) and/or stents and/or other adjuvant techniques (e.g., atherectomy). Those who favour a "best endovascular therapy first" (BET) approach point to lower procedural morbidity and mortality, and quicker recovery. Those who favour a "bypass surgery first" approach point to improved durability and a lower requirement for repeat procedures (Bradbury et al., 2010).

There is a conspicuous lack of "level 1" evidence from randomized controlled trials to guide decision making on revascularisation strategies for CLTI (Hunt et al., 2017; Mills Sr., 2019; Popplewell et al., 2016). The BEST-CLI trial suggests that bypass surgery is beneficial under certain conditions (Farber et al., 2022), while the BASIL 2 and BASIL 3 trials are due to report 2023.

The lack of good quality evidence means that practice (patient selection, bypass vs BET, type of bypass and endovascular procedures / devices used) varies considerably between and within countries and even between centres.

However, factors that influence decision-making in CLTI will typically include:

- Patient age and co-morbidity, and so their procedural risk and life-expectancy
- Severity of clinical presentation: ischaemic rest pain, and the presence and extent of tissue loss
- Anatomic extent and complexity of the underlying PAD

Clinical outcome following revascularisation should be reported:

Has the bypass or BET been associated with a meaningful improvement in patient symptoms and signs? For example, can a patient with IC walk further? Or has ischaemic rest pain been relieved and/or tissue loss healed in a patient with CLTI? This can be assessed objectively by the physician through history and physical examination, or subjectively by the patient using patient reported outcome measures (PROMs) and/or health related quality of life (HRQoL) instruments.

There is a growing consensus that clinical outcomes, especially PROMs and HRQoL are the most important as the primary goal of any treatment is to relieve the symptoms and signs that led the patients to seek medical advice.

Lastly, it is important to emphasise that revascularisation for both CLTI and IC is an adjunct, not an alternative, to best medical therapy (BMT). There is incontrovertible evidence to show that lifestyle changes (in particular smoking cessation), and the control of risk factors improve the short, medium, and long-term success of revascularisation (bypass and BET).

Main message: revascularisation should always be considered in case of CLTI and could be considered also in patients with intermittent claudication without meaningful symptom relief after a conservative treatment attempt

9. Angiogenesis therapy

Cell and gene therapies were hoped for to treat patients with IC or CLTI who are not eligible for revascularization, or, alternatively, as adjunct to such established therapies. Several pre-clinical and early clinical studies suggested that different types of genes, angiogenic factors, and stem cells with regenerative potential and paracrine ability could improve blood circulation and tissue perfusion, and thus improve claudication, induce healing of ischemic wounds, or prevent amputation via the induction of capillary or collateral growth in a process called

Table 2
Clinical trials of cell-based therapy using allogenic mesenchymal cells in peripheral arterial disease. ABPI: ankle-brachial pressure index; CLTI: chronic limb-threatening limb ischemia; DMC: data monitoring committee; DSA: digital subtraction angiography; IC: intermittent claudication; MWD: mean walking distance, TcPO2, transcutaneous partial pressure of oxygen.

Authors	Year	Phase	Indication	Cell	Delivery route	Pts treated/ control	Reference	Outcome
Kim et al	2006	I	Buerger's disease	Umbilical cord blood-derived multipotent stem cells	IM	4/0	(Kim et al., 2006)	Increased collateral branches and vascularities in foot based on angiography Resolution of rest pain Complete healing of necrotic lesion within 120 days
Das et al.	2013	I	CLTI	BM-MSCs	IA	13/0	(Das et al., 2013)	At 6 months compared to baseline: Improved rest pain, ABPI, TcPO2 86% limb salvage 6 of 7 ulcers completely healed
Gupta et al	2013	I/II	CLTI	BM-MSCs	IM	20/0	(Gupta et al., 2013)	Tolerated Trend for improvement of ABPI
Gupta et al.	2017	II	Buerger's disease/ CLTI	BM-MSCs	IM	18/0	(Gupta et al., 2017)	Improved rest pain and ulcer healing in high dose group more than low dose
Pluristem	2018	II	IC	Placebo-derived adherent stromal cells (PLX)	IM	172	(https://www.pluristem.com/news-and-events/pluristem-reports-positive-top-line-results-multinational-phase-ii-intermittent-claudication-study/, n.d.)	Unpublished Patients treated with 2 administrations of 300 million PLX-PAD cells showed statistically significant improvement ($p = 0.0008$) in MWD as compared to baseline at 52 weeks.
Pluristem (PACE)	2020	III	CLTI	Placenta-derived adherent stromal cells (PLX)	IM	164/82	(Norgren et al., 2019; https://www.pluristem.com/wp-content/uploads/2020/12/CLI-Interim-analysis-English-FINAL-VERSION-FOR-RELEASE.pdf, n.d.)	Unpublished Well tolerated DMC recommendation following interim analysis: Phase III CLI study unlikely to meet its primary endpoint by the time of the final analysis Trial terminated prematurely

"therapeutic angiogenesis" (Tateishi-Yuyama et al., 2002; Nikol et al., 2008). However, larger studies have so far failed to confirm benefit.

9.1. Gene therapy

Targeting different genes involved in angiogenesis (i.e., vascular endothelial growth factor VEGF, fibroblast growth factor 1 FGF1, hepatocyte growth factor HGF) using different vector systems (i.e., non-viral, liposomal, viral) have been investigated in patients. They showed throughout favourable safety profiles with low rates of adverse events.

The only large-scale phase III randomized trial TAMARIS with non-viral FGF1 plasmid applied worldwide in 525 patients with (CLTI) proved to be negative (Belch et al., 2011). A systematic review and meta-analysis of randomized, controlled gene therapy trials in PAD (Hammer and Steiner, 2013) identified 12 RCTs with a total of 1494 patients (29% females) included, with 64% suffering from CLTI. Meta-analysis showed neither a significant benefit nor harm for gene therapy. No differences were seen between patients with intermittent claudication or CLTI.

9.2. Cell therapy

Autologous cells obtained from the PAD patient and allogenic cells retrieved from donors have been used in studies. Most clinical trials have investigated the use of adult autologous bone marrow-derived mononuclear cells (BMMNC) or peripheral blood-derived mononuclear cells (PBMNC) (Perin et al., 2011; Benoit et al., 2013; Beltran-Camacho et al., 2021).

A meta-analysis of placebo-controlled trials using autologous bone marrow cells showed no advantage of stem cell therapy on the primary outcome measures of amputation, survival and amputation-free survival in patients with CLTI (Teraa et al., 2013a; Peeters Weem et al., 2015) (Fig. 6). The reasons may lie in the reduced availability and impaired quality of those cells deriving from patients with CV or vascular disease (Hill et al., 2003; Teraa et al., 2013b).

Allogenic mesenchymal stem cells have gained therapeutic interest in interventions aimed at tissue restoration because of their multipotent differentiation capacity and their cytoprotective and immunomodulatory effects (Lu et al., 2011; Altaner et al., 2013). Also, they derive from young healthy individuals and patients do not have to undergo bone marrow aspiration. Allogenic mesenchymal cells tested for angiogenic properties are neuronal, placenta-derived adherent stromal, endometrial, or adipose-tissue-derived (Table 2).

Benefit demonstrated in smaller phase I or II trials so far has not been confirmed in large phase III randomized placebo-controlled trials for angiogenic gene or cell therapies. Therefore, those experimental therapies should only be administrated when investigated within trials according to current PAD guidelines (Frank et al., 2019).

Main message: Therapeutic angiogenesis is still an experimental treatment, and should only be used in scientifically valid trials

Disclosures

The authors declare that there are no financial conflicts of interest.

All authors fulfil the criteria of authorship. All authors approved the submitted version without any institutional objections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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