Title page - consensus document

Exercise therapy for chronic symptomatic peripheral artery disease: a clinical consensus document of the ESC Working Group on Aorta & Peripheral Vascular Diseases in collaboration with the European Society of Vascular Medicine, and the European Society for Vascular Surgery

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Abstract

All guidelines worldwide strongly recommend exercise as a pillar of the management of patients affected by lower extremity peripheral artery disease (PAD). Exercise therapy in this setting presents different modalities, and a structured program provides optimal results. This clinical consensus paper is intended for clinicians to promote and assist for the set-up of comprehensive exercise programs to best advice in patients with symptomatic chronic PAD. Different exercise training protocols specific for patients with PAD are presented. Data on patient assessment and outcome measures are narratively described based on the current best evidence. The document ends by highlighting disparities in access to supervised exercise programs across Europe, and the series of gaps for evidence requiring further research.

Graphical abstract

Included patients

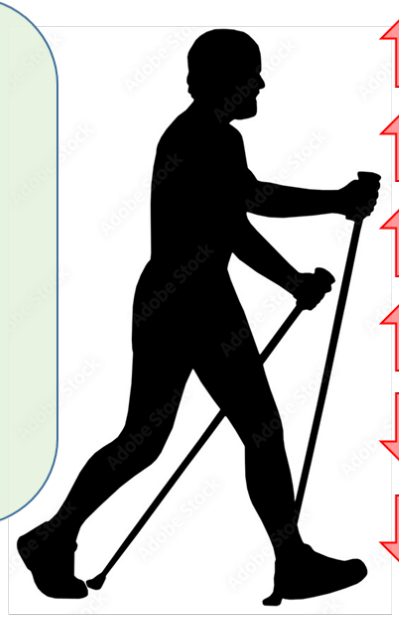
- Women and men with symptomatic chronic PAD
- Patients undergoing endovascular revascularisation

Exercise training programs

- Supervised exercise training or home-based exercise programs
- *Training modality*: walking training but also alternatives (resistance training, arm-cranking, cycling, Nordic walking, combinations of exercise) are effective
- *Training frequency*: at least 3 times per week
- *Session duration*: at least 30 min
- *Program duration*: at least 12 weeks
- *Training strategy*: different levels of claudication pain intensity should be considered
- *Training intensity*: high exercise intensity (77–95% of maximal heart rate or 14-17 on the Borg's scale) should be considered
- Programs should include advice and education about PAD, cardiovascular risk factors, and lifestyle aiming for longer-term behavior change.

Assessments prior and following exercise therapy

- Objective functional assessment (treadmill performance, 6-min walk test, SPPB test, muscular and cardiorespiratory fitness)
- Subjective functional assessment (generic and PAD-specific questionnaires)
- Vascular assessments (ABI, TBI, Ultrasound)



Walking performance

Functional status

Quality of life

Patient awareness and compliance

Symptoms

Global cardiovascular risk

Introduction

Physical activity, including regular exercise, is one of the pillars of cardiovascular (CV) health and a major component of management of patients with most CV diseases (CVD). In 2020, the European Society of Cardiology (ESC) issued a guidelines document covering main aspects of exercise therapy and sports practice for most cardiac diseases [1].

Lower extremity peripheral artery disease (PAD) is one of the most prevalent clinical presentations of atherosclerotic disease, affecting approximately 237 million patients worldwide [2]. The first symptoms of PAD are usually related to walking impairment, and the 2017 ESC/European Society for Vascular Surgery (ESVS) guidelines on the management of PAD underscored the importance of exercise therapy, preferably supervised, for the management of patients with intermittent claudication (IC) [3]. Similarly, the 2019 PAD guidelines of the European Society of Vascular Medicine (ESVM) encourage structured exercise for symptomatic PAD patients [4]. However, none of the aforementioned documents provided in-depth guidance for exercise therapy in this specific setting.

To fill this gap, the ESC Working Group on Aorta & Peripheral Vascular Disease, the ESVM, and the ESVS joined in a collaborative effort providing a roadmap and guidance for the set-up and implementation of exercise therapy programs for patients with PAD.

Consensus statements

- **Supervised exercise programs should be the first line treatment modalities in patients with PAD and intermittent claudication and/or other atypical pain. In those patients undergoing revascularization, supervised exercise programs should be advised as adjuvant therapy.**

- **Supervised exercise programs should be ideally coordinated by vascular physicians, and sessions should be supervised by clinical exercise physiologists or physiotherapists.**

- **Prior and following the supervised exercise programs, CV risk factors, vascular and cardio-pulmonary parameters, walking parameters, functional status, muscle strength, and health-related quality of life should be systematically assessed.**

- **Walking training (overground, pole striding, treadmill) should be proposed as first line exercise modality. When walking is not an option, alternative training modalities (resistance and strength training, arm-cranking, cycling, Nordic walking, combinations of exercise) might be proposed.**

- **The training frequency should be at least three times per week.**

- **The training session duration should last at least a minimum of 30 min.**

- **Patients with PAD should walk to the point of near-maximum leg pain assessed with the claudication pain scale (self-reported 3-4/4 pain intensity in the scale). Lower pain levels (mild pain or pain-free) should also be considered.**

- **Walking training performed at high intensity (77–95% of maximal heart rate or 14-17 on the Borg's scale) should be considered to improve walking performance. High intensity exercise should also be considered to improve cardiorespiratory fitness.**

- **When supervised exercise training is not feasible, structured, high-intensity pain, monitored (calls, log-books, connected devices) home–based programs should be proposed.**

- **Supervised exercise programs should include structured advice and education about PAD, cardiovascular risk factors, and lifestyle. Education should be delivered by trained specialists and aim for longer-term behavior change.**

Pathophysiology of intermittent claudication and functional impairment

Intermittent claudication (IC) is characterized by exertional leg pain limiting walking ability [5-7]. PAD induces a wide range of exercise-related symptoms experienced by nearly half of the PAD population [8]. The classical IC was first defined as calf pain, discomfort or fatigue appearing during exercise and forcing the patient to stop [9]. Typically, IC is relieved within 2-5 min after exertion discontinuation [9]. Apart from this typical symptom, it is now admitted that some patients with PAD may present atypical exercise-induced limb symptoms [10]. These may be localized in lower limb muscles other than calves, may be present at rest, may be described by patients as “burning”, “compressive” feeling, or just “fatigue” without pain and may mimic limb pain due to spinal stenosis. Exercise-induced limb symptoms in PAD are caused by a metabolic mismatch between oxygen demand and supply [5]. The mismatch is linked to the reduction of the arterial lumen by the atherosclerosis process but it also induces cellular and metabolic disorders that contribute to the functional impairment [11]. Mechanisms of exercise-induced symptoms are multifactorial among which nociceptive pain [12], nerve dysfunction [13], skeletal muscle abnormalities [11] are suggested.

Potential mechanistic drivers of exertional limb symptoms in addition to arterial obstruction and reduced perfusion include inflammation, vascular dysfunction, reduced microvascular flow, impaired angiogenesis, and altered skeletal muscle function [14-16] (Figure 1). A healthy vascular endothelium produces several vasodilator substances, including nitric oxide (NO), which has pluripotent vascular benefits such as platelet inhibition, smooth muscle cell proliferation inhibition, leukocyte adhesion prevention, and angiogenesis induction. Diminished NO bioactivity in the lower limbs

prevents increased blood flow with exercise [11]. Vascular dysfunction may also exacerbate the vasoconstrictive effects of catecholamines and limit flow-mediated dilation [17-20]. Inadequate angiogenesis and collateral vessel formation may potentiate limb ischemia and serve as a mechanism driving functional impairment [21]. Skeletal muscle ischemia may drive local inflammation, exacerbating symptoms and altering muscle metabolism [22-24].

People with PAD present impaired walking endurance [25], slower walking velocity [26-28], gait abnormalities [26,27,29-31], poorer muscle strength [32], and poorer balance [33,34] compared to individuals without PAD. Patients with PAD may also reduce their walking activity and total activity to avoid leg symptoms [35], and studies have shown a functional decline occurring over time [25,28,36].

Vascular, functional, and cardiopulmonary assessment in PAD

Vascular assessment

General assessment of CV risk factors should be performed prior to exercise training rehabilitation to improve preventive measures and reach preventive goals. Ankle-Brachial Index (ABI) should be assessed before starting a training program to detect and diagnose PAD and assess disease severity [3]. The measurement of ABI after exercise is also important to further detect ankle pressure drop, as some patients may have leg symptoms on exercise while ABI can be ≥0.91 at rest. A post-exercise ankle SBP drop >30mmHg or a post-exercise ABI decrease >20% should be considered for PAD diagnosis [37]. In patients with media calcinosis (for example in patients with diabetes or chronic kidney disease) measurement of ABI might not be possible because the arteries cannot be compressed by the cuff. In these cases, toe brachial

index (TBI) can be used as alternative assessment (the pathological threshold usually retained is <0.70) [3].

Walking distance assessment

Walking distance is considered an important clinical outcome both for patients and clinicians. Standardized exercise testing should be used for assessment of functional impairment in patients with PAD.

*Treadmill assessment***.** Treadmill testing should be performed with patients familiarized to the treadmill and under reproducible conditions (i.e. avoiding exercise and alcohol prior to assessment). Patients should be asked to walk until maximal levels of pain, lightly holding or not holding onto the treadmill. If the tests are stopped for reasons other than leg pain, then this should be recorded. Patients are asked to indicate the claudication pain score they reached during walking, especially the point at which pain begins, and recovery based on a five-point scale (0 = no pain, 1 = onset of pain, 2 = mild pain, 3 = moderate pain, 4 = severe/maximal pain) [38]. Common treadmill protocols include constant-load (single-stage) or graded exercise testing [39,40]. The latter is performed at constant speed varying the slope of the treadmill. Established graded protocols include the Gardner/Skinner (3.2 km/h and a 2% increase in slope every 2 minutes) or the Hiatt protocol (3.2 km/h and an increase in slope of 3.5% every 3 minutes). Constant-load treadmill tests are performed at a fixed speed of 2 to 4 km/h and fixed gradient of 10 to 12%. Constant-load protocols have poorer reliability both for pain-free walking distance (PFWD) and maximal walking distance (MWD) compared with graded protocols (coefficient of variance 30 and 45%, respectively) [41,42]. Treadmill tests have limitations including learning effect during repeated

evaluations. Also some patients are unable or are unwilling to perform a treadmill test, mainly due to balance impairment or limited walking abilities.

Six-minute Walk Test. The six-minute walk test (6MWT) is performed along a flat corridor with a length of 30m with turning points marked by a cone. Patients are asked to walk self-paced for the full duration and may stop and rest at any point in the test [43]. The total distance walked is measured and reported as the six-minute walking distance (6MWD) [43]. Any encouragement given/phrases used should be the same for every test performed [43]. Although treadmill-based exercise tests can establish maximum walking capacity, there may be a poor correlation between treadmill outcomes, habitual walking, and self-reported walking distance [44]. On the other hand, compared to treadmill test, the 6MWT has been shown to better represent daily life walking in patients with PAD [45]. The 6MWT is a well-validated and low-cost test. It has good reliability, with a correlation coefficient of 0.90 ($p<0.001$) and a coefficient of variation of 8.9% with testing performed one to two weeks apart [46]. Changes in the 6MWT can be used to predict mortality and mobility loss in patients with PAD [7,47]. The minimal detectable changes in the 6MWT are represented by a change >46 meters [48] and the minimal clinically important difference in the 6MWT in patients with PAD is represented by a 20m increase at least [49,50].

Connected Devices. A measure of “real-life” walking performances may be performed by use of global positioning systems (GPS) or commercially available devices such as activity trackers, smart watches and phones [51]. Research has shown that GPS recorders have good accuracy and reliability when compared to known distances walked [52,53], and measurement of step counts with mobile phones has been shown

to be highly reliable even at low walking speeds [54]. Further, GPS recorded walking distances correlate well with treadmill walking distances [55]. Patients should be able to note the initial onset of claudication pain and the maximal walking distance either in total or between bouts of walking.

Cardiopulmonary fitness assessment

Patients with PAD have lower cardiorespiratory fitness (CRF) compared to age-matched controls, which is closely related to their walking performance [56,57]. Cardiopulmonary exercise testing (CPET) is not mandatory in all PAD patients prior to SET. It may be suggested on a case by case basis depending of perceived patient risk. If deemed necessary, CPET should be assessed prior and following exercise interventions. It should be ECG monitored to detect ST-depression suggestive for severe coronary artery disease. Blood pressure should also be monitored at rest and during the CPET. Outcome measures of interest include peak oxygen uptake ($\dot{V}O_{2peak}$) and ventilatory thresholds. CPETs are primarily performed on a treadmill in other diseases, however, it may be inappropriate in PAD because of peripheral pain causing termination of exercise prior to criteria for $\dot{V}O_{2peak}$ being attained. Thus, cycling may be considered as an appropriate alternative and the primary mode. Protocols include an 'unloaded' phase, followed by ramping between 10–25 watts depending on patient ability. Patients should be asked to work until volitional exhaustion [58].

Muscle strength assessment

The presence of PAD is associated with impaired lower extremity muscle strength and function [59], which is associated with high prevalence of frailty and sarcopenia [60]. Muscle strength and function should therefore be assessed before and after SET.

There is heterogeneity in how muscle strength and function are assessed. Muscle isokinetic strength and endurance can be assessed via isokinetic dynamometry, which is a chair device that patients sit on and the specific joint is tested in an appropriate position with the dynamometer attached to the limb. Patients push against the dynamometer as it provides resistance to maintain a set speed. Isokinetic dynamometry has demonstrated good reliability at the ankle (reliability coefficients ranging from 0.77 to 0.96) [61]. Testing can be done in various joints, including ankle, knee, and hip, in various planes such as extension and flexion. As isokinetic dynamometry assessment dynamometry includes specialized equipment it may not be practical or convenient to assess patients using this device. As an alternative, a simple hand-grip assessment or a short physical performance battery (SPPB) which includes a 4-meter walk test, a sit-to-stand chair test, and a standing balance test, should be used [62]. A recent study showed that the sit-to-stand is a validated test to estimate muscle power in patients with symptomatic PAD [63]. Interestingly, muscle power assessed by the sit-to-stand test was related to overall functional performance prior and following SET [63].

Self-reported functional impairment and quality of life assessment

In addition to objective assessment of functional impairment, a subjective (self-reported) evaluation of walking abilities and health-related quality of life (HRQoL) should be incorporated to have a complete assessment of the functional status of the patient [64-66]. Following exercise interventions, assessing HRQoL is usually used to determine if an objective improvement in functional performance is also perceived by the patient in its daily life. Table 1 reports the most used subjective tools used for walking ability and HRQoL assessment in patients with PAD. PAD trials used a wide

variety of questionnaires of patient reported outcomes measurements (PROMs) [64-66]. The most used are the short-form health 36 (SF-36), a generic questionnaire including physical and mental items related to health), and the Walking Impairment Questionnaire (WIQ), a PAD-specific questionnaire focusing on PAD and functional limitations. Studies have shown that HRQoL burden is greater in magnitude in patients with PAD than without PAD in CVD patients [67]. In the PARTNERS study, the SF36 Physical Component Summary of the combines PAD-other-CVD group was 46.3 ± 1.2 compared with 55.5 ± 1.1 in other-CVD group [67]. Cross-sectional studies show that in patients with PAD the degree of difficulty in walking distance and stair climbing are significantly related to HRQoL [68].

The ESVS VASCUNET and the International Consortium of Vascular Registries consensus statement recommended the Vascu-QoL6 as a primary assessment of PROMs in patients with symptomatic PAD [64].

Greater amounts of physical activity are associated with higher ratings of both perceived health and HRQoL, correlating objective health outcomes and life expectancy [69]. One of the most important factors linked to both subjective and objective health, across both cognitive and physical domains, is physical activity [70].

Exercise therapy in patients with PAD

Supervised exercise training

Supervised exercise training (SET) is considered among first-line therapies for patients with chronic and symptomatic PAD [3,66,71,72]. SET is safe and is usually conducted in the hospital setting [73]. Over the past 50 years, many PAD trials have reported the effectiveness of SET on walking distances in these patients. The most recent Cochrane meta-analysis showed that SET improves PFWD (82 m; 95% IC: 72 – 92)

and MWD (120 m; 95% IC 51 – 190) in patients with PAD [74]. Similar findings were observed in another meta-analysis [PFWD: 128 m (95% IC: 92 – 165); MWD: 180 m (95% IC: 130 – 238)] [75]. Although less well investigated or usually reported as a secondary outcomes, SET also improved functional status, gait pattern, self-reported walking ability and quality of life [63,66,74,76-80]. It is interesting to note that cardiac rehabilitation programs also increase walking distance, HRQoL, and physical activity in patients with symptomatic PAD, suggesting that other types of rehabilitation than SET are also useful [81].

Training modalities. There are different types of exercise training for patients with PAD, but the common aim is to improve HRQoL by increasing walking capacity and reducing the symptoms. In addition, exercise should aim to improve balance and muscle strength to promote independence and a reduced risk of falling in the long-term [33]. Treadmill and overground walking are the most common and recommended training modalities in patients with IC [66,72]. However, due to severe exercise-induced ischemia, low pain tolerance, the risk of falling and/or other co-morbidities, some patients are unwilling or unable to perform walking sessions. In addition to walking training, there are several other forms of training that are used, although much less frequently, in the rehabilitation of patients with PAD. A recent meta-analysis reported that other nonwalking training modes are also effective as traditional walking training in improving walking performance, whereas there was no clear evidence for changes in quality of life following exercise interventions. However, the authors concluded that the certainty of this evidence was judged to be low [82]. Different training modes include strength training of large muscle groups [83,84], cycling [85], pole striding [86,87], multimodal training [76,77,88-91] and training with an arm-crank ergometer

[58,92]. The beneficial effect of these training modalities can usually be described as large and even reach those of typical walking training [93]. However, the PFWD and the MWD have the tendency to be higher with walking training than with strength training when all studies are considered [82]. In contrast, self-reported ability to climb stairs (assessed by the Walking Impairment Questionnaire) is more improved following strength training (29.2% vs. 43.8% after 6 months) compared to walking training on the treadmill (39.6% vs. 43.8% after 6 months) [94]. Therefore, when walking is not an option, alternative training modalities might also be effective. These training modalities also elicit lower or no pain during exertion compared to walking, which might lead to higher rates of adherence.

Training frequency. Based on a previous meta-analysis, and shared by most of the studies and guidelines, the training frequency associated with greater improvements in walking distance is at least 3 times per week [95,96].

Training duration. Identifying an optimal training duration is difficult to elucidate, mainly due to differences in training modalities, frequencies, and intensities among studies. Current guidelines reported that optimal training duration ranges between 12 and 24 weeks [66,72,95]. The optimal training session duration has not been widely investigated. Additionally, in most studies, the total session duration is usually reported without specifying the actual time spent exercising. The literature shows that exercise sessions lasting 30 to 60 min were the most effective to improve walking performance [95,96].

Training intensity. In most studies, no clear distinction is made between symptom intensity (claudication pain scale) and exercise training intensity [based on heart rate (HR), oxygen uptake ($\dot{V}O_2$) or rate of perceived exertion (RPE) on Borg's scale: 6: "very very light"; 20: "maximal effort"] to monitor the exercise therapy.

First, the majority of trials used claudication pain severity to provide guidance during the training sessions. In PAD research, the claudication pain scale, an ordinal scale from 0 (no pain) to 4 (severe/maximal pain), is the most used tool. A distinction is made between walking training with and without muscle pain caused by ischemia. With regards to claudication pain intensity, international guidelines are heterogeneous [38,66,72]. The UK NICE guideline encourages people to exercise to the point of maximal pain [97], the American Heart Association guideline recommends moderate to moderate/severe claudication pain as tolerated [66], while an international consensus as well as the Australian guideline does not specify pain intensity for exercise dosage [98]. It has recently been shown that one-year home-based walking training performed at high-intensity pain was more effective than walking training performed at low-intensity for improving walking and functional performance in patients with PAD [99,100]. These findings indicate that claudication pain intensity may be a key factor for walking improvement in these individuals. In contrast, others have reported that improvements in walking performance may be obtained with less severe claudication pain during exertion [93]. According with recent findings, walking training with pain is not clearly superior to walking training without pain regarding changes in walking distances [101-104]. It can be assumed that walking training with moderate, low, or no pain is associated with higher compliance and therefore long-term maintenance of training or change in activity behavior [104]. However, larger studies

with a higher number of cases and longer duration, taking compliance into account, are needed for a conclusive statement [105].

Second, the optimal no/low pain-based exercise training intensity is understudied in these patients. Fassora et al. [106] recently reported that both training modality and exercise intensity should be considered when looking for the best results in walking performance and cardiorespiratory fitness. Notably, these results showed that walking at vigorous intensity (%HR_{peak}: 77-96, %$\dot{V}O_{2peak}$: 64-90, RPE: 14-17) induced the greatest improvement in MWD, while cycling and other non-walking modalities performed at vigorous intensity elicited the greatest improvements in cardiorespiratory fitness [106]. These findings suggest that both walking and cardiorespiratory capacities are desirable outcomes but that they need different exercise therapy programs [106]. Table 2 summarizes the main exercise prescription recommendations with some practical applications.

Home-based exercise training

In comparison with patients not undergoing exercise training, a home-based training (HBT) strategy resulted in a non-significant increase of MWD in a recent meta-analysis (mean difference: 136 m; 95% CI: -2 to 273 m; P = 0.05) [107]. When comparing HBT with basic exercise advice, no improvement of MWD was observed in patients following a HBT strategy (mean difference: 39 m; 95% CI: -123.1 to 201.1 m; P = 0.64) [107]. Regarding PFWD, HBT led to a greater increase than exercise advice did (mean difference: 64.5 m; 95% CI: 14.1 to 114.8 m; P = 0.01) [107]. In comparison with HBT, SET was more effective in improving MWD (mean difference: 139 m; 95% CI: 45 to 232 m; P = 0.004) and PFWD (mean difference: 84 m; 95% CI: 25 to 143 m; P = 0.005) [107].

Considering the effect of monitoring in HBT, no difference in the change of MWD and PFWD were observed between monitored HBT and SET (mean difference in MWD: 8 m; 95% CI: -81 to 97 m; P = 0.86; mean difference in PFWD: 43 m; 95% CI: -29 to 114 m; P = 0.24) [107]. The equality in training efficacy of monitored HBT and SET emphasizes the role of monitoring in HBT programs. Apart from regular on-site visits or phone calls, patients' activity diaries or log books have been used for HBT monitoring [107]. Additional tools of self-monitoring, such as wrist-worn activity trackers with smartwatch-like functions or smartphone accelerometer applications have been assessed, however, it still needs to be clarified, which modality is most appropriate for HBT in patients with IC [54].

The effect of training on patients' daily physical activity was assessed by several studies implementing pedometer- and accelerometer-measurements. A network meta-analysis demonstrated improvements of daily physical activity in HBT to a similar extent as it was observed in patients undergoing SET [108].

Focusing on quality of life, most studies reported improvements in patients undergoing HBT [107]. In comparison with SET, improvements of individual SF-36 measures (pain and social functioning) and Walking Impairment Questionnaire measures (distance) were less pronounced in patients undergoing HBT [107]. In addition, HBT improves measures of self-efficacy for walking, satisfaction with functioning, pain acceptance and social functioning in patients with claudication [109]. Follow-up data of patients who had undergone HBT suggest sustaining improvements in measures of quality of life, functional and walking capacity after termination of the active training intervention [110,111].

Safety of HBT was analyzed in a systematic review including 27 studies, which reported a cardiac event rate of 1 per 49,270 and a non-cardiac event rate of one per

147,810 [112]. Event rates of HBT were lower than event rates reported for SET (HBT vs. SET: cardiac 1:49,270 vs. 1:13,788; non-cardiac: 1:147,810 vs. 1:41,363) [112]. Regarding overall mortality, retrospective data suggest a reduction of long-term mortality in patients undergoing HBT [113]. Comparing HBT with SET, overall mortality rates do not differ between patients undergoing HBT and patients following a SET program [114].

The results of the reported meta-analyses and reviews should be viewed with caution according to a moderate to low quality of evidence [107,114,115].

Due to the limited availability and utilization of SET programs, HBT programs serve as alternative training modality for patients with IC [116-119].

Data on gender-specific differences in the efficacy of HBT are inconsistent [120,121]. In women the efficacy of HBT appears to be more strongly related to the individual training intensity than in men [122]. Regarding co-morbidities, HBT seems to be less effective in patients with diabetes with respect to the potential increase in walking capacity [123]. In elderly patients, HBT potentially improves quality of life to a similar extent as revascularization does [124].

Considering the frequency of HBT training, 3 weekly sessions was the most commonly used strategy (range: 3 weekly sessions to daily sessions) [107]. For initiation, patients should start with a duration of 20 minutes per session, progressively increasing the duration to 60 minutes per session. HBT can be performed outside, around a track or in a hallway at a self-selected pace [49,125].

Mechanisms of response to exercise in PAD

Exercise represents a major challenge to whole-body homeostasis provoking widespread perturbations in numerous cells, tissues, and organs that are caused by or

are in response to the increased bio-energetic activity of the contracting skeletal musculature [126]. The exercise training-induced increase in functional capacity and the concomitant amelioration of diverse maladaptive responses that ultimately reduce claudication symptoms in patients with PAD, are underpinned by several inter-dependent physiological, metabolic, and mechanical mechanisms. After several months of exercise training there is extensive remodeling of the vascular system, and although direct sampling of the vasculature in humans *in vivo* is limited, the trained musculature provides a valid proxy, being the primary tissue involved in training adaptation [126]. The dynamic biochemical and mechanical environment around blood vessels arising from the forces provoked during skeletal muscle contractile activity (i.e., shear stress and passive stretch), as well as signals stimulated by the increases in muscle energetic demand (i.e., increases in AMP concentration, reduced oxygen delivery) activate several intracellular signaling pathways responsible for promoting a regulatory network governing the transcriptional control of mitochondrial biogenesis and respiratory function [127] along with enhanced expression of pro-angiogenic factors [128] (Figure 2).

Over time, this results in the initiation of capillary growth and a proliferation in the number of arterioles. Such structural remodeling is driven by a complex and often-redundant sequence of events that include nitric oxide, and prostaglandins. Indeed, mechanical, neural, and humoral factors, including those released from contracting skeletal muscle, have all been implicated in the remodeling response, with the vascular endothelial growth factor (VEGF) signaling pathway and downstream targets ultimately driving skeletal muscle capillary expansion [128]. Muscle activity increases VEGF in the muscle interstitium and subsequently acts on the VEGF receptors, VEGFR-1 and VEGFR-2 on the capillary endothelium, activating multiple downstream pathways via

signaling intermediates such as mitogen activated protein kinases (MAPK), phosphatidylinositol-3-Kinase [129]. The time-course of remodeling varies and is largely a function of the blood vessel size, and while many of these adaptations are restricted to the vascular beds of the trained muscles, improved endothelial function appears to be a whole-body response to exercise training, even in individuals with PAD.

VEGF expression is partially regulated by the hypoxia-inducible factor-1α (HIF-1α) but recently the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) has emerged as an important candidate in the exercise-induced angiogenic response. PGC-1α regulates the coordinated expression of mitochondrial proteins encoded in the nuclear and mitochondrial genomes and is rapidly induced after exercise. This protein has been called the “master regulator” of mitochondrial biogenesis, and controls various aspects of muscle oxidative phenotype, while transducing and integrating physiological signals governing metabolism, differentiation, and cell growth, and suppressing a broad inflammatory response [127]. Thus, the PGC-1 coactivators serve as a central component of the transcriptional regulatory circuitry that coordinates the energy-generating functions of mitochondria in accordance with the metabolic demands imposed by exercise training undertaken by patients with PAD.

Exercise and revascularization

Current guidelines recommend SET programs as an initial treatment modality for patients with IC [3,130]. Revascularization is recommended for patients with IC when they do not respond to initial exercise and medical therapies [131]. However, the role

of revascularization as an initial treatment option alone or as an upstream adjunct to SET in patients with IC remains controversial.

Several trials have compared endovascular therapies with or without SET versus SET alone as an initial treatment strategy for patients with PAD with IC and reported inconsistent results [132-135].

The relevant aspect of exercise training may be the reduction of the inflammatory process in patients with PAD. In a recent trial, reactive oxygen species (ROS) formation was measured using the luminol analogue L-012 for patients with IC, randomized either to home-based training alone or in addition to endovascular therapy (EVT) [136]. Follow-up was performed after 3 months. ROS production after NOX2 (NAPDH oxidase 2) stimulation showed a significant reduction in both groups at follow-up (EVT group: P = 0.002, exercise group: P = 0.019), with a higher relative reduction in ROS in the EVT group than in the exercise group (P = 0.014).

The data regarding the benefit of SET alone or in combination with EVT or EVT alone are rare. A robust evaluation of existing data comes from a meta-analysis comparing the different treatment approaches [137]. A total of 987 patients from 7 randomized control trials (constituting 9 total comparison arms) with a median follow-up duration of 12.4 months (range 10 to 18 months) were enrolled. Of these, 530 patients were randomized to EVT versus SET alone, and 457 patients to EVT plus SET versus SET alone [137].

For the effect of EVT alone versus SET alone (5 comparison arms) a random effects model showed no significant difference in the MWD (standardized mean difference (SMD): -0.11 (95% CI: -0.59 to 0.36); P = 0.64) on follow-up between the 2 groups, neither for the PFWD, need for revascularization or amputation.

On pooled analysis, the ABI was significantly higher among participants that underwent EVT alone as compared with SET only (SMD: 0.64; 95% CI: 0.38 to 0.90, P < 0.0001; weighted mean difference (WMD): 0.15; 95% CI: 0.10 to 0.19, P < 0.0001).

On pooled analysis using random effects models, EVT plus SET (4 comparison arms) was associated with significantly higher MWD on follow-up compared with SET alone (SMD: 0.79; 95% CI: 0.18 to 1.39, P = 0.01), as well as significantly higher ABI on follow-up compared with SET only (SMD: 0.62; 95% CI: 0.33 to 0.91; WMD: 0.14; 95% CI: 0.10 to 0.17, P < 0.0001).

The combination of EVT plus SET was also associated with a significantly lower risk of revascularization or amputation on follow-up (3.5% vs. 17.3%, OR: 0.19; 95% CI: 0.09 to 0.40, P < 0.0001). The corresponding number needed to treat was 8 patients (95% CI: 6 to 12). PFWD was reported in 2 studies with no difference between the 2 groups in random effects pooled analysis [137]. However, EVT alone is not associated with better outcomes than SET [137,138].

Among patients with stable PAD and IC, compared with SET alone, endovascular revascularization in combination with SET is associated with significantly improved outcomes.

Effect of exercise on health-related quality of life and cognitive function

Poor HRQoL is associated with higher rate of mortality in patients with PAD [139]. Randomized controlled trials have shown that exercise training versus usual medical care in patients with PAD not only improves the perceived walking distance and speed, but also the functional status as measured by specific impairment questionnaires, as the WIQ. When compared to controls, patients who complete any form of exercise

training significantly improve their WIQ speed (mean difference: 9.60; 95% CI: 6.98 to 12.23, P ≤ 0.001); WIQ distance (mean difference: 7.41; 95% CI: 4.49 to 10.33, P ≤ 0.001) and WIQ stair-climbing (mean difference: 5.07; 95% CI: 3.16 to 6.99, P ≤ 0.001) [78]. In addition, more general HRQoL evaluation scores (Short-Form Physical Component Summary) also showed significant improvement following exercise therapy (mean difference: 1.24; 95% CI: 0.48 to 2.01) [78]. Most of the studies showed that 3- [140-142], or 6/12-month [87,94,143] exercise training improves patient's perception of physical HRQoL, with lesser effects on mental HRQoL. However, in the current literature, findings are inconsistent [74,78,144] and other studies did not find the same effects [145-147]. It is interesting to note that the improvement in general HRQoL scores (as SF-36) were mainly predicted by physical functional markers, such as the distance covered during a 6MWT (6MWD) and the history of stumbling [148]. These data indicate that greater improvements in physical function following exercise therapy are expected to have greater improvements in self-perceived HRQoL [148]. It has recently been showed that improvements in 6MWD following SET are predictive of augmentations in general HRQoL in patients with PAD [89]. Interestingly, changes in treadmill performance, which are less representative of functional walking [45], were not related to improvements in HRQoL [89].

Regular physical activity is also known to improve cognitive functioning and brain health across the lifespan [149]. Cross-sectional and experimental studies show that greater amounts of physical activity are linked to better cognitive function in adults, with the best performances for exercise programs that are structured, individualized, higher intensity, longer duration, and multicomponent [150]. These results support a dose-dependent neuroprotective relationship between physical exercise and cognitive performance. Physical exercise interventions aimed at improving brain health through

neuroprotective mechanisms show promise for preserving cognitive performance [150]. Scientific evidence based on functional and neuroimaging approach has demonstrated that this relation could be mediated by improved brain integrity, including adaptations in cerebral blood flow, volume and white matter integrity [151].

Patient education

All patients with PAD should be offered oral and written information about their disease so they can share decision-making and understand what they can do to help manage their condition. The role of exercise should be clearly explained, and patients should be supported to exercise regularly (assuming no contraindications). The impact of patient education regarding exercise is probably dependent on several factors, including the specific information that is provided, the timing and mode of delivery, and the nature of any interventions that are delivered concomitantly (e.g., SET). Patient education in the form of brief exercise advice, when delivered in isolation, confers little benefit and results in minimal improvement in individuals' walking distances [152]. Structured education programs, on the other hand, may have greater potential to improve exercise behavior and walking distances by building the knowledge and skills of patients to enable them to successfully self-manage their condition [153]. Key program features include: a structured evidence-based curriculum that includes content on the nature of the condition and the role of exercise; delivery by trained educators; and embedded quality assurance processes [153].

A systematic review by Abaraogu et al. [153] identified six studies (1,087 participants) that had investigated the effects of structured education for people with PAD and IC. The interventions varied widely, but all included education sessions, exercise prescription, and behavior change techniques. Four trials reported improvements in

walking ability in intervention versus control comparisons [153]. Effects on physical activity and quality of life were mixed. Overall, the evidence was inconclusive and more rigorous trials are needed that include a clear and complete description of the education intervention. Participant feedback from three studies highlights intervention features that may be important for improving physical activity: providing information about PAD/IC and exercise; providing encouragement and support with self-monitoring; and having group interaction while allowing space for individual discussion [153].

Three other trials have tested exercise programs that had an educational component in patients with PAD [154-156]. The GOALS trial [155] randomized 194 participants either to a group-mediated cognitive behavioral intervention or an attention control group. The intervention consisted of group meetings with a facilitator once weekly for 6 months. Discussion topics included effective behavior change methods, self-monitoring, exercising in cold weather, managing leg pain during exercise, and overcoming other obstacles to exercise adherence. At the 6-month follow-up, the intervention group achieved a 53.5 meters greater increase in 6MWD compared with the control group. Next, the HONOR trial [156] tested the efficacy of telephone coaching combined with a wearable activity monitor and showed no improvement in 6MWD at the 9-month follow-up. Finally, the MOSAIC trial explored the effect of a physiotherapist-delivered motivational interviewing intervention in 190 people with PAD and IC [154]. A statistically significant mean difference of 16.7m in 6MWD was observed at 3 months follow-up compared with usual care control [154]. The contrasting results of these trials indicate that exercise programs that include education are more likely to be successful if they include periodic visits to a medical center to meet with a coach or include tailored behavior change components.

Gender and exercise

Prevalence of PAD in women is similar to men at all ages [157,158]. However, women are more likely to have asymptomatic PAD and less likely to report IC [159]. Decreased detection and subsequent intervention may then result in a higher proportion of women with severe disease and chronic limb-threatening ischemia. Further, women who undergo revascularization tend to be older and have more severe PAD compared to men, and these factors can affect outcomes of procedures adversely [160]. Contradictory results exist on women with PAD and mortality rates [161-163]. Population studies suggest a trend towards higher mortality rates in women with lower ABI [162].

Exercise performance has been used to suggest that women decline faster in terms of functional ability once PAD is established. However, this difference may in fact merely be due to the smaller muscles in the calves of women [164]. McDermott et al. [165] showed that at 4 years of follow-up, women were more likely to become unable to walk for 6 min continuously than men, more likely to develop mobility disability, had faster declines in walking velocity, and the distance achieved in the 6-min walk was less. However, these apparent sex differences in functional decline were attenuated after additional adjustment for baseline calf muscle area, and so may be attributable to smaller baseline calf muscle area in women. Interestingly poorer leg strength is associated with increased mortality in men, but not in women, with PAD [164].

The data on the efficacy of exercise rehabilitation in women with PAD compared to men are scarce. What is known, however, is that women with IC seem to have a poorer response to exercise rehabilitation, smaller changes in PFWD and MWD following three months of exercise than men (Δ 280 meters for men vs Δ 220 meters for women;

P = 0.04) [166]. This is particularly so in those with diabetes [120]. Reduced blood volume expansion and slower oxygen kinetics occur in the calf musculature during exercise in women with PAD with IC [167]. Further, recent data showed that this poor response to exercise in women with IC and diabetes was not related to where the intervention was performed, being impaired both in a supervised exercise class and a home exercise setting [120]. This poorer response to exercise was also demonstrated in the EXITPAD study, which showed that women with IC, independent of confounding factors including diabetes, benefit less from supervised exercise and have significantly lower MWD after 12 months. Higher level of metabolic syndrome presents in postmenopausal women compared with similarly aged men, may contribute to this [166]. On the contrary, it has recently been shown that multimodal SET (combining strengthening of lower limbs and Nordic walking) significantly improves walking performance (treadmill and overground) in women and men, with no difference between groups [91,168]. Although not significant, it is interesting to note that women had greater improvements (i.e., delta) than men [91].

The clinical implication is that women with IC may respond less well to current exercise interventions and either need a greater ‘dose’ of exercise, or another intervention separate or in combination with exercise, to obtain similar improvements in IC as that seen in men with exercise alone.

Situation in Europe

Despite of the large body of evidences highlighting benefits, SET is underused and its availability and adherence is low [116-118,169-172]. To note, the rate of clinicians referred a patient for SET in very low [116]. The reasons and barriers for not

participating in SET programs are lack of facilities, feeling worse, costs, time, lack of motivation, and comorbidities [116,118,169].

The situation with SET in Europe varies from country to country. A recent European survey showed that supervised exercise programs exist in Austria, Belgium, Czech Republic. France, Germany, Italy, Sweden, Switzerland, and United Kingdom [173]. However, SET is reimbursed by the health insurance only in Austria, Belgium, France, Germany, Sweden, and Switzerland [173]. In the United Kingdom, SET programs are funded by the National Health Service and United Kingdom. In contrast, SET is not reimbursed in Czech Republic, Italy, and it even does not exist for patients with PAD in Denmark, Greece, Ireland, Poland, Serbia, Slovakia, Slovenia, or Ukraine [173]. Similarly, the structured home-based exercise program is not routinely present in European countries [173].

Importantly, there is heterogeneity in form of SET in most of individual countries, with existence of individual programs or practice of each hospital or community [173]. They differ in respect of frequency, length and duration of training, type of exercise, as well as by supervised physician [173]. Mostly, the SET is coordinated by angiologist/vascular physician, but sessions are predominantly supervised by clinical exercise physiologists or physiotherapists. SET for patients with PAD is sometimes offered in cardiac rehabilitation centres. Training program duration is mostly 12 weeks or less than 12 weeks, with session duration 30-60 min. Most often used training modalities are combination of walking and resistance training, or walking training alone [173].

To standardize SET programs across Europe following steps include: 1) a more widespread availability of SET programs and standardized outcomes to assess their effectiveness; 2) a more defined harmonization of SET characteristics (establish

process of referral, supervision, coordination, selection of patients, SET protocols); 3) a health insurance reimbursement of costs; and 4) action to improve the public knowledge about SET benefits [173].

Gaps in evidence and further studies

Awareness and access to supervised exercise programs should be a field of further studies. Additionally, there are still many areas of insufficient or inconsistent evidence in the treatment of claudication with exercise therapy. We do not know the optimal therapy in terms of duration of the single walking session or intensity of training. We have few studies on the impact of no or low pain-based exercise and the data on gender differences are inconsistent. The combination of walking exercise with non-walking trainings has not been yet established. Also, we need more evidence to better understand the potential role of wearable monitoring during exercise interventions, and to evaluate on the efficacy of supportive interventions that can be used together with exercise therapy. For example, the effect of different hydration strategies used during exercise training needs more evidence. In a non-randomized study, Parodi et al. reported mean increase in treadmill walking from 100 meters to 535 meters in 131 patients, who were treated with hydration, determined as drinking at least 2000 mL of water during 24 hours for a period of 6 months and to ingest albumin and salt (3.5 g/day) [174]. Another area of future research should be dedicated to define best modalities to transition patients from supervised exercise programs to everyday life maintaining the beneficial effects. Finally, we need more research on how to measure the success in the exercise training treatment among patients in an accurate and reproducible way.

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