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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

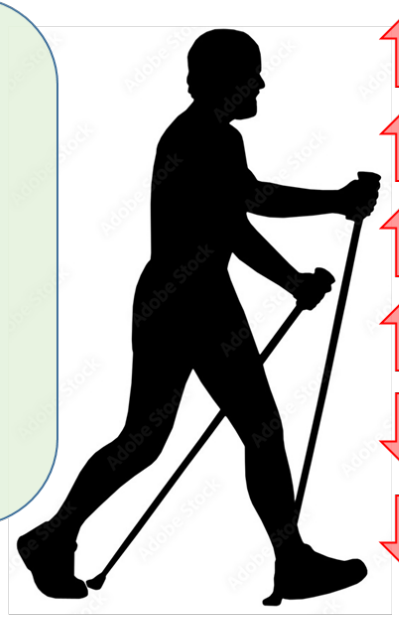
- Women and men with symptomatic chronic PAD
- Patients undergoing endovascular revascularisation

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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References

1. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J 2021;42:17-96.10.1093/eurheartj/ehaa605.
2. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. Lancet Glob Health 2019;7:e1020-e30.10.1016/S2214-109X(19)30255-4.
3. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.10.1093/eurheartj/ehx095.
4. Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. Vasa 2019;48:1-79.10.1024/0301-1526/a000834.
5. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. Circ Res 2015;116:1540-50.10.1161/CIRCRESAHA.114.303517.

6. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med 2002;136:873-83.
7. McDermott MM, Liu K, Ferrucci L, Tian L, Guralnik JM, Liao Y, et al. Decline in functional performance predicts later increased mobility loss and mortality in peripheral arterial disease. J Am Coll Cardiol 2011;57:962-70.10.1016/j.jacc.2010.09.053.
8. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. Circulation 1996;94:3026-49.10.1161/01.cir.94.11.3026.
9. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bull World Health Organ 1962;27:645-58.
10. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. Arch Intern Med 1999;159:387-92.10.1001/archinte.159.4.387.
11. Hiatt WR, Armstrong EJ, Larson CJ, Brass EP. Pathogenesis of the limb manifestations and exercise limitations in peripheral artery disease. Circ Res 2015;116:1527-39.10.1161/CIRCRESAHA.116.303566.
12. Seretny M, Colvin LA. Pain management in patients with vascular disease. Br J Anaesth 2016;117 Suppl 2:ii95-ii106.10.1093/bja/aew212.
13. Tew GA, Ouedraogo N, Nicolas G, Leftheriotis G, Copeland RJ, Abraham P. Impaired somatosensation in patients with isolated proximal-without-distal exercise-related lower-limb ischemia. Clin J Pain 2012;28:404-9.10.1097/AJP.0b013e3182340c01.

14. Hammad TA, Strefling JA, Zellers PR, Reed GW, Venkatachalam S, Lowry AM, et al. The Effect of Post-Exercise Ankle-Brachial Index on Lower Extremity Revascularization. JACC Cardiovasc Interv 2015;8:1238-44.10.1016/j.jcin.2015.04.021.
15. McDermott MM, Dayanidhi S, Kosmac K, Saini S, Slysz J, Leeuwenburgh C, et al. Walking Exercise Therapy Effects on Lower Extremity Skeletal Muscle in Peripheral Artery Disease. Circ Res 2021;128:1851-67.10.1161/CIRCRESAHA.121.318242.
16. Sheikh MA, Bhatt DL, Li J, Lin S, Bartholomew JR. Usefulness of postexercise ankle-brachial index to predict all-cause mortality. Am J Cardiol 2011;107:778-82.10.1016/j.amjcard.2010.10.060.
17. Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, et al. The assessment of endothelial function: from research into clinical practice. Circulation 2012;126:753-67.10.1161/CIRCULATIONAHA.112.093245.
18. Gokce N, Vita JA, Bader DS, Sherman DL, Hunter LM, Holbrook M, et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. Am J Cardiol 2002;90:124-7.10.1016/s0002-9149(02)02433-5.
19. Meredith IT, Currie KE, Anderson TJ, Roddy MA, Ganz P, Creager MA. Postischemic vasodilation in human forearm is dependent on endothelium-derived nitric oxide. Am J Physiol 1996;270:H1435-40.10.1152/ajpheart.1996.270.4.H1435.
20. Vita JA, Hamburg NM. Does endothelial dysfunction contribute to the clinical status of patients with peripheral arterial disease? Can J Cardiol 2010;26 Suppl A:45A-50A.10.1016/s0828-282x(10)71062-x.

21. Robbins JL, Jones WS, Duscha BD, Allen JD, Kraus WE, Regensteiner JG, et al. Relationship between leg muscle capillary density and peak hyperemic blood flow with endurance capacity in peripheral artery disease. J Appl Physiol (1985) 2011;111:81-6.10.1152/japplphysiol.00141.2011.
22. Beckman JA, Preis O, Ridker PM, Gerhard-Herman M. Comparison of usefulness of inflammatory markers in patients with versus without peripheral arterial disease in predicting adverse cardiovascular outcomes (myocardial infarction, stroke, and death). Am J Cardiol 2005;96:1374-8.10.1016/j.amjcard.2005.07.041.
23. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. Circulation 2005;112:976-83.10.1161/CIRCULATIONAHA.104.513085.
24. Vidula H, Tian L, Liu K, Criqui MH, Ferrucci L, Pearce WH, et al. Biomarkers of inflammation and thrombosis as predictors of near-term mortality in patients with peripheral arterial disease: a cohort study. Ann Intern Med 2008;148:85-93.10.7326/0003-4819-148-2-200801150-00003.
25. McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Liao Y, et al. Leg symptom categories and rates of mobility decline in peripheral arterial disease. J Am Geriatr Soc 2010;58:1256-62.10.1111/j.1532-5415.2010.02941.x.
26. Gardner AW, Forrester L, Smith GV. Altered gait profile in subjects with peripheral arterial disease. Vasc Med 2001;6:31-4.
27. Gommans LNM, Smid AT, Scheltinga MRM, Cancrinus E, Brooijmans FAM, Meijer K, et al. Prolonged stance phase during walking in intermittent claudication. J Vasc Surg 2017;66:515-22.10.1016/j.jvs.2017.02.033.

28. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453-61.10.1001/jama.292.4.453.
29. Gardner AW, Montgomery PS, Ritti-Dias RM, Forrester L. The effect of claudication pain on temporal and spatial gait measures during self-paced ambulation. Vasc Med 2010;15:21-6.10.1177/1358863X09106836.
30. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. J Vasc Surg 2010;52:340-7.10.1016/j.jvs.2010.03.005.
31. Koutakis P, Pipinos, II, Myers SA, Stergiou N, Lynch TG, Johanning JM. Joint torques and powers are reduced during ambulation for both limbs in patients with unilateral claudication. J Vasc Surg 2010;51:80-8.10.1016/j.jvs.2009.07.117.
32. Schieber MN, Hasenkamp RM, Pipinos, II, Johanning JM, Stergiou N, DeSpiegelaere HK, et al. Muscle strength and control characteristics are altered by peripheral artery disease. J Vasc Surg 2017;66:178-86 e12.10.1016/j.jvs.2017.01.051.
33. Gardner AW, Montgomery PS. Impaired balance and higher prevalence of falls in subjects with intermittent claudication. J Gerontol A Biol Sci Med Sci 2001;56:M454-8.
34. Gohil RA, Mockford KA, Mazari F, Khan J, Vanicek N, Chetter IC, et al. Balance impairment, physical ability, and its link with disease severity in patients with intermittent claudication. Ann Vasc Surg 2013;27:68-74.10.1016/j.avsg.2012.05.005.

35. Chaudru S, Jehannin P, de Mullenheim PY, Klein H, Jaquinandi V, Mahe G, et al. Using wearable monitors to assess daily walking limitations induced by ischemic pain in peripheral artery disease. Scand J Med Sci Sports 2019;29:1813-26.10.1111/sms.13511.
36. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, et al. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). J Am Coll Cardiol 2009;53:1056-62.10.1016/j.jacc.2008.09.063.
37. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation 2012;126:2890-909.10.1161/CIR.0b013e318276fbcb.
38. Treat-Jacobson D, McDermott MM, Beckman JA, Burt MA, Creager MA, Ehrman JK, et al. Implementation of Supervised Exercise Therapy for Patients With Symptomatic Peripheral Artery Disease: A Science Advisory From the American Heart Association. Circulation 2019;140:e700-e10.10.1161/CIR.0000000000000727.
39. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. Med Sci Sports Exerc 1991;23:402-8.
40. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. Vascular Clinical Trialists. Circulation 1995;92:614-21.10.1161/01.cir.92.3.614.

41. Hiatt WR, Rogers RK, Brass EP. The treadmill is a better functional test than the 6-minute walk test in therapeutic trials of patients with peripheral artery disease. Circulation 2014;130:69-78.10.1161/CIRCULATIONAHA.113.007003.
42. Nicolai SP, Viechtbauer W, Kruidenier LM, Candel MJ, Prins MH, Teijink JA. Reliability of treadmill testing in peripheral arterial disease: a meta-regression analysis. J Vasc Surg 2009;50:322-9.10.1016/j.jvs.2009.01.042.
43. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.10.1164/ajrccm.166.1.at1102.
44. Tew G, Copeland R, Le Faucheur A, Gernigon M, Nawaz S, Abraham P. Feasibility and validity of self-reported walking capacity in patients with intermittent claudication. J Vasc Surg 2013;57:1227-34.10.1016/j.jvs.2012.02.073.
45. McDermott MM, Guralnik JM, Criqui MH, Liu K, Kibbe MR, Ferrucci L. Six-minute walk is a better outcome measure than treadmill walking tests in therapeutic trials of patients with peripheral artery disease. Circulation 2014;130:61-8.10.1161/CIRCULATIONAHA.114.007002.
46. McDermott MM, Ades PA, Dyer A, Guralnik JM, Kibbe M, Criqui MH. Corridor-based functional performance measures correlate better with physical activity during daily life than treadmill measures in persons with peripheral arterial disease. J Vasc Surg 2008;48:1231-7, 7 e1.10.1016/j.jvs.2008.06.050.
47. McDermott MM, Guralnik JM, Tian L, Ferrucci L, Liu K, Liao Y, et al. Baseline functional performance predicts the rate of mobility loss in persons with peripheral arterial disease. J Am Coll Cardiol 2007;50:974-82.10.1016/j.jacc.2007.05.030.

48. Sandberg A, Cider A, Jivegard L, Nordanstig J, Wittboldt S, Back M. Test-retest reliability, agreement, and minimal detectable change in the 6-minute walk test in patients with intermittent claudication. J Vasc Surg 2020;71:197-203.10.1016/j.jvs.2019.02.056.
49. Gardner AW, Montgomery PS, Wang M. Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease. Vasc Med 2018;23:349-57.10.1177/1358863X18762599.
50. McDermott MM, Tian L, Criqui MH, Ferrucci L, Conte MS, Zhao L, et al. Meaningful change in 6-minute walk in people with peripheral artery disease. J Vasc Surg 2021;73:267-76 e1.10.1016/j.jvs.2020.03.052.
51. de Mullenheim PY, Chaudru S, Mahe G, Prioux J, Le Faucheur A. Clinical Interest of Ambulatory Assessment of Physical Activity and Walking Capacity in Peripheral Artery Disease. Scand J Med Sci Sports 2016;26:716-30.10.1111/sms.12512.
52. Abraham P, Noury-Desvaux B, Gernigon M, Mahe G, Sauvaget T, Leftheriotis G, et al. The inter- and intra-unit variability of a low-cost GPS data logger/receiver to study human outdoor walking in view of health and clinical studies. PLoS One 2012;7:e31338.10.1371/journal.pone.0031338.
53. Taoum A, Chaudru S, PY DEM, Congnard F, Emily M, Noury-Desvaux B, et al. Comparison of Activity Monitors Accuracy in Assessing Intermittent Outdoor Walking. Med Sci Sports Exerc 2021;53:1303-14.10.1249/MSS.0000000000002587.
54. Hochsmann C, Knaier R, Eymann J, Hintermann J, Infanger D, Schmidt-Trucksass A. Validity of activity trackers, smartphones, and phone applications

to measure steps in various walking conditions. Scand J Med Sci Sports 2018;28:1818-27.10.1111/sms.13074.

55. Le Faucheur A, Abraham P, Jaquinandi V, Bouye P, Saumet JL, Noury-Desvaux B. Measurement of walking distance and speed in patients with peripheral arterial disease: a novel method using a global positioning system. Circulation 2008;117:897-904.10.1161/CIRCULATIONAHA.107.725994.

56. Bauer TA, Brass EP, Nehler M, Barstow TJ, Hiatt WR. Pulmonary VO2 dynamics during treadmill and arm exercise in peripheral arterial disease. J Appl Physiol (1985) 2004;97:627-34.10.1152/japplphysiol.00612.2003.

57. Womack CJ, Hyman BA, Gardner AW. Prediction of peak oxygen consumption in patients with intermittent claudication. Angiology 1998;49:591-8.10.1177/000331979804900801.

58. Tew G, Nawaz S, Zwierska I, Saxton JM. Limb-specific and cross-transfer effects of arm-crank exercise training in patients with symptomatic peripheral arterial disease. Clin Sci (Lond) 2009;117:405-13.10.1042/CS20080688.

59. McDermott MM, Tian L, Ferrucci L, Liu K, Guralnik JM, Liao Y, et al. Associations between lower extremity ischemia, upper and lower extremity strength, and functional impairment with peripheral arterial disease. J Am Geriatr Soc 2008;56:724-9.10.1111/j.1532-5415.2008.01633.x.

60. Pizzimenti M, Meyer A, Charles AL, Giannini M, Chakfe N, Lejay A, et al. Sarcopenia and peripheral arterial disease: a systematic review. J Cachexia Sarcopenia Muscle 2020;11:866-86.10.1002/jcsm.12587.

61. Ritti-Dias RM, Basyches M, Camara L, Puech-Leao P, Battistella L, Wolosker N. Test-retest reliability of isokinetic strength and endurance tests in patients with intermittent claudication. Vasc Med 2010;15:275-8.10.1177/1358863X10371415.

62. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.
63. Lanzi S, Pousaz A, Calanca L, Mazzolai L. Sit-to-stand muscle power is related to functional performance at baseline and after supervised exercise training in patients with lower extremity peripheral artery disease. Eur J Vasc Endovasc Surg 2022;10.1016/j.ejvs.2022.12.029.
64. Arndt H, Nordanstig J, Bertges DJ, Budtz-Lilly J, Venermo M, Espada CL, et al. A Delphi Consensus on Patient Reported Outcomes for Registries and Trials Including Patients with Intermittent Claudication: Recommendations and Reporting Standard. Eur J Vasc Endovasc Surg 2022;64:526-33.10.1016/j.ejvs.2022.08.011.
65. Raja A, Spertus J, Yeh RW, Secemsky EA. Assessing health-related quality of life among patients with peripheral artery disease: A review of the literature and focus on patient-reported outcome measures. Vasc Med 2021;26:317-25.10.1177/1358863X20977016.
66. Treat-Jacobson D, McDermott MM, Bronas UG, Campia U, Collins TC, Criqui MH, et al. Optimal Exercise Programs for Patients With Peripheral Artery Disease: A Scientific Statement From the American Heart Association. Circulation 2019;139:e10-e33.10.1161/CIR.0000000000000623.
67. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New

Resources for Survival (PARTNERS) Program. Vasc Med 2008;13:15-24.10.1177/1358863X07084911.

68. Kim M, Kim Y, Ryu GW, Choi M. Functional Status and Health-Related Quality of Life in Patients with Peripheral Artery Disease: A Cross-Sectional Study. Int J Environ Res Public Health 2021;18:10.3390/ijerph182010941.

69. Franco OH, de Laet C, Peeters A, Jonker J, Mackenbach J, Nusselder W. Effects of physical activity on life expectancy with cardiovascular disease. Arch Intern Med 2005;165:2355-60.10.1001/archinte.165.20.2355.

70. Dostalova R, Stillman C, Erickson KI, Slepicka P, Mudrak J. The Relationship between Physical Activity, Self-Perceived Health, and Cognitive Function in Older Adults. Brain Sci 2021;11:10.3390/brainsci11040492.

71. Frank U, Nikol S, Belch J. 5 Conservative treatment for PAD - Risk factor management. Vasa 2019;48:1-12.10.1024/0301-1526/a000835.

72. Harwood A, Pymer S, Ingle L, Doherty P, Chetter I, Parmenter B, et al. Exercise training for intermittent claudication: a narrative review and summary of guidelines for practitioners. BMJ Open Sport & Exercise Medicine 2020;6:e000897.doi:10.1136/bmjsem-2020-000897.

73. Gommans LN, Fokkenrood HJ, van Dalen HC, Scheltinga MR, Teijink JA, Peters RJ. Safety of supervised exercise therapy in patients with intermittent claudication. J Vasc Surg 2015;61:512-8 e2.10.1016/j.jvs.2014.08.070.

74. Lane R, Harwood A, Watson L, Leng GC. Exercise for intermittent claudication. Cochrane Database Syst Rev 2017;12:CD000990.10.1002/14651858.CD000990.pub4.

75. Fakhry F, van de Luijtgaarden KM, Bax L, den Hoed PT, Hunink MG, Rouwet EV, et al. Supervised walking therapy in patients with intermittent claudication. J Vasc Surg 2012;56:1132-42.10.1016/j.jvs.2012.04.046.
76. Lanzi S, Boichat J, Calanca L, Aubertin P, Malatesta D, Mazzolai L. Gait changes after supervised exercise training in patients with symptomatic lower extremity peripheral artery disease. Vasc Med 2021;26:259-66.10.1177/1358863X20984831.
77. Lanzi S, Boichat J, Calanca L, Mazzolai L, Malatesta D. Supervised Exercise Training Improves 6 min Walking Distance and Modifies Gait Pattern during Pain-Free Walking Condition in Patients with Symptomatic Lower Extremity Peripheral Artery Disease. Sensors (Basel) 2021;21:7989.10.3390/s21237989.
78. Parmenter BJ, Dieberg G, Phipps G, Smart NA. Exercise training for health-related quality of life in peripheral artery disease: a systematic review and meta-analysis. Vasc Med 2015;20:30-40.10.1177/1358863X14559092.
79. Parmenter BJ, Dieberg G, Smart NA. Exercise training for management of peripheral arterial disease: a systematic review and meta-analysis. Sports Med 2015;45:231-44.10.1007/s40279-014-0261-z.
80. Schieber MN, Pipinos, II, Johanning JM, Casale GP, Williams MA, DeSpiegelaere HK, et al. Supervised walking exercise therapy improves gait biomechanics in patients with peripheral artery disease. J Vasc Surg 2019;71:575-83.10.1016/j.jvs.2019.05.044.
81. Siercke M, Jorgensen LP, Missel M, Thygesen LC, Moller SP, Sillesen H, et al. Cardiovascular Rehabilitation Increases Walking Distance in Patients With Intermittent Claudication. Results of the CIPIC Rehab Study: A Randomised

Controlled Trial. Eur J Vasc Endovasc Surg 2021;62:768-76.10.1016/j.ejvs.2021.04.004.

82. Jansen SC, Abaraogu UO, Lauret GJ, Fakhry F, Fokkenrood HJ, Teijink JA. Modes of exercise training for intermittent claudication. Cochrane Database Syst Rev 2020;8:CD009638.10.1002/14651858.CD009638.pub3.

83. Parmenter BJ, Raymond J, Dinnen P, Lusby RJ, Fiatarone Singh MA. High-intensity progressive resistance training improves flat-ground walking in older adults with symptomatic peripheral arterial disease. J Am Geriatr Soc 2013;61:1964-70.10.1111/jgs.12500.

84. Ritti-Dias RM, Wolosker N, de Moraes Forjaz CL, Carvalho CR, Cucato GG, Leao PP, et al. Strength training increases walking tolerance in intermittent claudication patients: randomized trial. J Vasc Surg 2010;51:89-95.10.1016/j.jvs.2009.07.118.

85. Sanderson B, Askew C, Stewart I, Walker P, Gibbs H, Green S. Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. J Vasc Surg 2006;44:119-27.10.1016/j.jvs.2006.03.037.

86. Collins EG, Edwin Langbein W, Orebaugh C, Bammert C, Hanson K, Reda D, et al. PoleStriding exercise and vitamin E for management of peripheral vascular disease. Med Sci Sports Exerc 2003;35:384-93.10.1249/01.MSS.0000053658.82687.FF.

87. Collins EG, Langbein WE, Orebaugh C, Bammert C, Hanson K, Reda D, et al. Cardiovascular training effect associated with polestriding exercise in patients with peripheral arterial disease. J Cardiovasc Nurs 2005;20:177-85.

88. Calanca L, Lanzi S, Ney B, Berchtold A, Mazzolai L. Multimodal Supervised Exercise Significantly Improves Walking Performances Without Changing

Hemodynamic Parameters in Patients With Symptomatic Lower Extremity Peripheral Artery Disease. Vasc Endovascular Surg 2020;54:605-11.10.1177/1538574420940090.

89. Lanzi S, Calanca L, Berchtold A, Mazzolai L. Improvement in 6-Minute Walking Distance after Supervised Exercise Training Is Related to Changes in Quality of Life in Patients with Lower Extremity Peripheral Artery Disease. J Clin Med 2021;10:3330.10.3390/jcm10153330.
90. Lanzi S, Calanca L, Borgeat Kaeser A, Mazzolai L. Walking performances and muscle oxygen desaturation are increased after supervised exercise training in Takayasu arteritis: a case report and a review of the literature. Eur Heart J Case Rep 2018;2:yty123.10.1093/ehjcr/yty123.
91. Ney B, Lanzi S, Calanca L, Mazzolai L. Multimodal Supervised Exercise Training Is Effective in Improving Long Term Walking Performance in Patients with Symptomatic Lower Extremity Peripheral Artery Disease. J Clin Med 2021;10:2057.10.3390/jcm10102057.
92. Treat-Jacobson D, Bronas UG, Leon AS. Efficacy of arm-ergometry versus treadmill exercise training to improve walking distance in patients with claudication. Vasc Med 2009;14:203-13.10.1177/1358863X08101858.
93. Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: Walking versus alternative exercise prescription as treatment for intermittent claudication. Atherosclerosis 2011;218:1-12.10.1016/j.atherosclerosis.2011.04.024.
94. McDermott MM, Ades P, Guralnik JM, Dyer A, Ferrucci L, Liu K, et al. Treadmill exercise and resistance training in patients with peripheral arterial disease with

and without intermittent claudication: a randomized controlled trial. JAMA 2009;301:165-74.10.1001/jama.2008.962.

95. Bulmer AC, Coombes JS. Optimising exercise training in peripheral arterial disease. Sports Med 2004;34:983-1003.10.2165/00007256-200434140-00004.

96. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA 1995;274:975-80.

97. NICE. The National Institute of Health and Care Excellence. Peripheral arterial disease: diagnosis and management clinical guideline [CG147]. National Institute for Health and Care Excellence. 2012;

98. Au TB, Golledge J, Walker PJ, Haigh K, Nelson M. Peripheral arterial disease - diagnosis and management in general practice. Aust Fam Physician 2013;42:397-400.

99. Hammond MM, Spring B, Rejeski WJ, Sufit R, Criqui MH, Tian L, et al. Effects of Walking Exercise at a Pace With Versus Without Ischemic Leg Symptoms on Functional Performance Measures in People With Lower Extremity Peripheral Artery Disease: The LITE Randomized Clinical Trial. J Am Heart Assoc 2022;11:e025063.10.1161/JAHA.121.025063.

100. McDermott MM, Spring B, Tian L, Treat-Jacobson D, Ferrucci L, Lloyd-Jones D, et al. Effect of Low-Intensity vs High-Intensity Home-Based Walking Exercise on Walk Distance in Patients With Peripheral Artery Disease: The LITE Randomized Clinical Trial. JAMA 2021;325:1266-76.10.1001/jama.2021.2536.

101. Mika P, Konik A, Januszek R, Petriczek T, Mika A, Nowobilski R, et al. Comparison of two treadmill training programs on walking ability and endothelial function in intermittent claudication. Int J Cardiol 2013;168:838-42.10.1016/j.ijcard.2012.10.003.

102. Novakovic M, Krevel B, Rajkovic U, Vizintin Cuderman T, Jansa Trontelj K, Fras Z, et al. Moderate-pain versus pain-free exercise, walking capacity, and cardiovascular health in patients with peripheral artery disease. J Vasc Surg 2019;70:148-56.10.1016/j.jvs.2018.10.109.
103. Perks J, Zaccardi F, Paterson C, Houghton JSM, Nickinson ATO, Pepper CJ, et al. Effect of high-pain versus low-pain structured exercise on walking ability in people with intermittent claudication: meta-analysis. Br J Surg 2022;109:686-94.10.1093/bjs/znac134.
104. Seed SA, Harwood AE, Sinclair J, Pymer S, Caldow E, Ingle L, et al. A Systematic Review of Exercise Prescription in Patients with Intermittent Claudication: Does Pain Matter? Ann Vasc Surg 2021;77:315-23.10.1016/j.avsg.2021.06.025.
105. Birkett ST, Sinclair J, Seed SA, Pymer S, Caldow E, Ingle L, et al. Effects of exercise prescribed at different levels of claudication pain on walking performance in patients with intermittent claudication: a protocol for a randomised controlled trial. Ther Adv Cardiovasc Dis 2022;16:17539447221108817.10.1177/17539447221108817.
106. Fassora M, Calanca L, Jaques C, Mazzolai L, Kayser B, Lanzi S. Intensity-dependent effects of exercise therapy on walking performance and aerobic fitness in symptomatic patients with lower-extremity peripheral artery disease: A systematic review and meta-analysis. Vasc Med 2022;27:158-70.10.1177/1358863X211034577.
107. Pymer S, Ibeggazene S, Palmer J, Tew GA, Ingle L, Smith GE, et al. An updated systematic review and meta-analysis of home-based exercise programs for individuals with intermittent claudication. J Vasc Surg 2021;74:2076-85 e20.10.1016/j.jvs.2021.03.063.

108. van den Houten MML, Hageman D, Gommans LNM, Kleijnen J, Scheltinga MRM, Teijink JAW. The Effect of Supervised Exercise, Home Based Exercise and Endovascular Revascularisation on Physical Activity in Patients With Intermittent Claudication: A Network Meta-analysis. Eur J Vasc Endovasc Surg 2019;58:383-92.10.1016/j.ejvs.2018.12.023.
109. Rejeski WJ, Spring B, Domanchuk K, Tao H, Tian L, Zhao L, et al. A group-mediated, home-based physical activity intervention for patients with peripheral artery disease: effects on social and psychological function. J Transl Med 2014;12:29.10.1186/1479-5876-12-29.
110. Fakhry F, Spronk S, de Ridder M, den Hoed PT, Hunink MG. Long-term effects of structured home-based exercise program on functional capacity and quality of life in patients with intermittent claudication. Arch Phys Med Rehabil 2011;92:1066-73.10.1016/j.apmr.2011.02.007.
111. McDermott MM, Guralnik JM, Criqui MH, Ferrucci L, Zhao L, Liu K, et al. Home-based walking exercise in peripheral artery disease: 12-month follow-up of the GOALS randomized trial. J Am Heart Assoc 2014;3:e000711.10.1161/JAHA.113.000711.
112. Waddell A, Seed S, Broom DR, McGregor G, Birkett ST, Harwood AE. Safety of home-based exercise for people with intermittent claudication: A systematic review. Vasc Med 2022;27:186-92.10.1177/1358863X211060388.
113. Lamberti N, Lopez-Soto PJ, Guerzoni F, Napoli N, Gasbarro V, Zamboni P, et al. Changes in exercise capacity and risk of all-cause mortality in patients with peripheral artery disease: a 10-year retrospective cohort study. Intern Emerg Med 2020;15:289-98.10.1007/s11739-019-02176-3.

114. Hageman D, Fokkenrood HJ, Gommans LN, van den Houten MM, Teijink JA. Supervised exercise therapy versus home-based exercise therapy versus walking advice for intermittent claudication. Cochrane Database Syst Rev 2018;4:CD005263.10.1002/14651858.CD005263.pub4.
115. Al-Jundi W, Madbak K, Beard JD, Nawaz S, Tew GA. Systematic review of home-based exercise programmes for individuals with intermittent claudication. Eur J Vasc Endovasc Surg 2013;46:690-706.10.1016/j.ejvs.2013.09.004.
116. Dua A, Gologorsky R, Savage D, Rens N, Gandhi N, Brooke B, et al. National assessment of availability, awareness, and utilization of supervised exercise therapy for peripheral artery disease patients with intermittent claudication. J Vasc Surg 2020;71:1702-7.10.1016/j.jvs.2019.08.238.
117. Haque A. Few UK vascular centres offer a fully NICE-compliant supervised exercise programme: a national audit. Ann R Coll Surg Engl 2021;10.1308/rcsann.2021.0126.
118. Harwood AE, Pymer S, Ibeggazene S, Ingle L, Caldow E, Birkett ST. Provision of exercise services in patients with peripheral artery disease in the United Kingdom. Vascular 2021;17085381211035259.10.1177/17085381211035259.
119. Makris GC, Lattimer CR, Lavida A, Geroulakos G. Availability of supervised exercise programs and the role of structured home-based exercise in peripheral arterial disease. Eur J Vasc Endovasc Surg 2012;44:569-75; discussion 76.10.1016/j.ejvs.2012.09.009.
120. Gardner AW, Parker DE, Montgomery PS, Blevins SM. Diabetic women are poor responders to exercise rehabilitation in the treatment of claudication. J Vasc Surg 2014;59:1036-43.10.1016/j.jvs.2013.10.058.

121. Manfredini R, Lamberti N, Manfredini F, Straudi S, Fabbian F, Rodriguez Borrego MA, et al. Gender Differences in Outcomes Following a Pain-Free, Home-Based Exercise Program for Claudication. J Womens Health (Larchmt) 2019;28:1313-21.10.1089/jwh.2018.7113.
122. Gardner AW, Parker DE, Montgomery PS. Sex-specific predictors of improved walking with step-monitored, home-based exercise in peripheral artery disease. Vasc Med 2015;20:424-31.10.1177/1358863X15596237.
123. Collins TC, Lunos S, Carlson T, Henderson K, Lightbourne M, Nelson B, et al. Effects of a home-based walking intervention on mobility and quality of life in people with diabetes and peripheral arterial disease: a randomized controlled trial. Diabetes Care 2011;34:2174-9.10.2337/dc10-2399.
124. Lamberti N, Malagoni AM, Ficarra V, Basaglia N, Manfredini R, Zamboni P, et al. Structured Home-Based Exercise Versus Invasive Treatment: A Mission Impossible? A Pilot Randomized Study in Elderly Patients With Intermittent Claudication. Angiology 2016;67:772-80.10.1177/0003319715618481.
125. McDermott MM, Polonsky TS. Home-Based Exercise: A Therapeutic Option for Peripheral Artery Disease. Circulation 2016;134:1127-9.10.1161/CIRCULATIONAHA.116.023691.
126. Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. Cell 2014;159:738-49.10.1016/j.cell.2014.10.029.
127. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature 2008;454:463-9.10.1038/nature07206.
128. Hoier B, Hellsten Y. Exercise-induced capillary growth in human skeletal muscle and the dynamics of VEGF. Microcirculation 2014;21:301-14.10.1111/micc.12117.

129. Egginton S. Invited review: activity-induced angiogenesis. Pflugers Arch 2009;457:963-77.10.1007/s00424-008-0563-9.
130. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;69:1465-508.10.1016/j.jacc.2016.11.008.
131. Heiss C, Olinic DM, Belch JJF, Brodmann M, Mazzolai L, Stanek A, et al. Management of chronic peripheral artery disease patients with indication for endovascular revascularization. Vasa 2022;10.1024/0301-1526/a000998.
132. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:1425-43.10.1161/CIR.0b013e31828b82aa.
133. Koelemay MJW, van Reijen NS, van Dieren S, Frans FA, Vermeulen EJG, Buscher H, et al. Editor's Choice - Randomised Clinical Trial of Supervised Exercise Therapy vs. Endovascular Revascularisation for Intermittent Claudication Caused by Iliac Artery Obstruction: The SUPER study. Eur J Vasc Endovasc Surg 2022;63:421-9.10.1016/j.ejvs.2021.09.042.
134. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, Cohen DJ, Reynolds MR, et al. Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease: six-month outcomes from the claudication:

exercise versus endoluminal revascularization (CLEVER) study. Circulation 2012;125:130-9.10.1161/CIRCULATIONAHA.111.075770.

135. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER, 3rd, Cohen DJ, Reynolds MR, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. J Am Coll Cardiol 2015;65:999-1009.10.1016/j.jacc.2014.12.043.
136. Koppe-Schmeisser F, Schwaderlapp M, Schmeisser J, Dopheide JF, Munzel T, Daiber A, et al. Influence of Peripheral Transluminal Angioplasty Alongside Exercise Training on Oxidative Stress and Inflammation in Patients with Peripheral Arterial Disease. J Clin Med 2021;10:10.3390/jcm10245851.
137. Pandey A, Banerjee S, Ngo C, Mody P, Marso SP, Brilakis ES, et al. Comparative Efficacy of Endovascular Revascularization Versus Supervised Exercise Training in Patients With Intermittent Claudication: Meta-Analysis of Randomized Controlled Trials. JACC Cardiovasc Interv 2017;10:712-24.10.1016/j.jcin.2017.01.027.
138. Fakhry F, Fokkenrood HJ, Spronk S, Teijink JA, Rouwet EV, Hunink MGM. Endovascular revascularisation versus conservative management for intermittent claudication. Cochrane Database Syst Rev 2018;3:CD010512.10.1002/14651858.CD010512.pub2.
139. Issa SM, Hoeks SE, Scholte op Reimer WJ, Van Gestel YR, Lenzen MJ, Verhagen HJ, et al. Health-related quality of life predicts long-term survival in patients with peripheral artery disease. Vasc Med 2010;15:163-9.10.1177/1358863X10364208.
140. Gardner AW, Parker DE, Montgomery PS, Scott KJ, Blevins SM. Efficacy of quantified home-based exercise and supervised exercise in patients with

intermittent claudication: a randomized controlled trial. Circulation 2011;123:491-8.10.1161/CIRCULATIONAHA.110.963066.

141. Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. J Vasc Surg 1997;25:312-8.10.1016/s0741-5214(97)70352-5.

142. Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF, et al. The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. J Intern Med 2002;252:448-55.10.1046/j.1365-2796.2002.01055.x.

143. Nicolai SP, Teijink JA, Prins MH, Exercise Therapy in Peripheral Arterial Disease Study G. Multicenter randomized clinical trial of supervised exercise therapy with or without feedback versus walking advice for intermittent claudication. J Vasc Surg 2010;52:348-55.10.1016/j.jvs.2010.02.022.

144. Guidon M, McGee H. Exercise-based interventions and health-related quality of life in intermittent claudication: a 20-year (1989-2008) review. Eur J Cardiovasc Prev Rehabil 2010;17:140-54.10.1097/HJR.0b013e3283377f08.

145. Guidon M, McGee H. One-year effect of a supervised exercise programme on functional capacity and quality of life in peripheral arterial disease. Disabil Rehabil 2013;35:397-404.10.3109/09638288.2012.694963.

146. Kakkos SK, Geroulakos G, Nicolaides AN. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: a randomised controlled trial. Eur J Vasc Endovasc Surg 2005;30:164-75.10.1016/j.ejvs.2005.03.011.

147. Savage P, Ricci MA, Lynn M, Gardner A, Knight S, Brochu M, et al. Effects of home versus supervised exercise for patients with intermittent claudication. J Cardiopulm Rehabil 2001;21:152-7.10.1097/00008483-200105000-00006.
148. Gardner AW, Montgomery PS, Wang M, Xu C. Predictors of health-related quality of life in patients with symptomatic peripheral artery disease. J Vasc Surg 2018;68:1126-34.10.1016/j.jvs.2017.12.074.
149. Erickson KI, Hillman C, Stillman CM, Ballard RM, Bloodgood B, Conroy DE, et al. Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. Med Sci Sports Exerc 2019;51:1242-51.10.1249/MSS.0000000000001936.
150. Kirk-Sanchez NJ, McGough EL. Physical exercise and cognitive performance in the elderly: current perspectives. Clin Interv Aging 2014;9:51-62.10.2147/CIA.S39506.
151. Gomez-Pinilla F, Hillman C. The influence of exercise on cognitive abilities. Compr Physiol 2013;3:403-28.10.1002/cphy.c110063.
152. Gommans LN, Saarloos R, Scheltinga MR, Houterman S, de Bie RA, Fokkenrood HJ, et al. Editor's choice--The effect of supervision on walking distance in patients with intermittent claudication: a meta-analysis. Eur J Vasc Endovasc Surg 2014;48:169-84.10.1016/j.ejvs.2014.04.019.
153. Abaraogu UO, Dall PM, Seenan CA. The Effect of Structured Patient Education on Physical Activity in Patients with Peripheral Arterial Disease and Intermittent Claudication: A Systematic Review. Eur J Vasc Endovasc Surg 2017;54:58-68.10.1016/j.ejvs.2017.04.003.
154. Bearne LM, Volkmer B, Peacock J, Sekhon M, Fisher G, Galea Holmes MN, et al. Effect of a Home-Based, Walking Exercise Behavior Change Intervention vs

Usual Care on Walking in Adults With Peripheral Artery Disease: The MOSAIC Randomized Clinical Trial. JAMA 2022;327:1344-55.10.1001/jama.2022.3391.

155. McDermott MM, Liu K, Guralnik JM, Criqui MH, Spring B, Tian L, et al. Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial. JAMA 2013;310:57-65.10.1001/jama.2013.7231.

156. McDermott MM, Spring B, Berger JS, Treat-Jacobson D, Conte MS, Creager MA, et al. Effect of a Home-Based Exercise Intervention of Wearable Technology and Telephone Coaching on Walking Performance in Peripheral Artery Disease: The HONOR Randomized Clinical Trial. JAMA 2018;319:1665-76.10.1001/jama.2018.3275.

157. Behrendt CA, Thomalla G, Rimmele DL, Petersen EL, Twerenbold R, Debus ES, et al. Prevalence of peripheral arterial disease, abdominal aortic aneurysm, and risk factors in the Hamburg City Health Study: A Cross-Sectional Analysis. Eur J Vasc Endovasc Surg 2023;10.1016/j.ejvs.2023.01.002.

158. Pabon M, Cheng S, Altin SE, Sethi SS, Nelson MD, Moreau KL, et al. Sex Differences in Peripheral Artery Disease. Circ Res 2022;130:496-511.10.1161/CIRCRESAHA.121.320702.

159. Behrendt CA, Sigvant B, Kuchenbecker J, Grima MJ, Schermerhorn M, Thomson IA, et al. Editor's Choice - International Variations and Sex Disparities in the Treatment of Peripheral Arterial Occlusive Disease: A Report from VASCUNET and the International Consortium of Vascular Registries. Eur J Vasc Endovasc Surg 2020;60:873-80.10.1016/j.ejvs.2020.08.027.

160. Detriche G, Guedon A, Mohamedi N, Sellami O, Cheng C, Galloula A, et al. Women Specific Characteristics and 1-Year Outcome Among Patients Hospitalized for Peripheral Artery Disease: A Monocentric Cohort Analysis in a

Tertiary Center. Front Cardiovasc Med 2022;9:824466.10.3389/fcvm.2022.824466.

161. Heidemann F, Kuchenbecker J, Peters F, Kotov A, Marschall U, L'Hoest H, et al. A health insurance claims analysis on the effect of female sex on long-term outcomes after peripheral endovascular interventions for symptomatic peripheral arterial occlusive disease. J Vasc Surg 2021;74:780-7 e7.10.1016/j.jvs.2021.01.066.

162. Hirsch AT, Allison MA, Gomes AS, Corriere MA, Duval S, Ershow AG, et al. A call to action: women and peripheral artery disease: a scientific statement from the American Heart Association. Circulation 2012;125:1449-72.10.1161/CIR.0b013e31824c39ba.

163. Kotov A, Heidemann F, Kuchenbecker J, Peters F, Marschall U, Acar L, et al. Sex Disparities in Long Term Outcomes After Open Surgery for Chronic Limb Threatening Ischaemia: A Propensity Score Matched Analysis of Health Insurance Claims. Eur J Vasc Endovasc Surg 2021;61:423-9.10.1016/j.ejvs.2020.11.006.

164. Singh N, Liu K, Tian L, Criqui MH, Guralnik JM, Ferrucci L, et al. Leg strength predicts mortality in men but not in women with peripheral arterial disease. J Vasc Surg 2010;52:624-31.10.1016/j.jvs.2010.03.066.

165. McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Kibbe M, et al. Women with peripheral arterial disease experience faster functional decline than men with peripheral arterial disease. J Am Coll Cardiol 2011;57:707-14.10.1016/j.jacc.2010.09.042.

166. Gommans LN, Scheltinga MR, van Sambeek MR, Maas AH, Bendermacher BL, Teijink JA. Gender differences following supervised exercise therapy in patients

with intermittent claudication. J Vasc Surg 2015;62:681-8.10.1016/j.jvs.2015.03.076.

167. Regensteiner JG, Bauer TA, Reusch JE, Brandenburg SL, Sippel JM, Vogelsong AM, et al. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. J Appl Physiol (1985) 1998;85:310-7.10.1152/jappl.1998.85.1.310.

168. Lanzi S, Pousaz A, Calanca L, Mazzolai L. Sex-based differences in supervised exercise therapy outcomes for symptomatic peripheral artery disease. Vasc Med 2023;1358863X221149454.10.1177/1358863X221149454.

169. Gupta T, Manning P, Kolte D, Smolderen KG, Stone N, Henry JG, et al. Exercise therapy referral and participation in patients with peripheral artery disease: Insights from the PORTRAIT registry. Vasc Med 2021;26:654-6.10.1177/1358863X211033649.

170. Harwood A, Smith G, Broadbent E, Cayton T, Carradice D, Chetter I. Access to supervised exercise services for peripheral vascular disease patients. Bull R Coll Surgeons Engl 2017;99:207–11.

171. Harwood AE, Smith GE, Cayton T, Broadbent E, Chetter IC. A Systematic Review of the Uptake and Adherence Rates to Supervised Exercise Programs in Patients with Intermittent Claudication. Ann Vasc Surg 2016;34:280-9.10.1016/j.avsg.2016.02.009.

172. Saxon JT, Safley DM, Mena-Hurtado C, Heyligers J, Fitridge R, Shishehbor M, et al. Adherence to Guideline-Recommended Therapy-Including Supervised Exercise Therapy Referral-Across Peripheral Artery Disease Specialty Clinics: Insights From the International PORTRAIT Registry. J Am Heart Assoc 2020;9:e012541.10.1161/JAHA.119.012541.

173. Lanzi S, Belch J, Brodmann M, Madaric J, Bura-Riviere A, Visona A, et al. Supervised exercise training in patients with lower extremity peripheral artery disease. Vasa 2022;51:267-74.10.1024/0301-1526/a001024.
174. Parodi JC, Fernandez S, Moscovich F, Pulmaria C. Hydration may reverse most symptoms of lower extremity intermittent claudication or rest pain. J Vasc Surg 2020;72:1459-63.10.1016/j.jvs.2020.05.066.