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CLINICAL PRACTICE GUIDELINE DOCUMENT

Editor's Choice – Exercise Therapy for Chronic Symptomatic Peripheral Artery Disease: A Clinical Consensus Document of the European Society of Cardiology Working Group on Aorta and 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 in the management of patients affected by lower extremity peripheral artery disease (PAD). Exercise therapy in this setting presents different modalities, and a structured programme provides optimal results. This clinical consensus paper is intended to promote and assist the set up of comprehensive exercise programmes and best advice for patients with symptomatic chronic PAD. Different exercise training protocols specific for patients with PAD are presented. Data on patient assessment and outcome measures are described based on the current best evidence. The document ends by highlighting supervised exercise programme access disparities across Europe and the evidence gaps requiring further research.

Keywords: Exercise training, Intermittent claudication, Physical activity, Quality of life, Vascular rehabilitation

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ABBREVIATIONS

6MWD	Six minute walking distance
6MWT	Six minute walk test
ABI	Ankle brachial index
AMP	Adenosine monophosphate
CV	Cardiovascular
CVD	Cardiovascular disease
ESVS	European Society for Vascular Surgery
GPS	Global positioning system
HR	Heart rate
HRQoL	Health related quality of life
IC	Intermittent claudication
MWD	Maximum walking distance
NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
PAD	Peripheral artery disease
PFWD	Pain free walking distance
RCT	Randomised controlled trial
RPE	Rate of perceived exertion
SET	Supervised exercise training
SF-36	Short Form Health 36
SMD	Standardised mean difference
VEGF	Vascular endothelial growth factor
WIQ	Walking Impairment Questionnaire

INTRODUCTION

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

In this consensus document, the acronym PAD will be used to indicate lower extremity peripheral artery disease. Peripheral artery disease is one of the most prevalent clinical presentations of atherosclerotic disease, affecting ~237 million people worldwide.[2] The first symptoms of PAD are usually related to walking impairment, and the 2017 European Society of Cardiology/European Society for Vascular Surgery (ESVS) guidelines on the management of PAD underscore 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 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 address this gap, the ESC Working Group on Aortic and Peripheral Vascular Diseases, the European Society of Vascular Medicine, and the ESVS joined in a collaborative effort aiming to provide a roadmap and guidance for the set up and implementation of exercise therapy programmes for patients with PAD (Supplementary Figure S1).

CONSENSUS STATEMENTS

1. For patients with PAD and exercise induced limb symptoms of vascular origin, supervised exercise programmes should be the first line treatment modality.
2. For patients with PAD undergoing revascularisation, supervised exercise programmes should be included as adjuvant therapy.
3. Supervised exercise programmes should ideally be coordinated by vascular physicians, and sessions should ideally be supervised by clinical exercise physiologists or physiotherapists.
4. Prior to the initiation of exercise training, a complete medical history, examination, and screening for contraindications should be investigated.
5. Measures of walking ability, functional status, and quality of life should be assessed at the beginning and end of the programme to determine the patient's response to exercise training. Clinical outcomes and patient experience should also be documented.
6. 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, combinations of exercise) should be performed.
7. The training frequency should be at least three times per week.
8. The training session duration should last a minimum of 30 minutes.
9. The training programme duration should last a minimum of three months.
10. Both claudication pain (A) and exercise intensity (B, based on common training intensity measures such as heart rate [HR] or the rate of perceived exertion [RPE] on Borg's scale) should be evaluated during training sessions:
    (A) The current consensus is that patients should exercise to moderate – high claudication pain based on strong evidence. However, some trials have recently demonstrated improvement in walking ability using a low or no pain approach. As claudication pain is a commonly cited barrier to exercise, the universal prescription of high pain exercise may lead to poor uptake of, and adherence to, exercise training programmes. A more flexible approach to exercise prescription may therefore be required, considering the patient's needs and preferences and what might achieve a high level of (long term) adherence.
    (B) Following a lead in period of low to moderate exercise intensity, a gradual progression to vigorous or high exercise intensity may be proposed if well tolerated by the patient.
11. If supervised exercise is not available or feasible, a structured community or home based exercise programme that includes behaviour change techniques should be proposed.
12. Supervised exercise programmes should include structured CVD and PAD risk factor reduction education and counselling. Smoking cessation should be a cornerstone of risk factor counselling.
13. Following initial exercise training (supervised or home based), patients are encouraged to sustain lifelong and high levels of regular physical activity.

PATHOPHYSIOLOGY OF INTERMITTENT CLAUDICATION AND FUNCTIONAL IMPAIRMENT

Intermittent claudication is characterised 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 symptomology was first defined as calf pain, discomfort, or fatigue appearing during exercise and forcing the patient to stop.[9] Typically, IC is relieved within two to five minutes of discontinuation of exertion.[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 localised in lower limb muscles other than the calf; 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 atherosclerotic 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] and skeletal muscle abnormalities[11] are proposed.

Potential exertional limb symptom driving mechanisms in addition to arterial obstruction and reduced perfusion include inflammation, vascular dysfunction, reduced microvascular flow, impaired angiogenesis, and altered skeletal muscle function[14–16] (Fig. 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, leucocyte 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 ischaemia and serve as a mechanism driving functional impairment.[21] Skeletal muscle ischaemia may drive local inflammation, exacerbating symptoms and altering muscle metabolism.[22–24]

Patients with PAD present with impaired walking endurance,[25] slower walking speed,[26–28] gait abnormalities,[26,27,29–31] poorer muscle strength,[32] and poorer balance[33,34] compared with individuals without PAD. They 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 AND FUNCTIONAL ASSESSMENT IN PERIPHERAL ARTERY DISEASE

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 programme to detect and diagnose PAD and assess disease severity (Fig. 2).[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, with a resting ABI $\geq$ 0.91. A post-exercise ankle systolic blood pressure drop $>$ 30 mmHg or a post-exercise ABI decrease $>$ 20% should be considered for a PAD diagnosis.[37] In patients with medial calcification (e.g., in patients with diabetes or chronic kidney disease) ABI measurement may not be possible because the arteries cannot be compressed by the cuff. In these cases, toe brachial index can be used as alternative assessment (the usual pathological threshold is $<$ 0.70).[3]

Walking distance assessment

Walking distance is considered an important clinical outcome for both patients and clinicians. Standardised

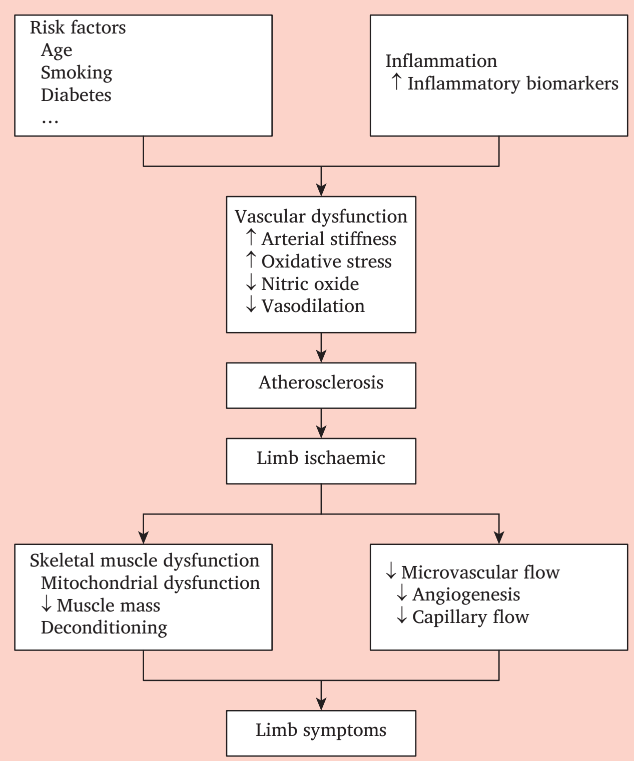

Figure 1. Pathophysiology of limb symptoms in peripheral artery disease

exercise testing should be used for the assessment of functional impairment in patients with PAD (Fig. 2).

Treadmill assessment. Treadmill testing should be performed with patients familiar with the treadmill and under reproducible conditions (i.e., avoiding exercise and alcohol prior to assessment). Patients should be asked to walk until maximum 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 or maximum 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/hour and a 2% slope increase every two minutes) or the Hiatt protocol (3.2 km/hour and a 3.5% slope increase every three minutes). Constant load treadmill tests are performed at a fixed speed of 2 – 4 km/hour and fixed gradient of 10 – 12%. Constant load protocols have less good reliability both for pain free walking distance (PFWD) and maximum 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 30 m with turning points marked by a cone. Patients are asked to walk at their own pace 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 or phrases used should be the same for every test performed to ensure test–retest reliability.[43] Further, there may be a learning effect so it is recommended that the best of two walks is recorded or the first test discounted.[44] Although treadmill based exercise tests can establish maximum walking capacity, there may be a poor correlation between treadmill outcomes, normal walking, and self reported walking distance.[45] On the other hand, compared with the treadmill test, the 6MWT has been shown to better represent daily life walking in patients with PAD.[46] The 6MWT is a well validated and low cost test. It has good reliability, with a correlation coefficient of 0.90 ($p < .001$) and a coefficient of variation of 8.9% with testing performed one to two weeks apart.[47] Changes in the 6MWT can be used to predict mortality and mobility loss in patients with PAD.[7,48] The minimum detectable changes (i.e., the statistical detectability of change beyond measurement error) in the 6MWT are represented by a change > 46 m.[49] The minimum clinically important difference (i.e., the clinical relevance or importance of the observed change from the patient's perspective) in the 6MWT in patients with PAD is represented by an improvement of eight[50] or nine metres[51] for small changes and 20[50] or 38 m[51] for large changes.

Connected devices. A measure of real life walking performance may be performed using global positioning systems (GPSs) or commercially available devices such as activity trackers, smart watches, and phones.[52] Research has shown that GPS recorders have good accuracy and reliability compared with known distances walked,[53,54] and measurement of step counts with mobile phones has been shown to be highly reliable even at low walking speeds.[55] Further, GPS recorded walking distances correlate well with treadmill walking distances.[56] Patients should be able to note the initial onset of claudication pain and the MWD either in total or between bouts of walking using the GPS system.

Muscle strength assessment

The presence of PAD is associated with impaired lower extremity muscle strength and function,[57] which is associated with a high prevalence of frailty and sarcopenia.[58] Muscle strength and function should therefore be assessed before and after supervised exercise training (SET; Fig. 2). There is heterogeneity in how muscle strength and function are assessed. Muscle isokinetic strength and endurance can be assessed by isokinetic dynamometry, which is a chair device that the patient sits 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

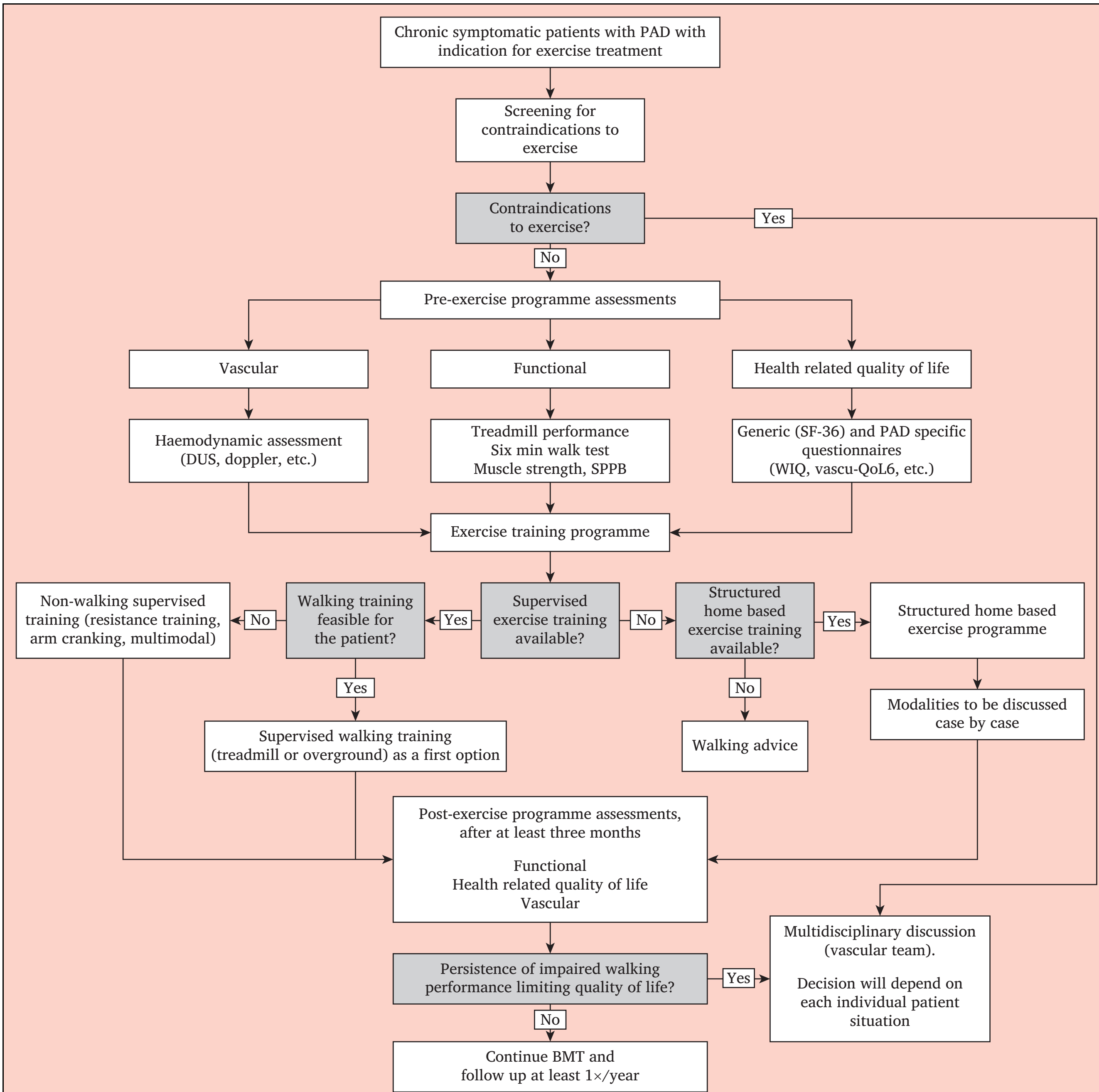

Figure 2. Algorithm of chronic symptomatic patients with PAD with indication for exercise treatment. PAD = peripheral artery disease; SPPB = short physical performance battery; BMT = best medical treatment (including pharmacological and non-pharmacological [lifestyle changes and exercise] approach); DUS = duplex ultrasound; SF-36 = Short form health 36 questionnaire; WIQ = Walking Impairment Questionnaire; Vascu-QoL6 = Vascular Quality of Life Questionnaire-6

speed. Isokinetic dynamometry has demonstrated good reliability at the ankle (reliability coefficients ranging from 0.77 to 0.96).[59] Testing can be done in various joints, including the ankle, knee, and hip, in various planes such as extension and flexion. As isokinetic dynamometry assessment includes specialised equipment, it may not be practical or convenient to assess patients using this device. As an alternative, the short physical performance battery that includes a 4 m walk test, a sit to stand chair test, and a standing balance test should be used.[60] A recent study showed that the sit to stand is a validated test to estimate muscle power in patients with symptomatic PAD.[61] Interestingly, muscle power assessed by the sit to stand test was related to overall functional performance prior to and following SET.[61]

Self reported functional impairment and quality of life assessment

To provide a complete assessment of the functional status of the patient a subjective (self reported) evaluation of walking abilities and health related quality of life (HRQoL) should be incorporated in addition to the

Table 1. Self reported evaluation of walking ability and health related quality of life (QoL) in patients with peripheral artery disease (PAD)

Questionnaire name	Type (functional or QoL)	Domains tested
EQ-5D	General	Mobility, self care, usual activity, pain and or discomfort, and anxiety and or depression
WHOQOL	General	Physical health, psychological health, social relationships, and environment
SEIQoL	General	Five dimensions chosen by the patient
VascuQOL	PAD specific	Pain, symptoms, activities, and social and emotional wellbeing
ICQ	PAD specific	Walking distance, walking speed, and stair climbing
PADQOL	PAD specific	Social relationship and interaction, self concept and feelings, symptoms and limitations in physical functioning, fear and uncertainty, and positive adaptation while living with PAD
SF-36	General	Physical function, bodily pain, general health, mental health, vitality, emotional wellbeing, and social functioning
NHP	General	Energy, emotional reaction, sleep, pain, social isolation, and physical mobility
Peripheral Artery Questionnaire (PAQ)	PAD specific	Physical limitations, symptoms, social function, treatment satisfaction, and quality of life
Walking Impaired Questionnaire (WIQ)	PAD specific	Physical limitations and symptoms
Walking Estimated Limitation Calculated by (WELCH)	PAD specific	Physical limitations and symptoms

PAD = Peripheral Artery Disease; QoL = Quality of Life; SF-36 = Short Form Health 36; EQ-5D = Euroqol five dimension; WHOQOL = World Health Organisation quality of life scale; SEIQoL = Schedule for the evaluation of individual quality of life; VascuQOL = Vascular quality of life questionnaire; ICQ = Intermittent claudication questionnaire; PADQOL = Peripheral arterial disease quality of life; NHP = Nottingham health profile

objective assessment of functional impairment (Fig. 2).[62–64] Following exercise interventions, HRQoL assessment is usually used to determine if an objective improvement in functional performance is also perceived by the patient in his or her daily life. Table 1 reports the most used subjective tools for walking ability and HRQoL assessment in patients with PAD. Trials used a wide variety of patient reported outcome measurement questionnaires.[62–64] 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 both PAD and CVD than in those with CVD alone.[65] In the PARTNERS study, the SF-36 Physical Component Summary of the combined PAD and CVD group was 46.3 $\pm$ 1.2 compared with 55.5 $\pm$ 1.1 in the CVD alone group.[65] Cross sectional studies show that in patients with PAD the degree of difficulty in walking distance and stair climbing are significantly related to HRQoL.[66] The European Society for Vascular Surgery VASCUNET and the International Consortium of Vascular Registries consensus statement recommended the Vascular Quality of Life Questionnaire 6 for the primary assessment of patient reported outcome measurements in patients with symptomatic PAD.[62]

Greater amounts of physical activity are associated with higher ratings of both perceived health and HRQoL, correlating with objective health outcomes and life expectancy.[67] One of the most important factors linked to both subjective and objective health, across both cognitive and physical domains, is physical activity.[68]

EXERCISE THERAPY IN PATIENTS WITH PERIPHERAL ARTERY DISEASE

Screening prior to exercise training participation

All patients should be medically screened before SET programme initiation (Fig. 2). A complete medical history and examination is suggested.[38] Patients with contraindications to exercise training (Table 2) should be excluded from SET until the relevant condition stabilises or is successfully treated. For patients with current or prior symptomatic cardiac disease (Table 3), referral for cardiology work up is recommended, including an exercise test to assess for evidence of exercise induced coronary ischaemia, to identify whether additional treatment for cardiac disease is required before proceeding with SET. Comorbidities (such as neurological and orthopaedic diseases leading to gait abnormalities) should be documented and how they may limit SET programme participation should be considered. After SET programme initiation, patients should continue to be closely monitored for changes in health status (e.g., any symptom or situation which may suggest an undiagnosed or incident cardiac condition, ischaemic limb pain at rest, and toe or foot wounds) that might necessitate interruption of the programme, at least temporarily.

Supervised exercise training

Supervised exercise training is considered among first line therapies for patients with chronic and symptomatic PAD

(Fig. 2).[3,64,69,70] Supervised exercise training is safe and is usually conducted in the hospital setting.[71] Over the past 60 years, many trials have reported the effectiveness of SET on walking distances in these patients.[72,73] The most recent Cochrane meta-analysis showed that SET improves PFWD (82 m; 95% confidence interval [CI] 72 — 92) and MWD (120 m, 95% CI 51 — 190).[74] Similar findings were observed in another meta-analysis (PFWD 128 m, 95% CI 92 — 165; MWD 180 m, 95% CI 130 — 238.[75] Although less well investigated or usually reported as a secondary outcome, SET also improved functional status, gait pattern, self reported walking ability, and quality of life.[64,74,76—82] It is interesting to note that cardiac rehabilitation programmes also increase walking distance, HRQoL, and physical activity in patients with symptomatic PAD, suggesting that types of rehabilitation other than SET may also be useful.[83] Finally, some vasoactive drugs such as cilostazol (phosphodiesterase type 3 inhibitor), pentoxifylline (xanthine derivative), bosentan, sildenafil, and others are claimed to increase walking capacity in patients with PAD.[84—87] However, the objective documentation of their effect to draw extensive conclusions is very limited.[84,88] More studies are needed to confirm the additive effect of drug therapies to supervised exercise.

Training modalities. There are different types of exercise training for patients with PAD, but the common aim is to improve walking capacity and reduce 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 (Fig. 2).[64,70] However, due to severe exercise induced ischaemia, low pain tolerance, the risk of falling, and or other comorbidities, 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 non-walking training modes are also as 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.[89] Different training modes include strength training of large muscle groups,[90,91] cycling,[92] pole striding,[93,94] multimodal training,[76,77,95—98] and training with an arm crank ergometer.[99,100] The beneficial effect of these training modalities can usually be described as large and even reach those of typical walking training.[101] However, the PFWD and the MWD tend to be higher with walking training than with strength training when all studies are considered.[89] In contrast, the self reported ability to climb stairs (assessed by the WIQ) is more improved following strength training (29.2% *vs.* 43.8% after six months) compared with walking training on the treadmill (39.6% *vs.* 43.8% after six months).[102] 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 with walking, which might lead to higher compliance rates.

Table 2. Absolute contraindications to exercise training

Acute coronary syndrome (within two days)
Unstable cardiac disease on interview or examination
Uncompensated heart failure
Acute thrombosis or recent embolism (pulmonary or systemic)
Active endocarditis
Acute myocarditis or pericarditis
Acute aortic dissection
Symptomatic severe aortic stenosis
Acute illness or fever
Uncontrolled hypertension ($\geq$ 180 mmHg systolic or $\geq$ 110 mmHg diastolic blood pressure at rest)
Uncontrolled sinus tachycardiac (resting heart rate > 120 beats/min)
Third degree atrioventricular block without pacemaker
Uncontrolled diabetes mellitus
Orthostatic drop in blood pressure (> 20 mmHg) with symptoms

Adapted from the American College of Sports Medicine (2022) *ACSM's Guidelines for Exercise Testing and Prescription*. 11th ed Guidelines for exercise testing and prescription. Philadelphia, PA: Lippincott Williams & Wilkins.

Table 3. Conditions requiring cardiological screening before exercise training participation

History of documented coronary artery disease
History of documented major dysrhythmia and atrial fibrillation
History of documented congenital heart disease
Any clinical sign or electrocardiogram suspicion for cardiac disease

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 three times per week.[103,104]

Training duration. Identifying an optimal training duration is difficult, mainly due to differences in training modalities, frequencies, and intensities among studies. Current guidelines have reported that the optimal training duration ranges between 12 and 24 weeks.[64,70,103] 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 — 60 minutes were the most effective for improving walking performance.[103,104]

Training intensity. In most studies, no clear distinction is made between symptom intensity (claudication pain scale) and exercise training intensity (based on HR, oxygen uptake [VO_2], or RPE on Borg's scale: 6, very very light; 20, maximum effort) to monitor the exercise therapy. The Borg scale is a subjective assessment tool used to measure an individual's perceived exertion or effort during physical activity. The scale assigns a numerical rating ranging from 6 to

20 to indicate the intensity of exertion experienced by the person.[105]

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 or maximum pain), is the most commonly used tool. A distinction is made between walking training with and without muscle pain caused by ischaemia. With regard to claudication pain intensity, international guidelines are heterogeneous.[38,64,70] The UK NICE guideline encourages patients to exercise to the point of maximum pain, the American Heart Association guideline recommends moderate to moderate or severe claudication pain as tolerated,[64] while an international consensus and the Australian guideline does not specify pain intensity for exercise dose.[106] Based on strong evidence,[64,73–75,104] the current consensus is that patients should exercise to moderate to high claudication pain to improve walking performance. Also, one year home based walking training performed at high intensity pain has been found to be more effective than walking training performed at low intensity for improving walking and functional performance in patients with PAD.[107,108] 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.[101] According to recent findings, walking training with pain is not clearly superior to walking training without pain regarding changes in walking distance.[109–112] It may be assumed that walking training with moderate, low, or no pain is associated with higher compliance and possibly long term maintenance of training or change in activity behaviour.[112] This indicates that a more flexible approach to exercise prescription may be required, considering the patient's needs and preferences, and what might achieve a high level of (long term) compliance. Larger studies with a higher number of cases and longer duration, taking compliance into account, are needed for a conclusive statement.[113]

Second, the optimal no or low pain based exercise training intensity is under studied in this population. Indeed, it is interesting to note that the claudication pain severity does not necessarily rely on common measures of exercise intensity.[78,114] For example, when performing vigorous intensity exercise, some patients may experience moderate to severe claudication pain, whereas others, suffer low levels of claudication only. Assuming that exercise intensity is a cornerstone determinant of the physiological response to training,[115] monitoring claudication pain only is limiting and prevents accurate comparison of exercise effectiveness in patients with PAD. This may also explain the large variability in the magnitude of improvements following exercise interventions.[64,103] Fassora *et al.*[78] 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 − 95, %VO_{2peak} 64 − 90, RPE $\geq$ 14[115]) induced the greatest improvement in MWD, while cycling and other non-walking modalities performed at vigorous intensity elicited the greatest improvements in cardiorespiratory fitness.[78] These findings suggest that both walking and cardiorespiratory capacities are desirable outcomes but that they need different exercise programmes.[78] However, it is important to note that training programmes should start with a lead in period performed at low to moderate exercise intensity and, if tolerated, gradually progress to vigorous exercise intensity. This approach may allow determination the patient's exercise response and tolerance, thereby reducing the risk of complications.

The monitoring of exercise intensity during a resistance training programme is mediated by the percentage of the one repetition maximum (1RM).[116] The determination of the 1RM plays a key role in the objective setting of an individualised resistance based programme.[116] Compared with direct assessment of the 1RM, the multiple RM assessments (such as 10RM, the maximum weight a person can lift for 10 repetitions) is considered to be a safe and well tolerated approach to evaluate muscle strength for a given muscle group in patients with CVD.[116] Following the multiple RM test, different prediction equations are available to estimate the 1RM.[117] As also used in the cardiac rehabilitation, a target exercise intensity of 30 − 70% of 1RM for the upper body and 40 − 80% of 1RM for the lower body should be considered.[117] Exercise intensity should be progressively increased to determine the patient's exercise response and exercise tolerance. It has been shown that resistance training improves walking performance and muscular strength in patients with PAD.[118] Notably, high intensity (i.e., 80% 1RM) induces the best improvements in walking performance compared with low to moderate (i.e., < 50% 1RM) strength training intensity.[90,118]

Table 4 summarises the main exercise prescription recommendations with some practical applications.

Home based exercise training

Compared 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 − 273 m; $p =$ .050).[119] When comparing HBT with basic exercise advice, no improvement of MWD was observed in patients following an HBT strategy (mean difference 39 m; 95% CI -123.1 − 201.1 m; $p =$ .64).[119] Regarding PFWD, HBT led to a greater increase than exercise advice (mean difference 64.5 m; 95% CI 14.1 − 114.8 m; $p =$ .010).[119] Compared with HBT, SET was more effective in improving MWD (mean difference 139 m; 95% CI 45 − 232 m; $p =$ .004) and PFWD (mean difference 84 m; 95% CI 25 − 143 m; $p =$ .005).[119]

Considering the effect of monitoring in HBT, no difference in the change of MWD and PFWD was observed between monitored HBT and SET (mean difference in MWD 8 m; 95% CI -81 − 97 m; $p =$ .86; mean difference in PFWD 43 m; 95% CI -29 − 114 m; $p =$ .24).[119] The equality in training efficacy of monitored HBT and SET emphasises the role of monitoring in HBT programmes. Apart from regular on site visits or phone calls, activity diaries or logbooks have been used for HBT monitoring.[119] Additional tools for self monitoring, such as wrist worn activity trackers with smartwatch like functions or smartphone accelerometer applications, have been assessed, however which modality is most appropriate still requires clarification.[55]

The effect of training on the patient's 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 was observed in patients undergoing SET.[120]

Focusing on quality of life, most studies reported improvements in patients undergoing HBT.[119] Compared with SET, improvements of individual SF-36 measures (pain and social functioning) and WIQ measures (distance) were less pronounced in patients undergoing HBT.[119] In addition, HBT improves measures of self efficacy for walking, satisfaction with functioning, pain acceptance, and social functioning in patients with claudication.[121] Follow up data of patients who had undergone HBT suggest sustained improvements in measures of quality of life and functional and walking capacity after termination of the active training intervention.[122,123]

HBT safety was analysed 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 1 per 147 810.[124] HBT event rates 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).[124] Regarding the overall mortality rate, retrospective data suggest a reduction of long term mortality in patients undergoing HBT.[125] Overall mortality rates do not differ between patients undergoing HBT and patients following a SET programme.[126] The results of the reported meta-analyses and reviews should be viewed with caution because of the moderate to low quality of evidence.[119,126,127] Due to the limited availability and utilisation of SET programmes, HBT programmes can be used as a valid alternative training modality for patients with IC.[128–131]

Data on sex specific differences in the efficacy of HBT are inconsistent.[132,133] In females, the efficacy of HBT appears to be more strongly related to the individual training intensity than in males.[134] Regarding comorbidities, HBT seems to be less effective in diabetic patients with respect to the potential increase in walking capacity.[135] In elderly patients, HBT potentially improves quality of life to a similar extent as revascularisation.[136] Considering the frequency of HBT training, three weekly sessions were the most common training strategy (range three weekly sessions to daily sessions).[119] For initiation, patients should start with a duration of 20 minutes per session, progressively increasing to 60 minutes per session. Home based training can be performed outside, around a track, or in a hallway at a self selected pace.[51,137]

Long term compliance with exercise therapy

In clinical practice, long term compliance with therapy is a major problem. Participating in SET programmes may help patients to acquire awareness of the disease and learn the importance of exercise and how to practice it. Supervised exercise training programmes can be regarded as a transition phase to improve self management and may serve as a bridge for those patients that need it to other forms of exercise approach such as community or home based exercise. Telemedical monitoring through step counting with pedometers or activity monitors proved to be effective,[138,139] as did supervised structured walking exercise to improve PFWD and MWD.[119] In addition to monitoring, factors such as education, self efficacy, goal setting, feedback, and a training plan were critical to successful outcomes.[119] This should be used more frequently in clinical practice to increase long term compliance but needs to be confirmed in long term studies.

Mechanisms of response to exercise in peripheral artery disease

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.[140] 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 interdependent physiological, metabolic, and mechanical mechanisms. After several months of exercise training, there is extensive remodelling 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.[140] 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) and signals stimulated by the increases in muscle energetic demand (i.e., increases in adenosine monophosphate (AMP) concentration and reduced oxygen delivery) activate several intracellular signalling pathways responsible for promoting a regulatory network governing the transcriptional control of mitochondrial biogenesis and respiratory function along with enhanced expression of pro-angiogenic factors[141] (Fig. 3).

Over time, this results in the initiation of capillary growth and proliferation in the number of arterioles. Such structural remodelling is driven by a complex and often redundant sequence of events that include NO and prostaglandins. Indeed, mechanical, neural, and humoral factors, including those released from contracting skeletal muscle, have all been implicated in the remodelling response, with the vascular endothelial growth factor (VEGF) signalling pathway and downstream targets ultimately driving skeletal muscle capillary expansion.[141] 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* signalling intermediates such as

Table 4. Training specificity and practical applications

Training modality	Training frequency	Training duration	Claudication pain intensity	Exercise intensity*	Example protocols
Walking (treadmill or overground)	At least 3× per week	Session duration Start with 10–15 min of actual exercise time. Increase progressively to 30–60 min of actual exercise time (including warm up).	Moderate to high Mild Pain free	Low to moderate HR_{peak}: ≤ 6% RPE: ≤13 Vigorous HR_{peak}: 77–95% RPE: ≥14	For people who are able and willing to walk at moderate to high pain intensity • Walk at a speed and or grade that induces moderate to high (3–4 on the claudication pain scale) claudication pain intensity • Rest until complete (or almost complete) pain resolution before resuming walking • Repeat this effort–rest cycle over 30–60 min, depending on exercise and pain tolerance
		Programme duration At least 12 weeks. Following initial exercise training, patients are encouraged to sustain lifelong and high levels of regular physical activity.			For people who are unable or unwilling to walk at moderate–high pain intensity • Walk at a speed and or grade that induces mild (2 on the claudication pain scale) claudication pain intensity. • Walk and cease the exercise at the onset of the claudication pain (1 on the claudication pain scale). • Rest until complete (or almost complete) pain resolution before resuming walking. • Repeat this effort – rest cycle over 30 – 60 min, depending on exercise and pain tolerance. In addition to the monitoring of the intensity of the claudication, exercise intensity* should also be considered during the sessions.
					Progression • First, exercise training should be set at low to moderate intensity. Then, if well tolerated by the patient, a gradual progression to vigorous or high exercise intensity may be proposed. • In general, during training programmes, the monitoring of a progressive increase in volume, intensity, and training load should be carefully considered.
Arm ergometer	At least 3× per week		Pain free	Low to moderate W_{peak}: 50–70% HR_{max}: ≤ 76% RPE: ≤ 13	First weeks of training • One minute effort at low to moderate exercise intensity interspersed with one or two minute rests. • Repeat this effort–rest cycle four times, depending on exercise tolerance.
Cycle ergometer	At least 3× per week		Mild to moderate	Vigorous W_{peak}: 70–100% HR_{peak}: 77–95% RPE: ≥ 14	Progression • Two minute effort at moderate to vigorous or vigorous exercise intensity interspersed with one or two minute rests. • Repeat this effort – rest cycle to 8 – 12 times, depending on exercise tolerance.
Resistance training	At least 3× per week		Mild to moderate	Low < 49% 1RM RPE: 9–11	First weeks of training • One to two sets of 12–15 repetitions (6–8 exercises) performed at low to moderate exercise intensity.
				Moderate 50–69% 1RM RPE: 12–13	Progression 1 • Two to three sets of 8–12 repetitions (6–8 exercises) performed at moderate to vigorous intensity.
				Vigorous 70–84% 1RM RPE: 14–17	Progression 2 • Two to four sets of 6–8 repetitions (6–8 exercises) performed at vigorous intensity.
					Example of exercises targeting the major muscle groups of the upper and lower body: Leg press, knee flexion, knee extension, calf press, chest press, seated row, hip abduction, and hip extension.

HR_{peak} = peak heart rate; RPE = rate of perceived exertion (Borg scale: 6, very very light; 20, maximum effort); W_{peak} = peak workload; 1RM = one repetition maximum.

* According to the American College of Sports Medicine guidelines for exercise testing and prescription.

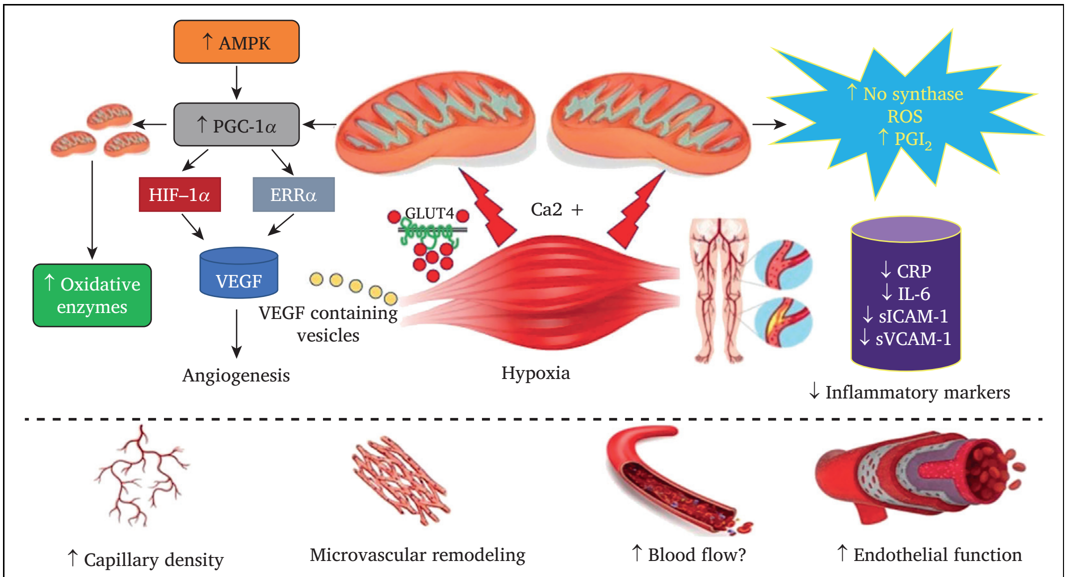

Figure 3. Dynamic exercise training induces extensive remodelling of the vascular system. Skeletal muscle contraction is associated with several physiological, metabolic, and mechanical mechanisms that when repeated over several weeks and months result in mitochondrial biogenesis, angiogenesis, and increases in the functional capacity of individuals with peripheral arterial disease. AMPK = AMP activated protein kinase; PGC-1α = peroxisome proliferator activated receptor gamma coactivator-1α; HIF-1α = hypoxia inducible factor 1-alpha; ERRα = oestrogen related receptor alpha; VEGF = vascular endothelial growth factor; NO = nitric oxide; ROS = reactive oxygen species; PGI_2 = prostacyclin; CRP = C reactive protein; IL-6 = interleukin 6; slCAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = circulating vascular cell adhesion molecule-1.

mitogen activated protein kinases and phosphatidylinositol-3-kinase.[142] The time course of remodelling 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, but recently, the peroxisome proliferator activated receptor gamma co-activator-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.[143] Thus, the PGC-1 co-activators serve as a central component of the transcriptional regulatory circuitry that coordinates the energy generating functions of the mitochondria in accordance with the metabolic demands imposed by exercise training undertaken by patients with PAD.

EXERCISE AND REVASCULARISATION

Current guidelines recommend SET programmes as an initial treatment modality for patients with IC.[3,144] Revascularisation is recommended for patients with IC when they do not respond to initial exercise and medical therapies.[145] However, the role of revascularisation 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 *vs.* SET alone as an initial treatment strategy for patients with PAD with IC and have reported inconsistent results.[146–149]

The relevant aspect of exercise training may be reduction of the inflammatory process in patients with PAD. In a recent trial, reactive oxygen species formation was measured using the luminol analogue L-012 for patients with IC, randomised either to HBT alone or in addition to endovascular therapy (EVT).[150] Follow up was performed after three months. ROS production after nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase 2 stimulation showed a significant reduction in both groups at follow up (EVT group, $p = .002$; exercise group, $p = .019$), with a higher relative ROS reduction in the EVT group than in the exercise group ($p = .014$).

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.[151] A total of 987 patients from seven randomised controlled trials (RCTs) (constituting nine total comparison arms) with a median follow up duration of 12.4 months (range 10 – 18 months) were enrolled. Of these, 530 patients were randomised to EVT *vs.* SET alone and 457 patients to EVT plus SET *vs.* SET alone.[151] For the effect of EVT alone *vs.* SET alone (five comparison arms), a random effects model showed no significant difference in the MWD (standardised mean difference [SMD] -0.11 95% CI -0.59 – 0.36; $p = .64$) on follow up between the two groups, either for the PFWD, need for revascularisation, or amputation. On pooled analysis, the ABI was significantly higher among participants who underwent EVT alone compared with SET only (SMD 0.64; 95% CI 0.38 – 0.90, $p < .001$; weighted mean difference [WMD] 0.15; 95% CI 0.10 – 0.19, $p < .001$).

On pooled analysis using random effects models, EVT plus SET (four comparison arms) was associated with significantly higher MWD on follow up compared with SET alone (SMD 0.79; 95% CI 0.18 – 1.39, $p = .010$), as well as significantly higher ABI on follow up compared with SET only (SMD 0.62; 95% CI 0.33 – 0.91; WMD 0.14; 95% CI 0.10 – 0.17, $p < .001$).

The combination of EVT plus SET was also associated with a significantly lower risk of revascularisation or amputation on follow up (3.5% *vs.* 17.3%, odds ratio [OR] 0.19; 95% CI 0.09 – 0.40, $p < .001$). The corresponding number needed to treat was eight (95% CI 6 – 12). Pain free walking distance was reported in two studies with no difference between the two groups in random effects pooled analysis.[151] However, EVT alone is not associated with better outcomes than SET.[151,152] Among patients with stable PAD and IC, compared with SET alone, endovascular revascularisation in combination with SET is associated with improved outcomes.

Exercise training after surgical revascularisation also improves outcomes compared with revascularisation without exercise training. Although much less investigated, few publications exist on the impact of exercise on outcome after surgical revascularisation of symptomatic PAD patients. One small RCT compared patients after bypass surgery ($n = 14$).[153] Group I had standard pre-operative and post-operative care, and the intervention group (Group II) had SET 4 – 10 weeks post-operatively. Maximum walking distance, mean increase in ABI, and improvement in WIQ were significantly better in Group II. In another recent study, patients who underwent above knee femoropopliteal bypass were divided into two groups: those who continued regular exercise after the bypass operation and those who discontinued exercise after surgery.[154] After propensity score matching, five year primary and secondary patency (primary patency 97% *vs.* 61%, $p = .004$; secondary patency 100% *vs.* 69%, $p = .002$) and freedom from major adverse CV events (61% *vs.* 24%, $p = .007$) were significantly better in patients who continued exercise. One systematic review included all RCTs with either surgical or endovascular revascularisation to evaluate the evidence for the efficacy of lower limb revascularisation combined with SET in patients with PAD.[155] Eight trials with 726 patients showed that combined therapy led to greater improvements in PFWD and MWD compared with revascularisation or supervised training alone. In two of eight studies, revascularisation was surgical and in six studies it was endovascular.

EFFECT OF EXERCISE ON HEALTH RELATED QUALITY OF LIFE AND COGNITIVE FUNCTION

Poor HRQoL is associated with a higher mortality rate in patients with PAD.[156] RCTs have shown that exercise training *vs.* usual medical care in patients with PAD improves not only the perceived walking distance and speed but also the functional status as measured by specific impairment questionnaires, such as the WIQ. Compared with controls, patients who complete any form of exercise training significantly improve their WIQ speed (mean difference 9.60; 95% CI 6.98 – 12.23, $p \leq .001$), WIQ distance (mean difference 7.41; 95% CI 4.49 – 10.33, $p \leq .001$), and WIQ stair climbing (mean difference 5.07; 95% CI 3.16 – 6.99, $p \leq .001$).[80] 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 – 2.01).[80] Most of the studies showed that three[157–159] or six to 12 months[94,102,160] of exercise training improves the patient's perception of physical HRQoL, with lesser effects on mental HRQoL. However, in the current literature, findings are inconsistent[74,80,161] and other studies did not find the same effects.[162–164] It is interesting to note that the improvement in general HRQoL scores (as SF-36) was mainly predicted by physical functional markers, such as the distance covered during a 6MWT (6MWD) and history of stumbling.[165] These data indicate that greater improvements in physical function following exercise therapy are expected to have greater improvements in self perceived HRQoL.[165] It has recently been showed that improvements in 6MWD following SET are predictive of augmentations in general HRQoL in patients with PAD.[96] Interestingly, changes in treadmill performance, which are less representative of functional walking,[46] were not related to improvements in HRQoL.[96]

Regular physical activity is also known to improve cognitive function and brain health across the lifespan.[166] 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 programmes that are structured, individualised, higher intensity, longer duration, and multicomponent.[167] 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.[167] Scientific evidence based on a functional and neuro-imaging approach has demonstrated that this relationship could be mediated by improved brain integrity, including adaptations in cerebral blood flow, volume, and white matter integrity.[168]

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 the individual's walking distances.[169] Structured education programmes, on the other hand, may have greater potential to improve exercise behaviour and walking distances by building the knowledge and skills of patients to enable them to successfully self manage their condition.[170] Key programme 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.[170]

A systematic review by Abaraogu *et al.*[170] identified six studies (1 087 participants) that had investigated the effects of structured education for patients with PAD and IC. The interventions varied widely, but all included education sessions, exercise prescription, and behaviour change techniques. Four trials reported improvements in walking ability in intervention *vs.* control comparisons.[170] 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 highlighted 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.[170]

Three other trials have tested exercise programmes that had an educational component in patients with PAD.[171–173] The GOALS trial[172] randomised 194 participants either to a group mediated cognitive behavioural intervention or an attention control group. The intervention consisted of group meetings with a facilitator once weekly for six months. Discussion topics included effective behaviour change methods, self monitoring, exercising in cold weather, managing leg pain during exercise, and overcoming other obstacles to exercise compliance. At the six month follow up, the intervention group achieved a 53.5 m greater increase in 6MWD compared with the control group. The HONOR trial[173] tested the efficacy of telephone coaching combined with a wearable activity monitor and showed no improvement in 6MWD at the nine month follow up. Finally, the MOSAIC trial explored the effect of a physiotherapist delivered motivational interview intervention in 190 patients with PAD and IC.[171] A statistically significant mean difference of 16.7 m in 6MWD was observed at the three month follow up compared with usual care control.[171] The contrasting results of these trials indicate that exercise programmes that include education are more likely to be successful if they include periodic visits to a medical centre to meet with a coach or include tailored behaviour change components.

SEX AND EXERCISE

The prevalence of PAD in women is similar to men at all ages.[174,175] However, women are more likely to have asymptomatic PAD and less likely to report IC.[176] Decreased detection and subsequent intervention may then result in a higher proportion of women with severe disease and chronic limb threatening ischaemia. Further, women who undergo revascularisation tend to be older and have more severe PAD than men, and these factors can affect procedure outcomes adversely.[177] There are contradictory mortality rates for women with PAD.[178–180] Population studies suggest a trend towards higher mortality rates in women with lower ABI.[179]

Exercise performance has been used to suggest that women decline faster in terms of functional ability once PAD is established. However, this difference may be due to the smaller muscle size of women's calves.[181] McDermott *et al.*[182] showed that at four years follow up, women were more likely to become unable to walk for six minutes continuously than men, more likely to develop mobility disability, and had faster declines in walking speed, and the distance achieved in the 6MWT 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 an increased mortality rate in men, but not in women, with PAD.[181]

Data on the efficacy of exercise rehabilitation in women with PAD compared with men are scarce. What is known, however, is that women with IC seem to have a poorer response to exercise rehabilitation, and smaller changes in PFWD and MWD following three months of exercise than men (Δ280 m for men *vs.* Δ220 m for women; $p = .040$).[183] This is particularly so in those with diabetes.[132] Reduced blood volume expansion and slower oxygen kinetics occur in the calf musculature during exercise in women with PAD with IC.[184] 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 in both a supervised exercise class and a home exercise setting.[132] 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 a significantly lower MWD after 12 months. The higher level of metabolic syndrome present in postmenopausal women compared with similarly aged men may contribute to this.[183] Conversely, it has recently been shown that multimodal SET (combining strengthening of lower limbs and Nordic walking) significantly improves walking performance (treadmill and over ground) in women and men, with no difference between groups.[98,185] Although not significant, it is interesting to note that women had greater improvements than men.[98]

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 to that seen in men with exercise alone.

SITUATION IN EUROPE

Despite of the large body of evidence highlighting benefits, SET is under used, and its availability and compliance are low.[128–130,186–192] The rate of clinicians referring a patient for SET is very low.[128] The reasons and barriers for not participating in SET programmes are lack of facilities, feeling worse, costs, time, lack of motivation, and comorbidities.[128,130,187]

The situation with SET in Europe varies from country to country. A recent European survey showed that supervised exercise programmes exist in Austria, Belgium, Czech Republic, France, Germany, Italy, Sweden, Switzerland, and the UK.[193] However, SET is reimbursed by health insurance only in Austria, Belgium, France, Germany, Sweden, and Switzerland.[193] In the UK, SET programmes are funded by the National Health Service. In contrast, SET is not reimbursed in Czech Republic and Italy, and it does not even exist for patients with PAD in Denmark, Greece, Ireland, Poland, Serbia, Slovakia, Slovenia, or Ukraine.[193] Similarly, the structured home based exercise programme is not routinely present in European countries.[193]

Importantly, there is heterogeneity in the form of SET in most individual countries, with existence of individual programmes or practices in each hospital or community.[193] They differ in respect of frequency, length, and duration of training, type of exercise, as well as by supervising professional.[193] Mostly, SET is coordinated by an angiologist or 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 programme duration is mostly 12 weeks or less, with session duration 30 – 60 minutes. The most frequently used training modalities are a combination of walking and resistance training or walking training alone.[193]

To standardise SET programmes and provision across Europe, the following steps are required: (1) more widespread availability of SET programmes and standardised outcomes to assess their effectiveness; (2) more defined harmonisation of SET characteristics (establish process of referral, supervision, coordination, selection of patients, and SET protocols); (3) health insurance reimbursement of costs; and (4) action to improve the public knowledge about the benefits of SET.[193]

GAPS IN EVIDENCE AND FURTHER STUDIES

Awareness and access to supervised exercise programmes should be a field for further studies. Additionally, there are still many areas of insufficient or inconsistent evidence in the treatment of claudication with exercise therapy. The optimal therapy in terms of duration of the single walking session or intensity of training is not known. There are few studies on the impact of no or low pain based exercise, and the data on sex differences are inconsistent. The combination of walking exercise with non-walking training has not been established. Also, more evidence is needed to better understand the potential role of wearable monitoring during exercise interventions and to evaluate 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-randomised study, Parodi *et al.*[194] reported a mean increase in treadmill walking from 100 to 535 m in 131 patients who were treated with hydration, defined as drinking at least 2000 mL of water during 24 hours for a period of six months and ingesting albumin and salt (3.5 g/day).

Moreover, data on the interference of exercise training, as well as of individual training modalities, with medical treatment in patients with IC are scarce: one historical RCT suggested an augmentation of the beneficial effect of exercise training by antiplatelet therapy.[195] Another more recent RCT suggested an additive effect of cilostazol in addition to exercise treatment on absolute claudication distance.[196] However, it needs to be taken into account that both studies had very small sample sizes. Therefore, larger prospective trials are needed to further elucidate the interaction between exercise training and medication in PAD.

Another area of future research should be exploration of the best modalities to transition patients from supervised exercise programmes to everyday life while maintaining the beneficial effects. Finally, more research is needed on how to measure success in exercise training in an accurate and reproducible way.

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None.

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APPENDIX A. SUPPLEMENTARY DATA

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