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 programme provides optimal results. This clinical consensus paper is intended for clinicians to promote and assist for the set-up of comprehensive exercise programmes 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 programmes across Europe, and the series of gaps for evidence requiring further research.

Graphical abstract

<u>Included patients</u>

- Women and men with symptomatic chronic peripheral artery disease
- Patients undergoing revascularisation

<u>Initial exercise training</u>

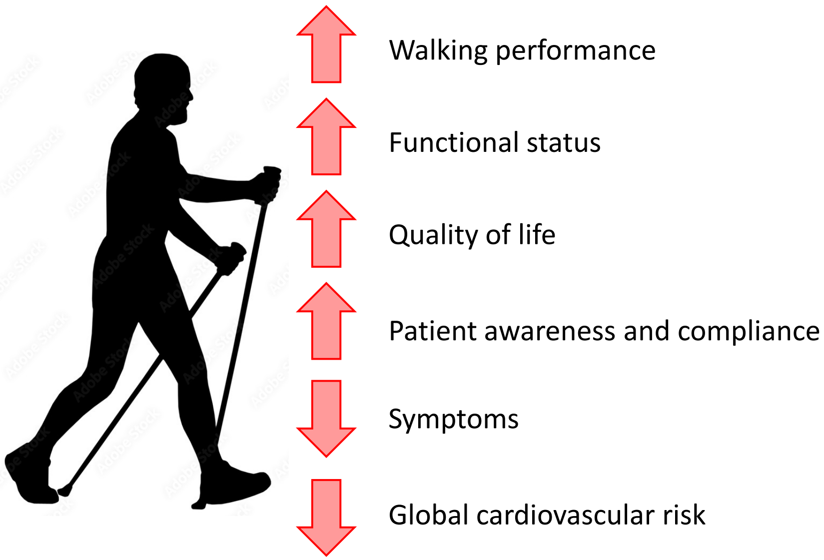
- Supervised exercise or home-based exercise training programmes
- *Training frequency*: at least 3 times per week
- *Training modality*: intermittent bouts of walking alternating with periods of rest are the first option. When walking is not an option, alternatives modalities (resistance training, arm-cranking, cycling, combinations of exercise) could also be considered.
- *Claudication pain intensity:* Based on strong evidence, patients should exercise to moderate-high claudication pain. No or low-pain approaches also shown improvement in walking ability, but the level of evidence is low. A flexible approach to pain intensity prescription is required, considering the patient's needs and preferences, and what might achieve high adherence.
- *Exercise intensity:* begin with a "lead-in period" of low-to-moderate intensity followed by, if tolerated, a gradual progression to vigorous exercise intensity.
- *Session duration*: at least 30 min
- *Programme duration*: at least 12 weeks
- Programmes should include advice and education about peripheral artery disease, cardiovascular risk factors, and lifestyle aiming for longer-term behavior change

<u>Assessments prior and following exercise therapy</u>

- Complete medical history, physical examination, and screening for contraindications
- Functional assessment
- Quality of life assessment
- Vascular assessments

<u>Chronic exercise training</u>

- Following initial exercise training (supervised or home-based), patients are encouraged to sustain lifelong and high levels of regular physical activity



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 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. PAD is one of the most prevalent clinical presentations of atherosclerotic disease, affecting approximately 237 million people 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 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 (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 address this gap, the ESC Working Group on Aorta & Peripheral Vascular Disease, the ESVM, 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.

Consensus statements

- **1. In patients with PAD and exercise-induced limb symptoms due to vascular origin, supervised exercise programmes should be the first line treatment modalities.**

- **2. In 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 be ideally supervised by clinical exercise physiologists or physiotherapists.**

- **4. Prior to exercise training initiation, complete medical history and 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 min.**

- **9. The training programme duration should last a minimum of 3 months.**

- **10. Both claudication pain (A) and exercise intensity (B, based on common training intensity measures such as heart rate 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, universally prescribing 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/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 education and counselling on cardiovascular disease and PAD risk factor reduction. 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

IC 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 2-5 min after 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 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] and 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].

Patients 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. 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 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 programme to detect and diagnose PAD and assess disease severity (Figure 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 while ABI can be ≥0.91 at rest. A post-exercise ankle systolic blood pressure 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. Standardised exercise testing should be used for assessment of functional impairment in patients with PAD (Figure 2).

*Treadmill assessment***.** Treadmill testing should be performed with patients familiarised 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 to ensure test-retest reliability [43]. Further, there may be a learning effect so it is recommended that the best out 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, habitual walking, and self-reported walking distance [45]. On the other hand, compared to 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 ($p<0.001$) 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 minimal detectable changes (i.e. the statistical detectability of change beyond measurement error) in the 6MWT are represented by a change >46 meters [49]. The minimal 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 8 [50] or 9 meters [51] for small changes, and 20 [50] or 38 meters [51] for large changes.

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 [52]. Research has shown that GPS recorders have good accuracy and reliability when compared to 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 maximal walking distance 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 high prevalence of frailty and sarcopenia [58]. Muscle strength and function should therefore be assessed before and after supervised exercise training (SET, Figure 2). 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) [59]. Testing can be done in various joints, including 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 (SPPB) which includes a 4-metre 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 and following SET [61].

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 (Figure 2) [62-64]. Following exercise interventions, assessing HRQoL is usually used to determine if an objective improvement in functional performance is also perceived by the patients in their daily life. Table 1 reports the most used subjective tools used for walking ability and HRQoL assessment in patients with PAD. Trials used a wide variety of questionnaires of patient reported outcomes measurements (PROMs) [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 with CVD alone [65]. In the PARTNERS study, the SF-36 Physical Component Summary of the combined PAD-other-CVD group was 46.3 ± 1.2 compared with 55.5 ± 1.1 in the other-CVD 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 ESVS VASCUNET and the International Consortium of Vascular Registries consensus statement recommended the Vascular Quality of Life Questionnaire-6 (Vascu-QoL6) as a primary assessment of PROMs 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 PAD

Screening prior to exercise training participation

All patients should be medically screened before SET programme initiation (Figure 2). It is suggested to include a complete medical history and examination [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), we recommend that they are referred for cardiology work-up, including an exercise test to assess for evidence of exercise-induced coronary ischaemia, to identify if additional treatment for cardiac disease is required before proceeding with SET. Comorbidities (such as neurological and orthopedic diseases leading to gait abnormalities) should be documented and considered for how they may limit SET programme participation feasibility. After SET programme initiation, patients should continue to be closely monitored for changes in health status (e.g., any symptom or situation which may suspect undiagnosed/incident cardiac condition, ischemic limb pain at rest, toe or foot wounds) that might necessitate interruption of the programme, at least temporarily.

Supervised exercise training

SET is considered among first-line therapies for patients with chronic and symptomatic PAD (Figure 2) [3,64,69,70]. SET 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% IC: 72 – 92) and MWD (120 m; 95% IC 51 – 190) [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 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 other types of rehabilitation 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 is very limited to draw extensive conclusions [84,88]. More studies are needed to confirm 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 (Figure 2) [64,70]. 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 non-walking 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 [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 have the tendency to be higher with walking training than with strength training when all studies are considered [89]. 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) [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 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 [103,104].

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 [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 to 60 min were the most effective to improve 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 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. 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/maximal pain), is the most commonly 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 [38,64,70]. The UK NICE guideline encourages patients to exercise to the point of maximal pain , the American Heart Association guideline recommends moderate to moderate/severe claudication pain as tolerated [64], while an international consensus as well as the Australian guideline does not specify pain intensity for exercise dosage [106]. Based on strong evidence [64,73-75,104], the current consensus is that patients should exercise to moderate-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 with recent findings, walking training with pain is not clearly superior to walking training without pain regarding changes in walking distances [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 therefore be required, considering the patient's needs and preferences, and what might achieve a high level of (long term) adherence. 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/low pain-based exercise training intensity is understudied 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, low levels of claudication only. Assuming that exercise intensity is a cornerstone determinant of 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, %$\dot{V}O_{2peak}$: 64-90, RPE: ≥ 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 therapy programmes [78].

It is however important to note that training programmes should start with a lead-in period performed at low-to-moderate exercise intensity and, if tolerated, gradually progressed to vigorous exercise intensity. This approach may allow to determine the patient's exercise response and tolerance, reducing the risk of complications.

The monitoring of the exercise intensity during a resistance training program is mediated by the percentage of the one repetition maximum (1RM) [116]. The determination of the 1RM plays a key role to objectively set an individualised resistance-based program [116]. Compared to a direct assessment of the 1RM, the multiple RM assessment (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 cardiovascular diseases [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 when compared to low-to-moderate (i.e. <50% 1RM) strength training intensity in these patients [90,118].

Table 4 summarises 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) [119]. 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) [119]. 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) [119]. 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) [119].

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) [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 log books 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, it still needs to be clarified, which modality is most appropriate [55]. 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 [120].

Focusing on quality of life, most studies reported improvements in patients undergoing HBT [119]. 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 [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, functional and walking capacity after termination of the active training intervention [122,123].

Safety of HBT 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 one per 147,810 [124]. 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) [124]. Regarding overall mortality, retrospective data suggest a reduction of long-term mortality in patients undergoing HBT [125]. Comparing HBT with SET, 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 according to a 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 co-morbidities, HBT seems to be less effective in patients with diabetes 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 does [136]. Considering the frequency of HBT training, 3 weekly sessions was the most commonly training strategy (range: 3 weekly sessions to daily sessions) [119]. 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 [51,137].

Long-term adherence to exercise therapy

In clinical practice, long-term adherence to 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. SET 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 pain-free and maximal walking distance [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 adherence but needs to be demonstrated in long-term studies.

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 [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 inter-dependent 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), as well as signals stimulated by the increases in muscle energetic demand (i.e., increases in AMP concentration, 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] (Figure 3).

Over time, this results in the initiation of capillary growth and a 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 mitogen activated protein kinases (MAPK), 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-1□ (HIF-1□) but recently the peroxisome proliferator-activated receptor gamma coactivator-1□ (PGC-1□) has emerged as an important candidate in the exercise-induced angiogenic response. PGC-1□ 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 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 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 versus SET alone as an initial treatment strategy for patients with PAD with IC and reported inconsistent results [146-149].

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, randomised either to home-based training alone or in addition to endovascular therapy (EVT) [150]. 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 [151]. 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 [151]. For the effect of EVT alone versus SET alone (5 comparison arms) a random effects model showed no significant difference in the MWD (standardised 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 revascularisation 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 revascularisation 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 [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 to revascularisation without exercise training. Although much less investigated, few publications exist on the impact of exercise on the outcome after surgical revascularisation of symptomatic PAD. One small RCT compared patients after bypass surgery (n=14) [153]. Group I had standard preoperative and postoperative care and the intervention group (group II) had SET 4-10 weeks postoperatively. MWD, 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 bypass operation with those who discontinued exercise after surgery [154]. After propensity score matching, 5-year primary and secondary patency (PP: 97% vs. 61%, p = 0.0041; SP: 100% vs. 69%, p = 0.0021), and freedom from major adverse cardiovascular events (61% vs.

24%, p = 0.0071) were significantly better in patients who continued exercise. One systematic review included all RCTs with either surgical or endovascular revascularisation to evaluate the evidence on the efficacy of lower limb revascularisation combined with supervised exercise training 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 2 out of 8 studies, revascularisation was surgical and in 6 studies it was endovascular.

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 [156]. Randomised 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, $p \leq 0.001$); WIQ distance (mean difference: 7.41; 95% CI: 4.49 to 10.33, $p \leq 0.001$) and WIQ stair-climbing (mean difference: 5.07; 95% CI: 3.16 to 6.99, $p \leq 0.001$) [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 to 2.01) [80]. Most of the studies showed that 3- [157-159], or 6/12-month [94,102,160] exercise training improves 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) were mainly predicted by physical functional markers, such as the distance covered during a 6MWT (6MWD) and the 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 functioning 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 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 [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 individuals' 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 versus 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 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 [170].

Three other trials have tested exercise programmes that had an educational component in patients with PAD [171-173]. The GOALS trial [172] randomized 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 6 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 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 [173] 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 patients with PAD and IC [171]. A statistically significant mean difference of 16.7 m in 6MWD was observed at 3 months 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

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 ischemia. Further, women who undergo revascularisation tend to be older and have more severe PAD compared to men, and these factors can affect outcomes of procedures adversely [177]. Contradictory results exist on women with PAD and mortality rates [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 in fact merely be due to the smaller muscles in the calves of women [181]. McDermott et al. [182] 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 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 increased mortality in men, but not in women, with PAD [181].

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; $p = 0.04$) [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 both in 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 significantly lower MWD after 12 months. Higher level of metabolic syndrome presents in postmenopausal women compared with similarly aged men, may contribute to this [183]. 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 [98,185]. Although not significant, it is interesting to note that women had greater improvements (i.e., delta) 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 as that seen in men with exercise alone.

Situation in Europe

Despite of the large body of evidence highlighting benefits, SET is underused, and its availability and adherence is low [128-130,186-192]. To note, the rate of clinicians referred a patient for SET in 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 United Kingdom [193]. However, SET is reimbursed by the health insurance only in Austria, Belgium, France, Germany, Sweden, and Switzerland [193]. In the United Kingdom, SET programmes are funded by the National Health Service. 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 [193]. Similarly, the structured home-based exercise programme is not routinely present in European countries [193].

Importantly, there is heterogeneity in form of SET in most of individual countries, with existence of individual programmes or practice of 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, 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 programme duration is mostly 12 weeks or less, with session duration 30-60 min. Most often used training modalities are 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) a more widespread availability of SET programmes and standardised outcomes to assess their effectiveness; 2) a more defined harmonisation of SET characteristics (establish process of referral, supervision, coordination, selection of patients, 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 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 sex differences are inconsistent. The combination of walking exercise with non-walking training 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-randomised 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) [194].

Moreover, data on the interference of exercise training, as well as of individual training modalities, with medical treatment in patients with IC is scarce: one historic 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 on top of 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, we need more research on how to measure success in exercise training in an accurate and reproducible way.

APPOINTED REVIEWERS

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Figures titles and abbreviations

Structured Graphical Abstract. Graphical summary of the exercise training approaches in patients with peripheral artery disease.

Figure 1. Pathophysiology of limb symptoms in peripheral artery disease.

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, exercise) approach); DUS = Duplex ultrasound; SF-36 = short-form health 36 questionnaire; WIQ* = Walking Impairment Questionnaire; *Vascu-QoL6 = Vascular Quality of Life Questionnaire-6.*

Figure 3. Dynamic exercise training induces extensive remodeling 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-1∝ = peroxisome proliferator-activated receptor gamma coactivator-1α; HIF-1α = hypoxia inducible factor 1-alpha; ERRα = Estrogen-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; sICAM-1 = soluble intercellular adhesion molecule-1; sVCAM-1 = circulating vascular cell adhesion molecule-1.*