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Exercise therapy for chronic symptomatic peripheral artery disease

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1 **Title page - consensus document**

2

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

7

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1 **Abstract**

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

Graphical abstract

Included patients

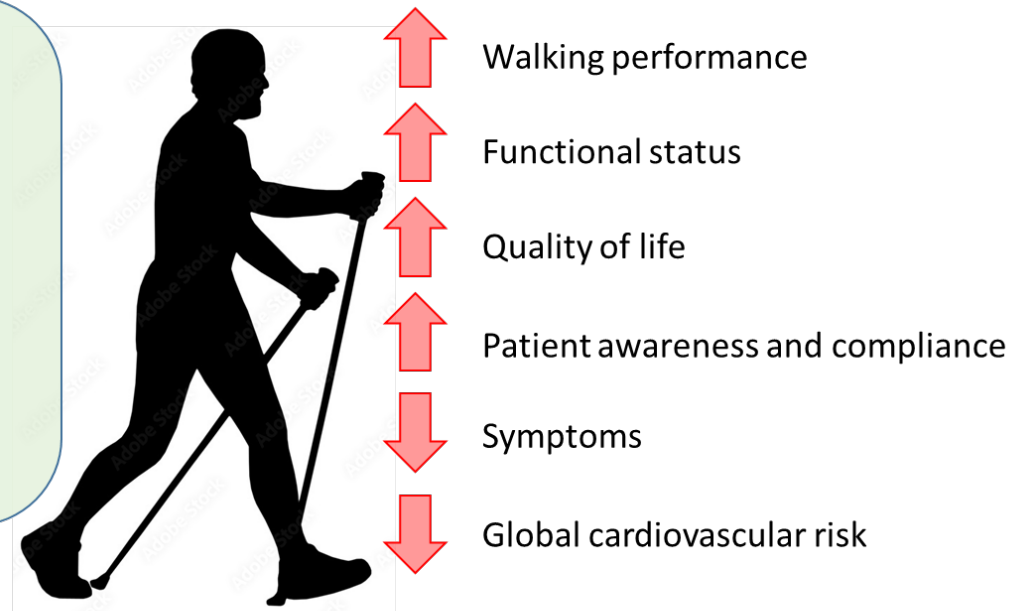
- Women and men with symptomatic chronic PAD
- Patients undergoing endovascular revascularisation

Exercise training programs

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

Assessments prior and following exercise therapy

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



1 **Introduction**

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

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

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

20

1 **Consensus statements**

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

6
7 ▪ **Supervised exercise programs should be ideally coordinated by vascular**
8 **physicians, and sessions should be supervised by clinical exercise**
9 **physiologists or physiotherapists.**

10
11 ▪ **Prior and following the supervised exercise programs, CV risk factors,**
12 **vascular and cardio-pulmonary parameters, walking parameters,**
13 **functional status, muscle strength, and health-related quality of life**
14 **should be systematically assessed.**

15
16 ▪ **Walking training (overground, pole striding, treadmill) should be**
17 **proposed as first line exercise modality. When walking is not an option,**
18 **alternative training modalities (resistance and strength training, arm-**
19 **cranking, cycling, Nordic walking, combinations of exercise) might be**
20 **proposed.**

21
22 ▪ **The training frequency should be at least three times per week.**

23
24 ▪ **The training session duration should last at least a minimum of 30 min.**

25

- 1 ▪ **Patients with PAD should walk to the point of near-maximum leg pain**
2 **assessed with the claudication pain scale (self-reported 3-4/4 pain**
3 **intensity in the scale). Lower pain levels (mild pain or pain-free) should**
4 **also be considered.**
- 5
- 6 ▪ **Walking training performed at high intensity (77–95% of maximal heart**
7 **rate or 14-17 on the Borg’s scale) should be considered to improve**
8 **walking performance. High intensity exercise should also be considered**
9 **to improve cardiorespiratory fitness.**
- 10
- 11 ▪ **When supervised exercise training is not feasible, structured, high-**
12 **intensity pain, monitored (calls, log-books, connected devices) home-**
13 **based programs should be proposed.**
- 14
- 15 ▪ **Supervised exercise programs should include structured advice and**
16 **education about PAD, cardiovascular risk factors, and lifestyle. Education**
17 **should be delivered by trained specialists and aim for longer-term**
18 **behavior change.**
- 19
- 20

1 Pathophysiology of intermittent claudication and functional 2 impairment

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

19 Potential mechanistic drivers of exertional limb symptoms in addition to arterial
20 obstruction and reduced perfusion include inflammation, vascular dysfunction, reduced
21 microvascular flow, impaired angiogenesis, and altered skeletal muscle function [14-
22 16] (Figure 1). A healthy vascular endothelium produces several vasodilator
23 substances, including nitric oxide (NO), which has pluripotent vascular benefits such
24 as platelet inhibition, smooth muscle cell proliferation inhibition, leukocyte adhesion
25 prevention, and angiogenesis induction. Diminished NO bioactivity in the lower limbs

1 prevents increased blood flow with exercise [11]. Vascular dysfunction may also
2 exacerbate the vasoconstrictive effects of catecholamines and limit flow-mediated
3 dilation [17-20]. Inadequate angiogenesis and collateral vessel formation may
4 potentiate limb ischemia and serve as a mechanism driving functional impairment [21].
5 Skeletal muscle ischemia may drive local inflammation, exacerbating symptoms and
6 altering muscle metabolism [22-24].
7 People with PAD present impaired walking endurance [25], slower walking velocity [26-
8 28], gait abnormalities [26,27,29-31], poorer muscle strength [32], and poorer balance
9 [33,34] compared to individuals without PAD. Patients with PAD may also reduce their
10 walking activity and total activity to avoid leg symptoms [35], and studies have shown
11 a functional decline occurring over time [25,28,36].

12

13 **Vascular, functional, and cardiopulmonary assessment in PAD**

14 ***Vascular assessment***

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

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

3

4 ***Walking distance assessment***

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

8 *Treadmill assessment.* Treadmill testing should be performed with patients familiarized
9 to the treadmill and under reproducible conditions (i.e. avoiding exercise and alcohol
10 prior to assessment). Patients should be asked to walk until maximal levels of pain,
11 lightly holding or not holding onto the treadmill. If the tests are stopped for reasons
12 other than leg pain, then this should be recorded. Patients are asked to indicate the
13 claudication pain score they reached during walking, especially the point at which pain
14 begins, and recovery based on a five-point scale (0 = no pain, 1 = onset of pain, 2 =
15 mild pain, 3 = moderate pain, 4 = severe/maximal pain) [38]. Common treadmill
16 protocols include constant-load (single-stage) or graded exercise testing [39,40]. The
17 latter is performed at constant speed varying the slope of the treadmill. Established
18 graded protocols include the Gardner/Skinner (3.2 km/h and a 2% increase in slope
19 every 2 minutes) or the Hiatt protocol (3.2 km/h and an increase in slope of 3.5% every
20 3 minutes). Constant-load treadmill tests are performed at a fixed speed of 2 to 4 km/h
21 and fixed gradient of 10 to 12%. Constant-load protocols have poorer reliability both
22 for pain-free walking distance (PFWD) and maximal walking distance (MWD)
23 compared with graded protocols (coefficient of variance 30 and 45%, respectively)
24 [41,42]. Treadmill tests have limitations including learning effect during repeated

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

3

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

20

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

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

5

6 ***Cardiopulmonary fitness assessment***

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

21

22 ***Muscle strength assessment***

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

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

17

18 ***Self-reported functional impairment and quality of life assessment***

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

1 variety of questionnaires of patient reported outcomes measurements (PROMs) [64-
2 66]. The most used are the short-form health 36 (SF-36), a generic questionnaire
3 including physical and mental items related to health), and the Walking Impairment
4 Questionnaire (WIQ), a PAD-specific questionnaire focusing on PAD and functional
5 limitations. Studies have shown that HRQoL burden is greater in magnitude in patients
6 with PAD than without PAD in CVD patients [67]. In the PARTNERS study, the SF36
7 Physical Component Summary of the combines PAD-other-CVD group was 46.3 ± 1.2
8 compared with 55.5 ± 1.1 in other-CVD group [67]. Cross-sectional studies show that
9 in patients with PAD the degree of difficulty in walking distance and stair climbing are
10 significantly related to HRQoL [68].

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

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

18

19 **Exercise therapy in patients with PAD**

20 ***Supervised exercise training***

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

1 and MWD (120 m; 95% IC 51 – 190) in patients with PAD [74]. Similar findings were
2 observed in another meta-analysis [PFWD: 128 m (95% IC: 92 – 165); MWD: 180 m
3 (95% IC: 130 – 238)] [75]. Although less well investigated or usually reported as a
4 secondary outcomes, SET also improved functional status, gait pattern, self-reported
5 walking ability and quality of life [63,66,74,76-80]. It is interesting to note that cardiac
6 rehabilitation programs also increase walking distance, HRQoL, and physical activity
7 in patients with symptomatic PAD, suggesting that other types of rehabilitation than
8 SET are also useful [81].

9
10 *Training modalities.* There are different types of exercise training for patients with PAD,
11 but the common aim is to improve HRQoL by increasing walking capacity and reducing
12 the symptoms. In addition, exercise should aim to improve balance and muscle
13 strength to promote independence and a reduced risk of falling in the long-term [33].
14 Treadmill and overground walking are the most common and recommended training
15 modalities in patients with IC [66,72]. However, due to severe exercise-induced
16 ischemia, low pain tolerance, the risk of falling and/or other co-morbidities, some
17 patients are unwilling or unable to perform walking sessions. In addition to walking
18 training, there are several other forms of training that are used, although much less
19 frequently, in the rehabilitation of patients with PAD. A recent meta-analysis reported
20 that other nonwalking training modes are also effective as traditional walking training
21 in improving walking performance, whereas there was no clear evidence for changes
22 in quality of life following exercise interventions. However, the authors concluded that
23 the certainty of this evidence was judged to be low [82]. Different training modes
24 include strength training of large muscle groups [83,84], cycling [85], pole striding
25 [86,87], multimodal training [76,77,88-91] and training with an arm-crank ergometer

1 [58,92]. The beneficial effect of these training modalities can usually be described as
2 large and even reach those of typical walking training [93]. However, the PFWD and
3 the MWD have the tendency to be higher with walking training than with strength
4 training when all studies are considered [82]. In contrast, self-reported ability to climb
5 stairs (assessed by the Walking Impairment Questionnaire) is more improved following
6 strength training (29.2% vs. 43.8% after 6 months) compared to walking training on the
7 treadmill (39.6% vs. 43.8% after 6 months) [94]. Therefore, when walking is not an
8 option, alternative training modalities might also be effective. These training modalities
9 also elicit lower or no pain during exertion compared to walking, which might lead to
10 higher rates of adherence.

11

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

15

16 *Training duration.* Identifying an optimal training duration is difficult to elucidate, mainly
17 due to differences in training modalities, frequencies, and intensities among studies.
18 Current guidelines reported that optimal training duration ranges between 12 and 24
19 weeks [66,72,95]. The optimal training session duration has not been widely
20 investigated. Additionally, in most studies, the total session duration is usually reported
21 without specifying the actual time spent exercising. The literature shows that exercise
22 sessions lasting 30 to 60 min were the most effective to improve walking performance
23 [95,96].

24

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

5 First, the majority of trials used claudication pain severity to provide guidance during
6 the training sessions. In PAD research, the claudication pain scale, an ordinal scale
7 from 0 (no pain) to 4 (severe/maximal pain), is the most used tool. A distinction is made
8 between walking training with and without muscle pain caused by ischemia. With
9 regards to claudication pain intensity, international guidelines are heterogeneous
10 [38,66,72]. The UK NICE guideline encourages people to exercise to the point of
11 maximal pain [97], the American Heart Association guideline recommends moderate
12 to moderate/severe claudication pain as tolerated [66], while an international
13 consensus as well as the Australian guideline does not specify pain intensity for
14 exercise dosage [98]. It has recently been shown that one-year home-based walking
15 training performed at high-intensity pain was more effective than walking training
16 performed at low-intensity for improving walking and functional performance in patients
17 with PAD [99,100]. These findings indicate that claudication pain intensity may be a
18 key factor for walking improvement in these individuals. In contrast, others have
19 reported that improvements in walking performance may be obtained with less severe
20 claudication pain during exertion [93]. According with recent findings, walking training
21 with pain is not clearly superior to walking training without pain regarding changes in
22 walking distances [101-104]. It can be assumed that walking training with moderate,
23 low, or no pain is associated with higher compliance and therefore long-term
24 maintenance of training or change in activity behavior [104]. However, larger studies

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

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

14

15 ***Home-based exercise training***

16 In comparison with patients not undergoing exercise training, a home-based training
17 (HBT) strategy resulted in a non-significant increase of MWD in a recent meta-analysis
18 (mean difference: 136 m; 95% CI: -2 to 273 m; P = 0.05) [107]. When comparing HBT
19 with basic exercise advice, no improvement of MWD was observed in patients
20 following a HBT strategy (mean difference: 39 m; 95% CI: -123.1 to 201.1 m; P = 0.64)
21 [107]. Regarding PFWD, HBT led to a greater increase than exercise advice did (mean
22 difference: 64.5 m; 95% CI: 14.1 to 114.8 m; P = 0.01) [107]. In comparison with HBT,
23 SET was more effective in improving MWD (mean difference: 139 m; 95% CI: 45 to
24 232 m; P = 0.004) and PFWD (mean difference: 84 m; 95% CI: 25 to 143 m; P = 0.005)
25 [107].

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

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

15 Focusing on quality of life, most studies reported improvements in patients undergoing
16 HBT [107]. In comparison with SET, improvements of individual SF-36 measures (pain
17 and social functioning) and Walking Impairment Questionnaire measures (distance)
18 were less pronounced in patients undergoing HBT [107]. In addition, HBT improves
19 measures of self-efficacy for walking, satisfaction with functioning, pain acceptance
20 and social functioning in patients with claudication [109]. Follow-up data of patients
21 who had undergone HBT suggest sustaining improvements in measures of quality of
22 life, functional and walking capacity after termination of the active training intervention
23 [110,111].

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

1 147,810 [112]. Event rates of HBT were lower than event rates reported for SET (HBT
2 vs. SET: cardiac 1:49,270 vs. 1:13,788; non-cardiac: 1:147,810 vs. 1:41,363) [112].
3 Regarding overall mortality, retrospective data suggest a reduction of long-term
4 mortality in patients undergoing HBT [113]. Comparing HBT with SET, overall mortality
5 rates do not differ between patients undergoing HBT and patients following a SET
6 program [114].
7 The results of the reported meta-analyses and reviews should be viewed with caution
8 according to a moderate to low quality of evidence [107,114,115].
9 Due to the limited availability and utilization of SET programs, HBT programs serve as
10 alternative training modality for patients with IC [116-119].
11 Data on gender-specific differences in the efficacy of HBT are inconsistent [120,121].
12 In women the efficacy of HBT appears to be more strongly related to the individual
13 training intensity than in men [122]. Regarding co-morbidities, HBT seems to be less
14 effective in patients with diabetes with respect to the potential increase in walking
15 capacity [123]. In elderly patients, HBT potentially improves quality of life to a similar
16 extent as revascularization does [124].
17 Considering the frequency of HBT training, 3 weekly sessions was the most commonly
18 used strategy (range: 3 weekly sessions to daily sessions) [107]. For initiation, patients
19 should start with a duration of 20 minutes per session, progressively increasing the
20 duration to 60 minutes per session. HBT can be performed outside, around a track or
21 in a hallway at a self-selected pace [49,125].

22

23 **Mechanisms of response to exercise in PAD**

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

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

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

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

7 VEGF expression is partially regulated by the hypoxia-inducible factor-1 α (HIF-1 α) but
8 recently the peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-
9 1 α) has emerged as an important candidate in the exercise-induced angiogenic
10 response. PGC-1 α regulates the coordinated expression of mitochondrial proteins
11 encoded in the nuclear and mitochondrial genomes and is rapidly induced after
12 exercise. This protein has been called the “master regulator” of mitochondrial
13 biogenesis, and controls various aspects of muscle oxidative phenotype, while
14 transducing and integrating physiological signals governing metabolism,
15 differentiation, and cell growth, and suppressing a broad inflammatory response [127].
16 Thus, the PGC-1 coactivators serve as a central component of the transcriptional
17 regulatory circuitry that coordinates the energy-generating functions of mitochondria in
18 accordance with the metabolic demands imposed by exercise training undertaken by
19 patients with PAD.

20

21 **Exercise and revascularization**

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

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

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

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

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

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

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

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

9 The combination of EVT plus SET was also associated with a significantly lower risk
10 of revascularization or amputation on follow-up (3.5% vs. 17.3%, OR: 0.19; 95% CI:
11 0.09 to 0.40, $P < 0.0001$). The corresponding number needed to treat was 8 patients
12 (95% CI: 6 to 12). PFWD was reported in 2 studies with no difference between the 2
13 groups in random effects pooled analysis [137]. However, EVT alone is not associated
14 with better outcomes than SET [137,138].

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

18

19 **Effect of exercise on health-related quality of life and cognitive** 20 **function**

21 Poor HRQoL is associated with higher rate of mortality in patients with PAD [139].

22 Randomized controlled trials have shown that exercise training versus usual medical
23 care in patients with PAD not only improves the perceived walking distance and speed,
24 but also the functional status as measured by specific impairment questionnaires, as
25 the WIQ. When compared to controls, patients who complete any form of exercise

1 training significantly improve their WIQ speed (mean difference: 9.60; 95% CI: 6.98 to
2 12.23, $P \leq 0.001$); WIQ distance (mean difference: 7.41; 95% CI: 4.49 to 10.33, $P \leq$
3 0.001) and WIQ stair-climbing (mean difference: 5.07; 95% CI: 3.16 to 6.99, $P \leq 0.001$)
4 [78]. In addition, more general HRQoL evaluation scores (Short-Form Physical
5 Component Summary) also showed significant improvement following exercise
6 therapy (mean difference: 1.24; 95% CI: 0.48 to 2.01) [78]. Most of the studies showed
7 that 3- [140-142], or 6/12-month [87,94,143] exercise training improves patient's
8 perception of physical HRQoL, with lesser effects on mental HRQoL. However, in the
9 current literature, findings are inconsistent [74,78,144] and other studies did not find
10 the same effects [145-147]. It is interesting to note that the improvement in general
11 HRQoL scores (as SF-36) were mainly predicted by physical functional markers, such
12 as the distance covered during a 6MWT (6MWD) and the history of stumbling [148].
13 These data indicate that greater improvements in physical function following exercise
14 therapy are expected to have greater improvements in self-perceived HRQoL [148]. It
15 has recently been showed that improvements in 6MWD following SET are predictive
16 of augmentations in general HRQoL in patients with PAD [89]. Interestingly, changes
17 in treadmill performance, which are less representative of functional walking [45], were
18 not related to improvements in HRQoL [89].

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

1 neuroprotective mechanisms show promise for preserving cognitive performance
2 [150]. Scientific evidence based on functional and neuroimaging approach has
3 demonstrated that this relation could be mediated by improved brain integrity, including
4 adaptations in cerebral blood flow, volume and white matter integrity [151].

5

6 **Patient education**

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

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

1 walking ability in intervention versus control comparisons [153]. Effects on physical
2 activity and quality of life were mixed. Overall, the evidence was inconclusive and more
3 rigorous trials are needed that include a clear and complete description of the
4 education intervention. Participant feedback from three studies highlights intervention
5 features that may be important for improving physical activity: providing information
6 about PAD/IC and exercise; providing encouragement and support with self-
7 monitoring; and having group interaction while allowing space for individual discussion
8 [153].

9 Three other trials have tested exercise programs that had an educational component
10 in patients with PAD [154-156]. The GOALS trial [155] randomized 194 participants
11 either to a group-mediated cognitive behavioral intervention or an attention control
12 group. The intervention consisted of group meetings with a facilitator once weekly for
13 6 months. Discussion topics included effective behavior change methods, self-
14 monitoring, exercising in cold weather, managing leg pain during exercise, and
15 overcoming other obstacles to exercise adherence. At the 6-month follow-up, the
16 intervention group achieved a 53.5 meters greater increase in 6MWD compared with
17 the control group. Next, the HONOR trial [156] tested the efficacy of telephone
18 coaching combined with a wearable activity monitor and showed no improvement in
19 6MWD at the 9-month follow-up. Finally, the MOSAIC trial explored the effect of a
20 physiotherapist-delivered motivational interviewing intervention in 190 people with
21 PAD and IC [154]. A statistically significant mean difference of 16.7m in 6MWD was
22 observed at 3 months follow-up compared with usual care control [154]. The
23 contrasting results of these trials indicate that exercise programs that include education
24 are more likely to be successful if they include periodic visits to a medical center to
25 meet with a coach or include tailored behavior change components.

1

2 **Gender and exercise**

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

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

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

1 P = 0.04) [166]. This is particularly so in those with diabetes [120]. Reduced blood
2 volume expansion and slower oxygen kinetics occur in the calf musculature during
3 exercise in women with PAD with IC [167]. Further, recent data showed that this poor
4 response to exercise in women with IC and diabetes was not related to where the
5 intervention was performed, being impaired both in a supervised exercise class and a
6 home exercise setting [120]. This poorer response to exercise was also demonstrated
7 in the EXITPAD study, which showed that women with IC, independent of confounding
8 factors including diabetes, benefit less from supervised exercise and have significantly
9 lower MWD after 12 months. Higher level of metabolic syndrome presents in
10 postmenopausal women compared with similarly aged men, may contribute to this
11 [166]. On the contrary, it has recently been shown that multimodal SET (combining
12 strengthening of lower limbs and Nordic walking) significantly improves walking
13 performance (treadmill and overground) in women and men, with no difference
14 between groups [91,168]. Although not significant, it is interesting to note that women
15 had greater improvements (i.e., delta) than men [91].
16 The clinical implication is that women with IC may respond less well to current exercise
17 interventions and either need a greater 'dose' of exercise, or another intervention
18 separate or in combination with exercise, to obtain similar improvements in IC as that
19 seen in men with exercise alone.

20

21 **Situation in Europe**

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

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

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

13 Importantly, there is heterogeneity in form of SET in most of individual countries, with
14 existence of individual programs or practice of each hospital or community [173]. They
15 differ in respect of frequency, length and duration of training, type of exercise, as well
16 as by supervised physician [173]. Mostly, the SET is coordinated by
17 angiologist/vascular physician, but sessions are predominantly supervised by clinical
18 exercise physiologists or physiotherapists. SET for patients with PAD is sometimes
19 offered in cardiac rehabilitation centres. Training program duration is mostly 12 weeks
20 or less than 12 weeks, with session duration 30-60 min. Most often used training
21 modalities are combination of walking and resistance training, or walking training alone
22 [173].

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

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

4

5 **Gaps in evidence and further studies**

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

25

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Figure 1. Pathophysiology of limb symptoms in peripheral artery disease

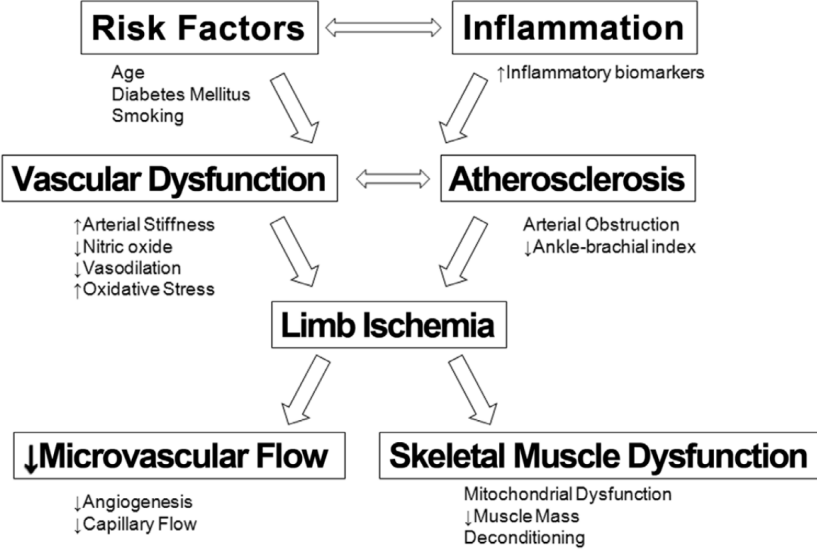
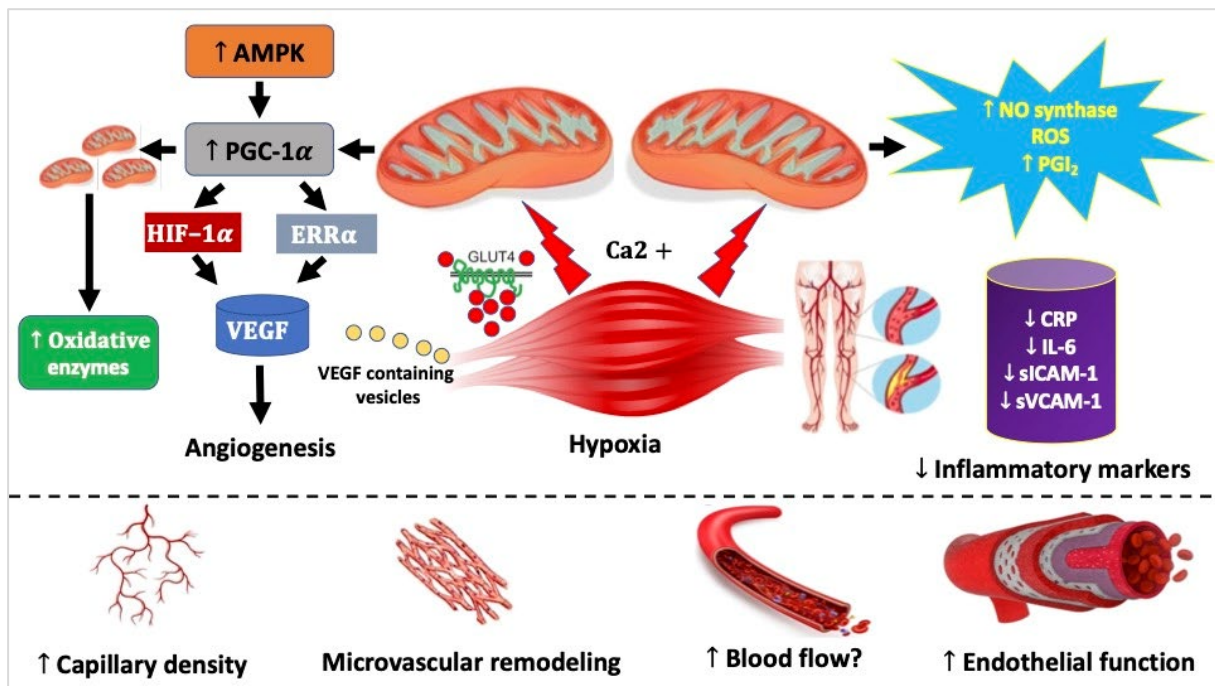


Figure 2. Dynamic exercise training induces extensive remodeling of the vascular system.



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 α , peroxisome proliferator-activated receptor gamma coactivator-1 α ; HIF-1 α , hypoxia inducible factor 1-alpha; ERR α , Estrogen-related receptor alpha; VEGF, Vascular endothelial growth factor; NO, nitric oxide; ROS, reactive oxygen species; PGI₂, prostacyclin; CRP, C-reactive protein; IL-6, interleukin-6; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, circulating vascular cell adhesion molecule-1.

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

Questionnaire name	Type (functional/QOL)	Domains tested
EQ-5D	General	Mobility, Self-Care, Usual Activity, Pain/Discomfort, Anxiety/Depression
WHOQOL	General	Physical health, psychological health, social relationships, environment
SEIQoL	General	5 dimensions chosen by the patient.
VascuQOL	PAD-specific	Pain, Symptoms, Activities and Social and Emotional well-being
ICQ	PAD-specific	Walking distance, walking speed, stair climbing
PADQOL	PAD-specific	Social relationship and interaction, self-concept and feelings, symptoms and limitations in physical functioning, fear and uncertainty, positive adaptation while living with PAD
SF-36	General	Physical function, bodily pain, general health, mental health, vitality, emotional well-being and social functioning
NHP	General	Energy, emotional reaction, sleep, pain, social isolation, physical mobility
Peripheral Artery Questionnaire (PAQ)	PAD-specific	Physical limitations, symptoms, social function, treatment satisfaction, quality of life
Walking impaired questionnaire (WIQ)	PAD-specific	Physical limitations, symptoms
Walking Estimated-Limitation Calculated by History (WELCH)	PAD-specific	Physical limitations, symptoms

Table 2. Training specificity and practical applications.

Training modality	Training frequency	Training duration	Claudication pain intensity	Exercise intensity [#]	Example protocol
Walking (treadmill or overground)	At least 3x per week	<p><u>Session's duration</u> Start at 10-15 min of actual exercise time</p> <p>Increase progressively up to 30-60 min of actual exercise time (including warm-up)</p> <p><u>Program duration</u> At least 12 weeks</p>	Near-maximum	<p><u>Low-to-moderate</u> HR_{peak}: ≤ 76% RPE: ≤ 13</p> <p><u>Vigorous</u> HR_{peak}: 77-96% RPE: 14 -17</p>	<p><u>Basic protocol (based on claudication pain intensity)</u></p> <ul style="list-style-type: none"> - Walk at a speed that induces the onset of claudication pain (2 out of 5 on the claudication pain scale) within 3 to 5 min and near-maximum claudication pain (4 out of 5 on the claudication pain scale) within 8 to 10 min. - Rest for 2 to 5 min (until pain resolution) before resuming walking. - Repeat this effort-rest cycle over 30-60 min, depending on exercise and pain tolerance. <p><u>Progression 1 (based on claudication pain intensity)</u></p> <ul style="list-style-type: none"> - If able to walk more than 10 min without reaching moderate claudication pain, increase the speed and/or the grade (treadmill) <p><u>Progression 2 (based on exercise intensity)</u></p> <ul style="list-style-type: none"> - If tolerated, perform walking bout at moderate-to-vigorous or vigorous exercise intensity. To that end, increase the walking speed and reduce the duration of each walking bout (1 to 4 min). This protocol also elicits targeted claudication pain.
Arm-ergometer	At least 3x per week		Pain-free	<p><u>Low-to-moderate</u> W_{peak}: 50-70% HR_{max}: ≤ 76% RPE: ≤ 13</p> <p><u>Vigorous</u> W_{peak}: 70-100%</p>	<p><u>First weeks of training</u></p> <ul style="list-style-type: none"> - 1-min effort at moderate-to-vigorous exercise intensity interspersed with 1 or 2-min rest. <p><u>Progression</u></p> <ul style="list-style-type: none"> - 2-min effort at moderate-to-vigorous or vigorous exercise intensity interspersed with 1 or 2-min rest.

Cycle-ergometer	At least 3x per week		Low to moderate	HR _{peak} : 77-96% RPE: 14 - 17	- Repeat this effort-rest cycle 4 (at the beginning) to 10-12 times, depending on exercise tolerance.
Resistance training	At least 3x per week		Low to moderate	<u>Low</u> <49% 1RM RPE : 9-11 <u>Moderate</u> 50-69% 1RM RPE : 12-13 <u>Vigorous</u> 70-84% 1RM RPE : 14-17	<u>First weeks of training</u> - 1 to 2 sets of 12-15 repetitions (6-8 exercises) performed at low-to-moderate exercise intensity. <u>Progression 1</u> - 2-3 sets of 8-12 repetitions (6-8 exercises) performed at moderate-to-vigorous intensity. <u>Progression 2</u> - 2-4 sets of 6-8 repetitions (6-8 exercises) performed at vigorous intensity. <u>Example of exercises targeting the major muscle groups of the upper and lower body</u> leg press, knee flexion, knee extension, calf press, chest press, seated row, hip abduction, hip extension.

HR_{peak}: peak heart rate; **RPE**: rate of perceived exertion [Borg's scale (6: "very very light"; 20: "maximal effort")]; **W_{peak}**: peak workload; **1RM**: one repetition maximum. #According to American College of Sports Medicine guidelines for exercise testing and prescription.