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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 programme
5 provides optimal results. This clinical consensus paper is intended for clinicians to
6 promote and assist for the set-up of comprehensive exercise programmes to best
7 advice in patients with symptomatic chronic PAD. Different exercise training protocols
8 specific for patients with PAD are presented. Data on patient assessment and outcome
9 measures are narratively described based on the current best evidence. The document
10 ends by highlighting disparities in access to supervised exercise programmes across
11 Europe, and the series of gaps for evidence requiring further research.

Graphical abstract

Included patients

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

Initial exercise training

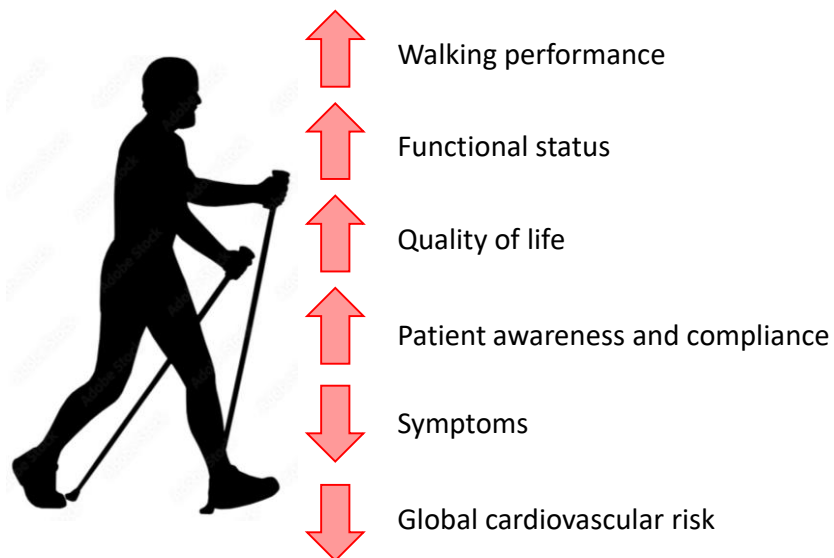
- Supervised exercise or home-based exercise training programmes
- *Training frequency*: at least 3 times per week
- *Training modality*: intermittent bouts of walking alternating with periods of rest are the first option. When walking is not an option, alternatives modalities (resistance training, arm-cranking, 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

Assessments prior and following exercise therapy

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

Chronic exercise training

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



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 guideline
5 document addressing the main aspects of exercise therapy and sports practice for
6 cardiac diseases ¹.

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

18 To address this gap, the ESC Working Group on Aorta & Peripheral Vascular Disease,
19 the ESVM, and the ESVS joined in a collaborative effort aiming to provide a roadmap
20 and guidance for the set-up and implementation of exercise therapy programmes for
21 patients with PAD.

1 **Consensus statements**

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

5
6 ▪ **2. In patients with PAD undergoing revascularisation, supervised exercise**
7 **programmes should be included as adjuvant therapy.**

8
9 ▪ **3. Supervised exercise programmes should ideally be coordinated by**
10 **vascular physicians, and sessions should be ideally supervised by**
11 **clinical exercise physiologists or physiotherapists.**

12
13 ▪ **4. Prior to exercise training initiation, complete medical history and**
14 **examination, and screening for contraindications should be investigated.**

15
16 ▪ **5. Measures of walking ability, functional status, and quality of life should**
17 **be assessed at the beginning and end of the programme to determine the**
18 **patient's response to exercise training. Clinical outcomes and patient**
19 **experience should also be documented.**

20
21 ▪ **6. Walking training (overground, pole striding, treadmill) should be**
22 **proposed as first line exercise modality. When walking is not an option,**
23 **alternative training modalities (resistance and strength training, arm-**
24 **cranking, cycling, combinations of exercise) should be performed.**

25

- 1 ▪ **7. The training frequency should be at least three times per week.**
- 2
- 3 ▪ **8. The training session duration should last a minimum of 30 min.**
- 4
- 5 ▪ **9. The training programme duration should last a minimum of 3 months.**
- 6
- 7 ▪ **10. Both claudication pain (A) and exercise intensity (B, based on common**
- 8 **training intensity measures such as heart rate or the rate of perceived**
- 9 **exertion (RPE) on Borg’s scale) should be evaluated during training**
- 10 **sessions:**
- 11 **A) The current consensus is that patients should exercise to moderate-**
- 12 **high claudication pain based on strong evidence. However, some**
- 13 **trials have recently demonstrated improvement in walking ability**
- 14 **using a low, or no pain approach. As claudication pain is a commonly**
- 15 **cited barrier to exercise, universally prescribing high-pain exercise**
- 16 **may lead to poor uptake of, and adherence to, exercise training**
- 17 **programmes. A more flexible approach to exercise prescription may**
- 18 **therefore be required, considering the patient’s needs and**
- 19 **preferences, and what might achieve a high level of (long term)**
- 20 **adherence.**
- 21 **B) Following a “lead-in period” of low-to-moderate exercise intensity, a**
- 22 **gradual progression to vigorous/high exercise intensity may be**
- 23 **proposed if well tolerated by the patient.**
- 24

- 1 ▪ **11. If supervised exercise is not available or feasible, a structured**
2 **community- or home-based exercise programme that includes behaviour**
3 **change techniques should be proposed.**
- 4
- 5 ▪ **12. Supervised exercise programmes should include structured education**
6 **and counselling on cardiovascular disease and PAD risk factor reduction.**
7 **Smoking cessation should be a cornerstone of risk factor counselling.**
- 8
- 9 ▪ **13. Following initial exercise training (supervised or home-based),**
10 **patients are encouraged to sustain lifelong and high levels of regular**
11 **physical activity.**

1 **Pathophysiology of intermittent claudication and functional impairment**

2 IC is characterised by exertional leg pain limiting walking ability⁵⁻⁷. PAD induces a wide
3 range of exercise-related symptoms experienced by nearly half of the PAD population
4⁸. The classical IC symptomology was first defined as calf pain, discomfort or fatigue
5 appearing during exercise and forcing the patient to stop⁹. Typically, IC is relieved
6 within 2-5 min after discontinuation of exertion⁹. Apart from this typical symptom, it is
7 now admitted that some patients with PAD may present atypical exercise-induced limb
8 symptoms¹⁰. These may be localised in lower limb muscles other than calves, may be
9 present at rest, may be described by patients as “burning”, “compressive” feeling, or
10 just “fatigue” without pain and may mimic limb pain due to spinal stenosis. Exercise-
11 induced limb symptoms in PAD are caused by a metabolic mismatch between oxygen
12 demand and supply⁵. The mismatch is linked to the reduction of the arterial lumen by
13 the atherosclerosis process, but it also induces cellular and metabolic disorders that
14 contribute to the functional impairment¹¹. Mechanisms of exercise-induced symptoms
15 are multifactorial among which nociceptive pain¹², nerve dysfunction¹³ and skeletal
16 muscle abnormalities¹¹ are suggested.

17 Potential mechanistic drivers of exertional limb symptoms in addition to arterial
18 obstruction and reduced perfusion include inflammation, vascular dysfunction, reduced
19 microvascular flow, impaired angiogenesis, and altered skeletal muscle function¹⁴⁻¹⁶
20 (Figure 1). A healthy vascular endothelium produces several vasodilator substances,
21 including nitric oxide (NO), which has pluripotent vascular benefits such as platelet
22 inhibition, smooth muscle cell proliferation inhibition, leukocyte adhesion prevention,
23 and angiogenesis induction. Diminished NO bioactivity in the lower limbs prevents
24 increased blood flow with exercise¹¹. Vascular dysfunction may also exacerbate the
25 vasoconstrictive effects of catecholamines and limit flow-mediated dilation¹⁷⁻²⁰.

1 Inadequate angiogenesis and collateral vessel formation may potentiate limb ischemia
2 and serve as a mechanism driving functional impairment ²¹. Skeletal muscle ischemia
3 may drive local inflammation, exacerbating symptoms and altering muscle metabolism
4 ²²⁻²⁴.

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

10

11 **Vascular and functional assessment in PAD**

12 ***Vascular assessment***

13 General assessment of CV risk factors should be performed prior to exercise training
14 rehabilitation to improve preventive measures and reach preventive goals. Ankle-
15 Brachial Index (ABI) should be assessed before starting a training programme to detect
16 and diagnose PAD and assess disease severity (Figure 2) ³. The measurement of ABI
17 after exercise is also important to further detect ankle pressure drop, as some patients
18 may have leg symptoms on exercise while ABI can be ≥ 0.91 at rest. A post-exercise
19 ankle systolic blood pressure drop $>30\text{mmHg}$ or a post-exercise ABI decrease $>20\%$
20 should be considered for PAD diagnosis ³⁷. In patients with media calcinosis (for
21 example in patients with diabetes or chronic kidney disease) measurement of ABI
22 might not be possible because the arteries cannot be compressed by the cuff. In these
23 cases, toe brachial index (TBI) can be used as alternative assessment (the
24 pathological threshold usually retained is <0.70) ³.

25 ***Walking distance assessment***

1 Walking distance is considered an important clinical outcome both for patients and
2 clinicians. Standardised exercise testing should be used for assessment of functional
3 impairment in patients with PAD (Figure 2).

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

23 *Six-minute Walk Test.* The six-minute walk test (6MWT) is performed along a flat
24 corridor with a length of 30m with turning points marked by a cone. Patients are asked
25 to walk self-paced for the full duration and may stop and rest at any point in the test⁴³.

1 The total distance walked is measured and reported as the six-minute walking distance
2 (6MWD) ⁴³. Any encouragement given/phrases used should be the same for every test
3 performed to ensure test-retest reliability ⁴³. Further, there may be a learning effect so
4 it is recommended that the best out of two walks is recorded or the first test discounted
5 ⁴⁴. Although treadmill-based exercise tests can establish maximum walking capacity,
6 there may be a poor correlation between treadmill outcomes, habitual walking, and
7 self-reported walking distance ⁴⁵. On the other hand, compared to treadmill test, the
8 6MWT has been shown to better represent daily life walking in patients with PAD ⁴⁶.
9 The 6MWT is a well-validated and low-cost test. It has good reliability, with a correlation
10 coefficient of 0.90 (p<0.001) and a coefficient of variation of 8.9% with testing
11 performed one to two weeks apart ⁴⁷. Changes in the 6MWT can be used to predict
12 mortality and mobility loss in patients with PAD ^{7,48}. The minimal detectable changes
13 (i.e. the statistical detectability of change beyond measurement error) in the 6MWT are
14 represented by a change >46 meters ⁴⁹. The minimal clinically important difference (i.e.
15 the clinical relevance or importance of the observed change from the patient's
16 perspective) in the 6MWT in patients with PAD is represented by an improvement of 8
17 ⁵⁰ or 9 meters ⁵¹ for small changes, and 20 ⁵⁰ or 38 meters ⁵¹ for large changes.

18

19 *Connected Devices.* A measure of “real-life” walking performances may be performed
20 by use of global positioning systems (GPS) or commercially available devices such as
21 activity trackers, smart watches and phones ⁵². Research has shown that GPS
22 recorders have good accuracy and reliability when compared to known distances
23 walked ^{53,54}, and measurement of step counts with mobile phones has been shown to
24 be highly reliable even at low walking speeds ⁵⁵. Further, GPS recorded walking
25 distances correlate well with treadmill walking distances ⁵⁶. Patients should be able to

1 note the initial onset of claudication pain and the maximal walking distance either in
2 total or between bouts of walking using the GPS system.

3

4 ***Muscle strength assessment***

5 The presence of PAD is associated with impaired lower extremity muscle strength and
6 function ⁵⁷, which is associated with high prevalence of frailty and sarcopenia ⁵⁸.
7 Muscle strength and function should therefore be assessed before and after
8 supervised exercise training (SET, Figure 2). There is heterogeneity in how muscle
9 strength and function are assessed. Muscle isokinetic strength and endurance can be
10 assessed via isokinetic dynamometry, which is a chair device that patients sit on and
11 the specific joint is tested in an appropriate position with the dynamometer attached to
12 the limb. Patients push against the dynamometer as it provides resistance to maintain
13 a set speed. Isokinetic dynamometry has demonstrated good reliability at the ankle
14 (reliability coefficients ranging from 0.77 to 0.96) ⁵⁹. Testing can be done in various
15 joints, including ankle, knee, and hip, in various planes such as extension and flexion.
16 As isokinetic dynamometry assessment includes specialised equipment it may not be
17 practical or convenient to assess patients using this device. As an alternative, the short
18 physical performance battery (SPPB) which includes a 4-metre walk test, a sit-to-stand
19 chair test, and a standing balance test, should be used ⁶⁰. A recent study showed that
20 the sit-to-stand is a validated test to estimate muscle power in patients with
21 symptomatic PAD ⁶¹. Interestingly, muscle power assessed by the sit-to-stand test was
22 related to overall functional performance prior and following SET ⁶¹.

23

24

25

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

2 In addition to objective assessment of functional impairment, a subjective (self-
3 reported) evaluation of walking abilities and health-related quality of life (HRQoL)
4 should be incorporated to have a complete assessment of the functional status of the
5 patient (Figure 2) ⁶²⁻⁶⁴. Following exercise interventions, assessing HRQoL is usually
6 used to determine if an objective improvement in functional performance is also
7 perceived by the patients in their daily life. Table 1 reports the most used subjective
8 tools used for walking ability and HRQoL assessment in patients with PAD. Trials used
9 a wide variety of questionnaires of patient reported outcomes measurements (PROMs)
10 ⁶²⁻⁶⁴. The most used are the short-form health 36 (SF-36), a generic questionnaire
11 including physical and mental items related to health), and the Walking Impairment
12 Questionnaire (WIQ), a PAD-specific questionnaire focusing on PAD and functional
13 limitations. Studies have shown that HRQoL burden is greater in magnitude in patients
14 with both PAD and CVD than with CVD alone ⁶⁵. In the PARTNERS study, the SF-36
15 Physical Component Summary of the combined PAD-other-CVD group was 46.3 ± 1.2
16 compared with 55.5 ± 1.1 in the other-CVD group ⁶⁵. Cross-sectional studies show that
17 in patients with PAD the degree of difficulty in walking distance and stair climbing are
18 significantly related to HRQoL ⁶⁶. The ESVS VASCUNET and the International
19 Consortium of Vascular Registries consensus statement recommended the Vascular
20 Quality of Life Questionnaire-6 (VasCu-QoL6) as a primary assessment of PROMs in
21 patients with symptomatic PAD ⁶².

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

1 **Exercise therapy in patients with PAD**

2 ***Screening prior to exercise training participation***

3 All patients should be medically screened before SET programme initiation (Figure 2).
4 It is suggested to include a complete medical history and examination ³⁸. Patients with
5 contraindications to exercise training (Table 2) should be excluded from SET until the
6 relevant condition stabilises or is successfully treated. For patients with current or prior
7 symptomatic cardiac disease (Table 3), we recommend that they are referred for
8 cardiology work-up, including an exercise test to assess for evidence of exercise-
9 induced coronary ischaemia, to identify if additional treatment for cardiac disease is
10 required before proceeding with SET. Comorbidities (such as neurological and
11 orthopedic diseases leading to gait abnormalities) should be documented and
12 considered for how they may limit SET programme participation feasibility. After SET
13 programme initiation, patients should continue to be closely monitored for changes in
14 health status (e.g., any symptom or situation which may suspect undiagnosed/incident
15 cardiac condition, ischemic limb pain at rest, toe or foot wounds) that might necessitate
16 interruption of the programme, at least temporarily.

17

18 ***Supervised exercise training***

19 SET is considered among first-line therapies for patients with chronic and symptomatic
20 PAD (Figure 2) ^{3,64,69,70}. SET is safe and is usually conducted in the hospital setting ⁷¹.
21 Over the past 60 years, many trials have reported the effectiveness of SET on walking
22 distances in these patients ^{72,73}. The most recent Cochrane meta-analysis showed that
23 SET improves PFWD (82 m; 95% IC: 72 – 92) and MWD (120 m; 95% IC 51 – 190) ⁷⁴.
24 Similar findings were observed in another meta-analysis [PFWD: 128 m (95% IC: 92 –
25 165); MWD: 180 m (95% IC: 130 – 238)] ⁷⁵. Although less well investigated or usually

1 reported as a secondary outcome, SET also improved functional status, gait pattern,
2 self-reported walking ability and quality of life ^{64,74,76-82}. It is interesting to note that
3 cardiac rehabilitation programmes also increase walking distance, HRQoL, and
4 physical activity in patients with symptomatic PAD, suggesting that other types of
5 rehabilitation than SET may also be useful ⁸³. Finally, some vasoactive drugs such as
6 cilostazol (phosphodiesterase type 3 inhibitor), pentoxifylline (xanthine derivative),
7 bosentan, sildenafil and others are claimed to increase walking capacity in patients
8 with PAD ⁸⁴⁻⁸⁷. However, the objective documentation of their effect is very limited to
9 draw extensive conclusions ^{84,88}. More studies are needed to confirm additive effect of
10 drug therapies to supervised exercise.

11

12 *Training modalities.* There are different types of exercise training for patients with PAD,
13 but the common aim is to improve walking capacity and reduce symptoms. In addition,
14 exercise should aim to improve balance and muscle strength to promote independence
15 and a reduced risk of falling in the long-term ³³. Treadmill and overground walking are
16 the most common and recommended training modalities in patients with IC (Figure 2)
17 ^{64,70}. However, due to severe exercise-induced ischemia, low pain tolerance, the risk
18 of falling and/or other co-morbidities, some patients are unwilling or unable to perform
19 walking sessions. In addition to walking training, there are several other forms of
20 training that are used, although much less frequently, in the rehabilitation of patients
21 with PAD. A recent meta-analysis reported that other non-walking training modes are
22 also effective as traditional walking training in improving walking performance, whereas
23 there was no clear evidence for changes in quality of life following exercise
24 interventions. However, the authors concluded that the certainty of this evidence was
25 judged to be low ⁸⁹. Different training modes include strength training of large muscle

1 groups^{90,91}, cycling⁹², pole striding^{93,94}, multimodal training^{76,77,95-98} and training with
2 an arm-crank ergometer^{99,100}. The beneficial effect of these training modalities can
3 usually be described as large and even reach those of typical walking training¹⁰¹.
4 However, the PFW and the MWD have the tendency to be higher with walking training
5 than with strength training when all studies are considered⁸⁹. In contrast, self-reported
6 ability to climb stairs (assessed by the Walking Impairment Questionnaire) is more
7 improved following strength training (29.2% vs. 43.8% after 6 months) compared to
8 walking training on the treadmill (39.6% vs. 43.8% after 6 months)¹⁰². Therefore, when
9 walking is not an option, alternative training modalities might also be effective. These
10 training modalities also elicit lower or no pain during exertion compared to walking,
11 which might lead to higher rates of adherence.

12

13 *Training frequency.* Based on a previous meta-analysis, and shared by most of the
14 studies and guidelines, the training frequency associated with greater improvements
15 in walking distance is at least 3 times per week^{103,104}.

16

17 *Training duration.* Identifying an optimal training duration is difficult to elucidate, mainly
18 due to differences in training modalities, frequencies, and intensities among studies.
19 Current guidelines reported that optimal training duration ranges between 12 and 24
20 weeks^{64,70,103}. The optimal training session duration has not been widely investigated.
21 Additionally, in most studies, the total session duration is usually reported without
22 specifying the actual time spent exercising. The literature shows that exercise sessions
23 lasting 30 to 60 min were the most effective to improve walking performance^{103,104}.

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. The Borg scale is a
5 subjective assessment tool used to measure an individual's perceived exertion or effort
6 during physical activity. The scale assigns a numerical rating ranging from 6 to 20 to
7 indicate the intensity of exertion experienced by the person ¹⁰⁵.

8 First, the majority of trials used claudication pain severity to provide guidance during
9 the training sessions. In PAD research, the claudication pain scale, an ordinal scale
10 from 0 (no pain) to 4 (severe/maximal pain), is the most commonly used tool. A
11 distinction is made between walking training with and without muscle pain caused by
12 ischemia. With regards to claudication pain intensity, international guidelines are
13 heterogeneous ^{38,64,70}. The UK NICE guideline encourages patients to exercise to the
14 point of maximal pain , the American Heart Association guideline recommends
15 moderate to moderate/severe claudication pain as tolerated ⁶⁴, while an international
16 consensus as well as the Australian guideline does not specify pain intensity for
17 exercise dosage ¹⁰⁶. Based on strong evidence ^{64,73-75,104}, the current consensus is that
18 patients should exercise to moderate-high claudication pain to improve walking
19 performance. Also, one-year home-based walking training performed at high-intensity
20 pain has been found to be more effective than walking training performed at low-
21 intensity for improving walking and functional performance in patients with PAD ^{107,108}.

22 These findings indicate that claudication pain intensity may be a key factor for walking
23 improvement in these individuals. In contrast, others have reported that improvements
24 in walking performance may be obtained with less severe claudication pain during
25 exertion ¹⁰¹. According with recent findings, walking training with pain is not clearly

1 superior to walking training without pain regarding changes in walking distances ¹⁰⁹⁻¹¹².

2 It may be assumed that walking training with moderate, low, or no pain is associated
3 with higher compliance and possibly long-term maintenance of training or change in
4 activity behaviour ¹¹². This indicates that a more flexible approach to exercise
5 prescription may therefore be required, considering the patient's needs and
6 preferences, and what might achieve a high level of (long term) adherence. Larger
7 studies with a higher number of cases and longer duration, taking compliance into
8 account, are needed for a conclusive statement ¹¹³.

9 Second, the optimal no/low pain-based exercise training intensity is understudied in
10 this population. Indeed, it is interesting to note that the claudication pain severity does
11 not necessarily rely on common measures of exercise intensity ^{78,114}. For example,
12 when performing vigorous-intensity exercise, some patients may experience
13 moderate-to-severe claudication pain, whereas others, low levels of claudication only.
14 Assuming that exercise intensity is a cornerstone determinant of physiological
15 response to training ¹¹⁵, monitoring claudication pain only is limiting and prevents
16 accurate comparison of exercise effectiveness in patients with PAD. This may also
17 explain the large variability in the magnitude of improvements following exercise
18 interventions ^{64,103}. Fassora et al. ⁷⁸ recently reported that both training modality and
19 exercise intensity should be considered when looking for the best results in walking
20 performance and cardiorespiratory fitness. Notably, these results showed that walking
21 at vigorous intensity ($\%HR_{peak}$: 77-95, $\% \dot{V}O_{2peak}$: 64-90, RPE: ≥ 14 ¹¹⁵) induced the
22 greatest improvement in MWD, while cycling and other non-walking modalities
23 performed at vigorous intensity elicited the greatest improvements in cardiorespiratory
24 fitness ⁷⁸. These findings suggest that both walking and cardiorespiratory capacities
25 are desirable outcomes but that they need different exercise therapy programmes ⁷⁸.

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

5 The monitoring of the exercise intensity during a resistance training program is
6 mediated by the percentage of the one repetition maximum (1RM) ¹¹⁶. The
7 determination of the 1RM plays a key role to objectively set an individualised
8 resistance-based program ¹¹⁶. Compared to a direct assessment of the 1RM, the
9 multiple RM assessment (such as 10RM, the maximum weight a person can lift for 10
10 repetitions) is considered to be a safe and well tolerated approach to evaluate muscle
11 strength for a given muscle group in patients with cardiovascular diseases ¹¹⁶.

12 Following the multiple RM test, different prediction equations are available to estimate
13 the 1RM ¹¹⁷. As also used in the cardiac rehabilitation, a target exercise intensity of 30-
14 70% of 1RM for the upper body, and 40–80% of 1RM for the lower body should be
15 considered ¹¹⁷. Exercise intensity should be progressively increased to determine the
16 patient's exercise response and exercise tolerance. It has been shown that resistance
17 training improves walking performance and muscular strength in patients with PAD ¹¹⁸.

18 Notably, high intensity (i.e. 80% 1RM) induces the best improvements in walking
19 performance when compared to low-to-moderate (i.e. <50% 1RM) strength training
20 intensity in these patients ^{90,118}.

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

23
24
25

1 ***Home-based exercise training***

2 In comparison with patients not undergoing exercise training, a home-based training
3 (HBT) strategy resulted in a non-significant increase of MWD in a recent meta-analysis
4 (mean difference: 136 m; 95% CI: -2 to 273 m; $p = 0.05$) ¹¹⁹. When comparing HBT
5 with basic exercise advice, no improvement of MWD was observed in patients
6 following a HBT strategy (mean difference: 39 m; 95% CI: -123.1 to 201.1 m; $p = 0.64$)
7 ¹¹⁹. Regarding PFWD, HBT led to a greater increase than exercise advice did (mean
8 difference: 64.5 m; 95% CI: 14.1 to 114.8 m; $p = 0.01$) ¹¹⁹. In comparison with HBT,
9 SET was more effective in improving MWD (mean difference: 139 m; 95% CI: 45 to
10 232 m; $p = 0.004$) and PFWD (mean difference: 84 m; 95% CI: 25 to 143 m; $p = 0.005$)
11 ¹¹⁹.

12 Considering the effect of monitoring in HBT, no difference in the change of MWD and
13 PFWD were observed between monitored HBT and SET (mean difference in MWD: 8
14 m; 95% CI: -81 to 97 m; $p = 0.86$; mean difference in PFWD: 43 m; 95% CI: -29 to 114
15 m; $p = 0.24$) ¹¹⁹. The equality in training efficacy of monitored HBT and SET
16 emphasises the role of monitoring in HBT programmes. Apart from regular on-site
17 visits or phone calls, activity diaries or log books have been used for HBT monitoring
18 ¹¹⁹. Additional tools for self-monitoring, such as wrist-worn activity trackers with
19 smartwatch-like functions or smartphone accelerometer applications have been
20 assessed, however, it still needs to be clarified, which modality is most appropriate ⁵⁵.
21 The effect of training on patients' daily physical activity was assessed by several
22 studies implementing pedometer- and accelerometer-measurements. A network meta-
23 analysis demonstrated improvements of daily physical activity in HBT to a similar
24 extent as it was observed in patients undergoing SET ¹²⁰.

1 Focusing on quality of life, most studies reported improvements in patients undergoing
2 HBT ¹¹⁹. In comparison with SET, improvements of individual SF-36 measures (pain
3 and social functioning) and Walking Impairment Questionnaire measures (distance)
4 were less pronounced in patients undergoing HBT ¹¹⁹. In addition, HBT improves
5 measures of self-efficacy for walking, satisfaction with functioning, pain acceptance
6 and social functioning in patients with claudication ¹²¹. Follow-up data of patients who
7 had undergone HBT suggest sustained improvements in measures of quality of life,
8 functional and walking capacity after termination of the active training intervention
9 ^{122,123}.

10 Safety of HBT was analysed in a systematic review including 27 studies, which
11 reported a cardiac event rate of 1 per 49,270 and a non-cardiac event rate of one per
12 147,810 ¹²⁴. Event rates of HBT were lower than event rates reported for SET (HBT
13 vs. SET: cardiac 1:49,270 vs. 1:13,788; non-cardiac: 1:147,810 vs. 1:41,363) ¹²⁴.
14 Regarding overall mortality, retrospective data suggest a reduction of long-term
15 mortality in patients undergoing HBT ¹²⁵. Comparing HBT with SET, overall mortality
16 rates do not differ between patients undergoing HBT and patients following a SET
17 programme ¹²⁶. The results of the reported meta-analyses and reviews should be
18 viewed with caution according to a moderate to low quality of evidence ^{119,126,127}. Due
19 to the limited availability and utilisation of SET programmes, HBT programmes can be
20 used as a valid alternative training modality for patients with IC ¹²⁸⁻¹³¹.

21 Data on sex-specific differences in the efficacy of HBT are inconsistent ^{132,133}. In
22 females, the efficacy of HBT appears to be more strongly related to the individual
23 training intensity than in males ¹³⁴. Regarding co-morbidities, HBT seems to be less
24 effective in patients with diabetes with respect to the potential increase in walking
25 capacity ¹³⁵. In elderly patients, HBT potentially improves quality of life to a similar

1 extent as revascularisation does ¹³⁶. Considering the frequency of HBT training, 3
2 weekly sessions was the most commonly training strategy (range: 3 weekly sessions
3 to daily sessions) ¹¹⁹. For initiation, patients should start with a duration of 20 minutes
4 per session, progressively increasing the duration to 60 minutes per session. HBT can
5 be performed outside, around a track or in a hallway at a self-selected pace ^{51,137}.

7 ***Long-term adherence to exercise therapy***

8 In clinical practice, long-term adherence to therapy is a major problem. Participating in
9 SET programmes may help patients to acquire awareness of the disease and learn the
10 importance of exercise and how to practice it. SET programmes can be regarded as a
11 transition phase to improve self-management and may serve as a bridge for those
12 patients that need it to other forms of exercise approach such as community or home-
13 based exercise. Telemedical monitoring through step counting with pedometers or
14 activity monitors proved to be effective ^{138,139}, as did supervised structured walking
15 exercise to improve pain-free and maximal walking distance ¹¹⁹. In addition to
16 monitoring, factors such as education, self-efficacy, goal setting, feedback, and a
17 training plan were critical to successful outcomes ¹¹⁹. This should be used more
18 frequently in clinical practice to increase long-term adherence but needs to be
19 demonstrated in long-term studies.

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

22 Exercise represents a major challenge to whole-body homeostasis provoking
23 widespread perturbations in numerous cells, tissues, and organs that are caused by or
24 are in response to the increased bio-energetic activity of the contracting skeletal
25 musculature ¹⁴⁰. The exercise training-induced increase in functional capacity and the

1 concomitant amelioration of diverse maladaptive responses that ultimately reduce
2 claudication symptoms in patients with PAD, are underpinned by several inter-
3 dependent physiological, metabolic, and mechanical mechanisms. After several
4 months of exercise training there is extensive remodelling of the vascular system, and
5 although direct sampling of the vasculature in humans *in vivo* is limited, the trained
6 musculature provides a valid proxy, being the primary tissue involved in training
7 adaptation ¹⁴⁰. The dynamic biochemical and mechanical environment around blood
8 vessels arising from the forces provoked during skeletal muscle contractile activity (i.e.,
9 shear stress and passive stretch), as well as signals stimulated by the increases in
10 muscle energetic demand (i.e., increases in AMP concentration, reduced oxygen
11 delivery) activate several intracellular signalling pathways responsible for promoting a
12 regulatory network governing the transcriptional control of mitochondrial biogenesis
13 and respiratory function along with enhanced expression of pro-angiogenic factors ¹⁴¹
14 (Figure 3).

15 Over time, this results in the initiation of capillary growth and a proliferation in the
16 number of arterioles. Such structural remodelling is driven by a complex and often-
17 redundant sequence of events that include NO, and prostaglandins. Indeed,
18 mechanical, neural, and humoral factors, including those released from contracting
19 skeletal muscle, have all been implicated in the remodelling response, with the
20 vascular endothelial growth factor (VEGF) signalling pathway and downstream targets
21 ultimately driving skeletal muscle capillary expansion ¹⁴¹. Muscle activity increases
22 VEGF in the muscle interstitium and subsequently acts on the VEGF receptors,
23 VEGFR-1 and VEGFR-2 on the capillary endothelium, activating multiple downstream
24 pathways via signalling intermediates such as mitogen activated protein kinases
25 (MAPK), phosphatidylinositol-3-Kinase ¹⁴². The time-course of remodelling varies and

1 is largely a function of the blood vessel size, and while many of these adaptations are
2 restricted to the vascular beds of the trained muscles, improved endothelial function
3 appears to be a whole-body response to exercise training, even in individuals with
4 PAD.

5 VEGF expression is partially regulated by the hypoxia-inducible factor-1 α (HIF-1 α) but
6 recently the peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-
7 1 α) has emerged as an important candidate in the exercise-induced angiogenic
8 response. PGC-1 α regulates the coordinated expression of mitochondrial proteins
9 encoded in the nuclear and mitochondrial genomes and is rapidly induced after
10 exercise. This protein has been called the “master regulator” of mitochondrial
11 biogenesis, and controls various aspects of muscle oxidative phenotype, while
12 transducing and integrating physiological signals governing metabolism,
13 differentiation, and cell growth, and suppressing a broad inflammatory response ¹⁴³.
14 Thus, the PGC-1 coactivators serve as a central component of the transcriptional
15 regulatory circuitry that coordinates the energy-generating functions of mitochondria in
16 accordance with the metabolic demands imposed by exercise training undertaken by
17 patients with PAD.

18

19 **Exercise and revascularisation**

20 Current guidelines recommend SET programmes as an initial treatment modality for
21 patients with IC ^{3,144}. Revascularisation is recommended for patients with IC when they
22 do not respond to initial exercise and medical therapies ¹⁴⁵. However, the role of
23 revascularisation as an initial treatment option alone or as an upstream adjunct to SET
24 in patients with IC remains controversial.

1 Several trials have compared endovascular therapies with or without SET versus SET
2 alone as an initial treatment strategy for patients with PAD with IC and reported
3 inconsistent results ¹⁴⁶⁻¹⁴⁹.

4 The relevant aspect of exercise training may be the reduction of the inflammatory
5 process in patients with PAD. In a recent trial, reactive oxygen species (ROS) formation
6 was measured using the luminol analogue L-012 for patients with IC, randomised
7 either to home-based training alone or in addition to endovascular therapy (EVT) ¹⁵⁰.
8 Follow-up was performed after 3 months. ROS production after NOX2 (NAPDH
9 oxidase 2) stimulation showed a significant reduction in both groups at follow-up (EVT
10 group: $p = 0.002$, exercise group: $p = 0.019$), with a higher relative reduction in ROS
11 in the EVT group than in the exercise group ($p = 0.014$).

12 The data regarding the benefit of SET alone or in combination with EVT or EVT alone
13 are rare. A robust evaluation of existing data comes from a meta-analysis comparing
14 the different treatment approaches ¹⁵¹. A total of 987 patients from 7 randomized
15 control trials (constituting 9 total comparison arms) with a median follow-up duration of
16 12.4 months (range 10 to 18 months) were enrolled. Of these, 530 patients were
17 randomized to EVT versus SET alone, and 457 patients to EVT plus SET versus SET
18 alone ¹⁵¹. For the effect of EVT alone versus SET alone (5 comparison arms) a random
19 effects model showed no significant difference in the MWD (standardised mean
20 difference (SMD): -0.11 (95% CI: -0.59 to 0.36); $p = 0.64$) on follow-up between the 2
21 groups, neither for the PFWD, need for revascularisation or amputation. On pooled
22 analysis, the ABI was significantly higher among participants that underwent EVT
23 alone as compared with SET only (SMD: 0.64 ; 95% CI: 0.38 to 0.90 , $p < 0.0001$;
24 weighted mean difference (WMD): 0.15 ; 95% CI: 0.10 to 0.19 , $p < 0.0001$).

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

6 The combination of EVT plus SET was also associated with a significantly lower risk
7 of revascularisation or amputation on follow-up (3.5% vs. 17.3%, OR: 0.19; 95% CI:
8 0.09 to 0.40, $P < 0.0001$). The corresponding number needed to treat was 8 patients
9 (95% CI: 6 to 12). PFWD was reported in 2 studies with no difference between the 2
10 groups in random effects pooled analysis ¹⁵¹. However, EVT alone is not associated
11 with better outcomes than SET ^{151,152}. Among patients with stable PAD and IC,
12 compared with SET alone, endovascular revascularisation in combination with SET is
13 associated with improved outcomes.

14 Exercise training after surgical revascularisation also improves outcomes compared to
15 revascularisation without exercise training. Although much less investigated, few
16 publications exist on the impact of exercise on the outcome after surgical
17 revascularisation of symptomatic PAD. One small RCT compared patients after bypass
18 surgery ($n=14$) ¹⁵³. Group I had standard preoperative and postoperative care and the
19 intervention group (group II) had SET 4-10 weeks postoperatively. MWD, mean
20 increase in ABI and improvement in WIQ were significantly better in group II. In another
21 recent study, patients who underwent above knee femoropopliteal bypass were divided
22 into two groups: those who continued regular exercise after bypass operation with
23 those who discontinued exercise after surgery ¹⁵⁴. After propensity score matching, 5-
24 year primary and secondary patency (PP: 97% vs. 61%, $p = 0.0041$; SP: 100% vs.
25 69%, $p = 0.0021$), and freedom from major adverse cardiovascular events (61% vs.

1 24%, $p = 0.0071$) were significantly better in patients who continued exercise. One
2 systematic review included all RCTs with either surgical or endovascular
3 revascularisation to evaluate the evidence on the efficacy of lower limb
4 revascularisation combined with supervised exercise training in patients with PAD ¹⁵⁵.
5 Eight trials with 726 patients showed that combined therapy led to greater
6 improvements in PFWD and MWD compared with revascularisation or supervised
7 training alone. In 2 out of 8 studies, revascularisation was surgical and in 6 studies it
8 was endovascular.

9

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

11 Poor HRQoL is associated with higher rate of mortality in patients with PAD ¹⁵⁶.
12 Randomised controlled trials have shown that exercise training versus usual medical
13 care in patients with PAD not only improves the perceived walking distance and speed,
14 but also the functional status as measured by specific impairment questionnaires, as
15 the WIQ. When compared to controls, patients who complete any form of exercise
16 training significantly improve their WIQ speed (mean difference: 9.60; 95% CI: 6.98 to
17 12.23, $p \leq 0.001$); WIQ distance (mean difference: 7.41; 95% CI: 4.49 to 10.33, $p \leq$
18 0.001) and WIQ stair-climbing (mean difference: 5.07; 95% CI: 3.16 to 6.99, $p \leq 0.001$)
19 ⁸⁰. In addition, more general HRQoL evaluation scores (Short-Form Physical
20 Component Summary) also showed significant improvement following exercise
21 therapy (mean difference: 1.24; 95% CI: 0.48 to 2.01) ⁸⁰. Most of the studies showed
22 that 3- ¹⁵⁷⁻¹⁵⁹, or 6/12-month ^{94,102,160} exercise training improves patient's perception of
23 physical HRQoL, with lesser effects on mental HRQoL. However, in the current
24 literature, findings are inconsistent ^{74,80,161} and other studies did not find the same
25 effects ¹⁶²⁻¹⁶⁴. It is interesting to note that the improvement in general HRQoL scores

1 (as SF-36) were mainly predicted by physical functional markers, such as the distance
2 covered during a 6MWT (6MWD) and the history of stumbling ¹⁶⁵. These data indicate
3 that greater improvements in physical function following exercise therapy are expected
4 to have greater improvements in self-perceived HRQoL ¹⁶⁵. It has recently been
5 showed that improvements in 6MWD following SET are predictive of augmentations in
6 general HRQoL in patients with PAD ⁹⁶. Interestingly, changes in treadmill
7 performance, which are less representative of functional walking ⁴⁶, were not related
8 to improvements in HRQoL ⁹⁶.

9 Regular physical activity is also known to improve cognitive functioning and brain
10 health across the lifespan ¹⁶⁶. Cross-sectional and experimental studies show that
11 greater amounts of physical activity are linked to better cognitive function in adults,
12 with the best performances for exercise programmes that are structured,
13 individualised, higher intensity, longer duration, and multicomponent ¹⁶⁷. These results
14 support a dose-dependent neuroprotective relationship between physical exercise and
15 cognitive performance. Physical exercise interventions aimed at improving brain health
16 through neuroprotective mechanisms show promise for preserving cognitive
17 performance ¹⁶⁷. Scientific evidence based on functional and neuroimaging approach
18 has demonstrated that this relation could be mediated by improved brain integrity,
19 including adaptations in cerebral blood flow, volume and white matter integrity ¹⁶⁸.

20

21 **Patient education**

22 All patients with PAD should be offered oral and written information about their disease
23 so they can share decision-making and understand what they can do to help manage
24 their condition. The role of exercise should be clearly explained, and patients should
25 be supported to exercise regularly (assuming no contraindications). The impact of

1 patient education regarding exercise is probably dependent on several factors,
2 including the specific information that is provided, the timing and mode of delivery, and
3 the nature of any interventions that are delivered concomitantly (e.g., SET). Patient
4 education in the form of brief exercise advice, when delivered in isolation, confers little
5 benefit and results in minimal improvement in individuals' walking distances ¹⁶⁹.
6 Structured education programmes, on the other hand, may have greater potential to
7 improve exercise behaviour and walking distances by building the knowledge and skills
8 of patients to enable them to successfully self-manage their condition ¹⁷⁰. Key
9 programme features include: a structured evidence-based curriculum that includes
10 content on the nature of the condition and the role of exercise; delivery by trained
11 educators; and embedded quality assurance processes ¹⁷⁰.

12 A systematic review by Abaraogu et al. ¹⁷⁰ identified six studies (1,087 participants)
13 that had investigated the effects of structured education for patients with PAD and IC.
14 The interventions varied widely, but all included education sessions, exercise
15 prescription, and behaviour change techniques. Four trials reported improvements in
16 walking ability in intervention versus control comparisons ¹⁷⁰. Effects on physical
17 activity and quality of life were mixed. Overall, the evidence was inconclusive and more
18 rigorous trials are needed that include a clear and complete description of the
19 education intervention. Participant feedback from three studies highlights intervention
20 features that may be important for improving physical activity: providing information
21 about PAD/IC and exercise; providing encouragement and support with self-
22 monitoring; and having group interaction while allowing space for individual discussion
23 ¹⁷⁰.

24 Three other trials have tested exercise programmes that had an educational
25 component in patients with PAD ¹⁷¹⁻¹⁷³. The GOALS trial ¹⁷² randomized 194

1 participants either to a group-mediated cognitive behavioural intervention or an
2 attention control group. The intervention consisted of group meetings with a facilitator
3 once weekly for 6 months. Discussion topics included effective behaviour change
4 methods, self-monitoring, exercising in cold weather, managing leg pain during
5 exercise, and overcoming other obstacles to exercise adherence. At the 6-month
6 follow-up, the intervention group achieved a 53.5 meters greater increase in 6MWD
7 compared with the control group. Next, the HONOR trial ¹⁷³ tested the efficacy of
8 telephone coaching combined with a wearable activity monitor and showed no
9 improvement in 6MWD at the 9-month follow-up. Finally, the MOSAIC trial explored
10 the effect of a physiotherapist-delivered motivational interviewing intervention in 190
11 patients with PAD and IC ¹⁷¹. A statistically significant mean difference of 16.7 m in
12 6MWD was observed at 3 months follow-up compared with usual care control ¹⁷¹. The
13 contrasting results of these trials indicate that exercise programmes that include
14 education are more likely to be successful if they include periodic visits to a medical
15 centre to meet with a coach or include tailored behaviour change components.

16

17 **Sex and exercise**

18 Prevalence of PAD in women is similar to men at all ages ^{174,175}. However, women are
19 more likely to have asymptomatic PAD and less likely to report IC ¹⁷⁶. Decreased
20 detection and subsequent intervention may then result in a higher proportion of women
21 with severe disease and chronic limb-threatening ischemia. Further, women who
22 undergo revascularisation tend to be older and have more severe PAD compared to
23 men, and these factors can affect outcomes of procedures adversely ¹⁷⁷. Contradictory
24 results exist on women with PAD and mortality rates ¹⁷⁸⁻¹⁸⁰. Population studies suggest
25 a trend towards higher mortality rates in women with lower ABI ¹⁷⁹.

1 Exercise performance has been used to suggest that women decline faster in terms of
2 functional ability once PAD is established. However, this difference may in fact merely
3 be due to the smaller muscles in the calves of women ¹⁸¹. McDermott et al. ¹⁸² showed
4 that at 4 years of follow-up, women were more likely to become unable to walk for 6
5 min continuously than men, more likely to develop mobility disability, had faster
6 declines in walking velocity, and the distance achieved in the 6MWT was less.
7 However, these apparent sex differences in functional decline were attenuated after
8 additional adjustment for baseline calf muscle area, and so may be attributable to
9 smaller baseline calf muscle area in women. Interestingly poorer leg strength is
10 associated with increased mortality in men, but not in women, with PAD ¹⁸¹.

11 The data on the efficacy of exercise rehabilitation in women with PAD compared to
12 men are scarce. What is known, however, is that women with IC seem to have a poorer
13 response to exercise rehabilitation, smaller changes in PFWD and MWD following
14 three months of exercise than men (Δ 280 meters for men vs Δ 220 meters for women;
15 $p = 0.04$) ¹⁸³. This is particularly so in those with diabetes ¹³². Reduced blood volume
16 expansion and slower oxygen kinetics occur in the calf musculature during exercise in
17 women with PAD with IC ¹⁸⁴. Further, recent data showed that this poor response to
18 exercise in women with IC and diabetes was not related to where the intervention was
19 performed, being impaired both in a supervised exercise class and a home exercise
20 setting ¹³². This poorer response to exercise was also demonstrated in the EXITPAD
21 study, which showed that women with IC, independent of confounding factors including
22 diabetes, benefit less from supervised exercise and have significantly lower MWD after
23 12 months. Higher level of metabolic syndrome presents in postmenopausal women
24 compared with similarly aged men, may contribute to this ¹⁸³. On the contrary, it has
25 recently been shown that multimodal SET (combining strengthening of lower limbs and

1 Nordic walking) significantly improves walking performance (treadmill and overground)
2 in women and men, with no difference between groups ^{98,185}. Although not significant,
3 it is interesting to note that women had greater improvements (i.e., delta) than men ⁹⁸.
4 The clinical implication is that women with IC may respond less well to current exercise
5 interventions and either need a greater 'dose' of exercise, or another intervention
6 separate or in combination with exercise, to obtain similar improvements in IC as that
7 seen in men with exercise alone.

8

9 **Situation in Europe**

10 Despite of the large body of evidence highlighting benefits, SET is underused, and its
11 availability and adherence is low ^{128-130,186-192}. To note, the rate of clinicians referred a
12 patient for SET is very low ¹²⁸. The reasons and barriers for not participating in SET
13 programmes are lack of facilities, feeling worse, costs, time, lack of motivation, and
14 comorbidities ^{128,130,187}.

15 The situation with SET in Europe varies from country to country. A recent European
16 survey showed that supervised exercise programmes exist in Austria, Belgium, Czech
17 Republic, France, Germany, Italy, Sweden, Switzerland, and United Kingdom ¹⁹³.
18 However, SET is reimbursed by the health insurance only in Austria, Belgium, France,
19 Germany, Sweden, and Switzerland ¹⁹³. In the United Kingdom, SET programmes are
20 funded by the National Health Service. In contrast, SET is not reimbursed in Czech
21 Republic, Italy, and it even does not exist for patients with PAD in Denmark, Greece,
22 Ireland, Poland, Serbia, Slovakia, Slovenia, or Ukraine ¹⁹³. Similarly, the structured
23 home-based exercise programme is not routinely present in European countries ¹⁹³.
24 Importantly, there is heterogeneity in form of SET in most of individual countries, with
25 existence of individual programmes or practice of each hospital or community ¹⁹³. They

1 differ in respect of frequency, length and duration of training, type of exercise, as well
2 as by supervising professional ¹⁹³. Mostly, the SET is coordinated by
3 angiologist/vascular physician, but sessions are predominantly supervised by clinical
4 exercise physiologists or physiotherapists. SET for patients with PAD is sometimes
5 offered in cardiac rehabilitation centres. Training programme duration is mostly 12
6 weeks or less, with session duration 30-60 min. Most often used training modalities
7 are combination of walking and resistance training or walking training alone ¹⁹³.
8 To standardise SET programmes and provision across Europe, the following steps are
9 required: 1) a more widespread availability of SET programmes and standardised
10 outcomes to assess their effectiveness; 2) a more defined harmonisation of SET
11 characteristics (establish process of referral, supervision, coordination, selection of
12 patients, SET protocols); 3) health insurance reimbursement of costs; and 4) action to
13 improve the public knowledge about the benefits of SET ¹⁹³.

14

15 **Gaps in evidence and further studies**

16 Awareness and access to supervised exercise programmes should be a field of further
17 studies. Additionally, there are still many areas of insufficient or inconsistent evidence
18 in the treatment of claudication with exercise therapy. We do not know the optimal
19 therapy in terms of duration of the single walking session or intensity of training. We
20 have few studies on the impact of no, or low pain-based exercise and the data on sex
21 differences are inconsistent. The combination of walking exercise with non-walking
22 training has not been yet established. Also, we need more evidence to better
23 understand the potential role of wearable monitoring during exercise interventions, and
24 to evaluate on the efficacy of supportive interventions that can be used together with
25 exercise therapy. For example, the effect of different hydration strategies used during

1 exercise training needs more evidence. In a non-randomised study, Parodi et al.
2 reported mean increase in treadmill walking from 100 meters to 535 meters in 131
3 patients, who were treated with hydration, determined as drinking at least 2000 mL of
4 water during 24 hours for a period of 6 months and to ingest albumin and salt (3.5
5 g/day) ¹⁹⁴.

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

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

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1 **Figures titles and abbreviations**

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

4

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

6

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

13

14 **Figure 3.** Dynamic exercise training induces extensive remodeling of the vascular
15 system. *Skeletal muscle contraction is associated with several physiological, metabolic
16 and mechanical mechanisms that when repeated over several weeks and months,
17 result in mitochondrial biogenesis, angiogenesis, and increases in the functional
18 capacity of individuals with peripheral arterial disease. AMPK = AMP-activated protein
19 kinase; PGC-1 α = peroxisome proliferator-activated receptor gamma coactivator-1 α ;
20 HIF-1 α = hypoxia inducible factor 1-alpha; ERR α = Estrogen-related receptor alpha;
21 VEGF = Vascular endothelial growth factor; NO = nitric oxide; ROS = reactive oxygen
22 species; PGI₂ = prostacyclin; CRP = C-reactive protein; IL-6 = interleukin-6; sICAM-1
23 = soluble intercellular adhesion molecule-1; sVCAM-1 = circulating vascular cell
24 adhesion molecule-1.*