

BMJ Open Short-duration aerobic high-intensity intervals versus moderate exercise training intensity in patients with peripheral artery disease: study protocol for a randomised controlled trial (the Angiof-HIIT Study)

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To cite: Lanzi S, Pousaz A, Fresa M, *et al.* Short-duration aerobic high-intensity intervals versus moderate exercise training intensity in patients with peripheral artery disease: study protocol for a randomised controlled trial (the Angiof-HIIT Study). *BMJ Open* 2024;**14**:e081883. doi:10.1136/bmjopen-2023-081883

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2023-081883>).

Received 09 November 2023
Accepted 25 March 2024



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ABSTRACT

Introduction Supervised exercise training is among the first-line therapies for patients with peripheral artery disease (PAD). Current recommendations for exercise include guidance focusing on claudication pain, programme and session duration, and frequency. However, no guidance is offered regarding exercise training intensity. This study aims to compare the effects of 12-week-long supervised walking exercise training (high-intensity interval training (HIIT) vs moderate-intensity exercise (MOD)) in patients with chronic symptomatic PAD.

Methods and analysis This study is a monocentric, interventional, non-blinded randomised controlled trial. 60 patients (30 in each group) will be randomly allocated (by using the random permuted blocks) to 12 weeks (three times a week) of HIIT or MOD. For HIIT, exercise sessions will consist of alternating brief high-intensity ($\geq 85\%$ of the peak heart rate (HR_{peak})) periods (≤ 60 s) of work with periods of passive rest. Patients will be asked to complete 1 and then 2 sets of 5–7 (progressing to 10–15 $\times$ 60 s) walking intervals. For the MOD group, exercise training sessions will consist of an alternation of periods of work performed at moderate intensity ($\leq 76\% HR_{peak}$) and periods of passive rest. Interventions will be matched by training load. The primary outcome will be the maximal walking distance. Secondary outcomes will include functional performance, functional capacity, health-related quality of life, self-perceived walking abilities, physical activity and haemodynamic parameters.

Ethics and dissemination The Angiof-HIIT Study was approved by the Human Research Ethics Committee of the Canton de Vaud (study number: 2022-01752). Written consent is mandatory prior to enrolment and randomisation. The results will be disseminated via national and international scientific meetings, scientific peer-reviewed journals and social media.

Trial registration number NCT05612945.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This monocentric, interventional, non-blinded randomised controlled trial compares the effects of 12-week-long supervised short-duration high-intensity walking versus moderate-intensity exercise training in patients with chronic symptomatic peripheral artery disease.
- ⇒ The study includes large panel assessments aimed at investigating the effects of exercise training intensity on different components of functional performance, functional capacity, health-related quality of life, self-perceived walking abilities, physical activity and haemodynamic parameters.
- ⇒ Training programmes will be conducted on a block periodisation paradigm basis and will be matched for training load allowing for a precise investigation of the impact of exercise intensity on the different outcomes.
- ⇒ Due to the nature of the study, the intervention cannot be blinded.

INTRODUCTION

Peripheral artery disease (PAD) is a chronic atherosclerotic vascular disease characterised by narrowing or occlusion of the lower limb arteries, thus resulting in reduced blood flow perfusion.¹ The incidence of PAD is increasing worldwide and is now recognised as being a serious public health problem.^{1–3} Intermittent claudication (IC) is a typical symptom of PAD. IC is defined as reproducible ischaemic lower limb muscle pain occurring during exertion, which is due to an imbalance between oxygen supply and demand, and it is rapidly relieved with rest.¹ IC negatively affects physical activities of daily life.⁴ Patients with PAD also exhibit functional impairments,⁴ gait abnormalities⁵

and muscle strength weakness.⁶ This leads to decreased health-related quality of life (HRQoL).⁷ Participation in light (eg, regular walking or household chores) and moderate (eg, brisk walking) physical activity is related to a lower risk of all-cause and cardiovascular mortality in these patients.⁸

Supervised exercise training (SET) is considered among the first-line therapies for patients with PAD.^{2-4,9-11} SET improves walking performance, which is usually considered as the primary outcome.^{4,9,12-14} Cardiorespiratory fitness (peak oxygen uptake ($\% \text{VO}_{2\text{peak}}$)) and HRQoL have also been found to be improved with this training.^{4,13-16} The current recommendations include guidance in terms of optimal claudication pain severity, programme and session duration, and frequency and modality.^{2,4,9,10,17-19} However, little guidance is offered regarding training intensity. Training session monitoring using common training intensity measures, such as $\%$ of peak heart rate ($\% \text{HR}_{\text{peak}}$), cardiorespiratory fitness ($\% \text{VO}_{2\text{peak}}$) or the rate of perceived exertion (RPE), remains underused.^{9,15,20} PAD trials did not distinguish between symptom intensity and common training intensity measures.^{4,9,11-13,16,21-24} Claudication pain severity does not necessarily correlate with exercise intensity.^{15,20} When assuming that exercise intensity is a determinant of the physiological response to training,²³ the sole monitoring of claudication pain is limiting. This may prevent the comparison of the effectiveness of exercise training in these patients²⁰ and also potentially explain the variability usually observed in the extent of improvements.^{4,25} In this context, it has been demonstrated that vigorous-intensity exercise can improve $\text{VO}_{2\text{peak}}$ more than light-to-moderate exercise therapy intensity in these patients.^{13,15} Furthermore, it has recently been shown that walking at vigorous intensity led to the greatest improvement in maximal walking distance (MWD).¹⁵

High-intensity interval training (HIIT) is characterised by short, repeated bouts of exercise performed at a vigorous intensity interspersed by periods of active or passive recovery.²⁶ HIIT is more time-efficient than low-to-moderate exercise training and could be a more attractive training mode. The benefits, safety and feasibility of HIIT have been shown in patients with cardiovascular diseases.²⁷⁻³¹ Despite initial evidence suggesting that HIIT may provide benefits in patients with PAD,³² very few existing studies have confirmed this effect.^{15,32} It seems that short-duration high-intensity bouts (≤ 60 s) are the most well-received HIIT protocols in patients with cardiovascular diseases.³³ When considering the claudication pain during exertion in patients with PAD, especially if the exercise is performed at high intensity, the choice of a short-interval duration seems to be relevant to ensure feasibility. To our knowledge, only one study has recently investigated the feasibility of a short-duration (≤ 60 s) HIIT approach.³⁴ The findings of that study³⁴ showed that, with relevant prescreening, HIIT may be safe, well tolerated and effective in patients with symptomatic PAD. However, this study³⁴ did not include a comparator group

performing moderate-intensity exercise training (MOD). The performance of a randomised controlled trial (RCT) is crucial to discern which exercise training intensity induces better improvements in walking performance and other common disease-related outcomes. This would be helpful in optimising the effectiveness of exercise therapeutic care.

Aims

This study aims to compare the effects of 12-week-long supervised walking exercise training (short-duration HIIT intervals vs moderate exercise intensity) on MWD in patients with chronic symptomatic PAD. The secondary objective of this study is to compare the effects of training on cardiorespiratory fitness, functional performance, HRQoL, physical activity and haemodynamic parameters.

It is hypothesised that treadmill performance would be improved to a greater extent after HIIT. Greater improvements in cardiorespiratory fitness, functional performance, HRQoL and physical activity after HIIT would also be expected.

METHODS AND ANALYSIS

This protocol for the Angiof-HIIT Study adheres to the Standard Protocol Items: Recommendations for Clinical Trials reporting guidance (online supplemental appendix 1).³⁵

Study design

This study is a monocentric, interventional, non-blinded RCT. Patients will be randomly allocated to 12 weeks of HIIT or MOD exercise training. The interventions and outcome assessments will be conducted by research staff.

Study setting

The interventions and outcome assessments will take place in the Angiology Department and Sports Medicine Department of the Lausanne University Hospital (CHUV), Lausanne, Switzerland. The study began in March 2023, and it is currently ongoing. The study is planned to be completed by December 2027.

Eligibility criteria

The eligibility criteria are presented in [Box 1](#).

Study recruitment and procedures

[Figure 1](#) displays the patient pathway of the Angiof-HIIT Study. Patients with symptomatic chronic PAD who are eligible to participate in a supervised or home-based exercise training programme at the Angiology Department will be asked to participate in the Angiof-HIIT Study and be given the study information sheet. Recruitment will be performed during routine vascular medicine visits. At least 48 hours later, a phone call will confirm their willingness to participate in the study.

Patients who are willing to enter the study will be directed for the inclusion procedures ([figure 1](#)). Before inclusion, each patient will be systematically evaluated

Box 1 Eligibility criteria

Inclusion criteria

- ⇒ Adult patients with chronic symptomatic PAD (Fontaine stage IIa/b).
- ⇒ ABI ≤ 0.9 or drop by 20% following exercise treadmill test, or TBI ≤ 0.6 if incompressible arteries.
- ⇒ Signed written informed consent form.

Exclusion criteria

- ⇒ Age < 18 years.
- ⇒ Critical limb-threatening ischaemia.
- ⇒ Previous participation in SET programmes ≤ 1 year.
- ⇒ Cardiac contraindication to exercise.
- ⇒ Neurological and neuromuscular disorders and other comorbidities (orthopaedic, rheumatological) leading to gait abnormalities.
- ⇒ Prior leg/foot amputation.
- ⇒ Incapacity of discernment.

ABI, ankle-brachial index; PAD, peripheral artery disease; SET, supervised exercise training; TBI, toe-brachial index.

by a cardiologist to assess the absence of contraindications to exercise.^{36–38} Subsequently, patients will sign the informed consent form (online supplemental appendix 2) and be referred to the baseline assessment (figure 1).

Patients who decide not to take part in the study will be proposed to participate in our multimodal SET^{39–45} or home-based programme. If the patient declines these options, verbal advice on the importance of physical activity will be given (figure 1).

Intervention

Both training interventions (HIIT and MOD) will consist of 36 supervised treadmill sessions spread over 12 weeks (three sessions per week). Each session will last between 30 and 60 min.^{49 11 25} Each training session will be supervised by a clinical exercise physiologist.⁹ Training interventions will be performed at the Division of Angiology on a treadmill (Cosmed T150, Italy) equipped with a harness and chest belt to secure the patients and to prevent any incidence of falling. HR and RPE on the Borg's scale⁴⁶ will be used for the monitoring of objective and subjective exercise training intensity, respectively.⁹ Treadmill speed and slope will be continuously adjusted to ensure the intensity target for each training intervention. Each training session will start and end with a 5 min warm-up and cool-down period. The number of patients who have sufficiently adhered to the treatment protocol, such as completing a minimum of 80% of sessions over 12 weeks (29 of 36 sessions), will be reported. A minimum of 80% completion rate is most frequently used as a surrogate of satisfactory adherence in patients with PAD and cardiovascular diseases.^{47 48}

Block periodisation and training load

The 12-week (HIIT and MOD) exercise training period will be conducted on a block periodisation paradigm basis (figure 2). HIIT and MOD will consist of three 4-week blocks of training (figure 2). HIIT and MOD will be designed to be matched by the total exercise training load

by using the TRaining IMPulseS (TRIMPS) approach.⁴⁹ TRIMPS will be calculated by using Banister's method⁴⁹:

$$TRIMPS = \text{session duration (min)} \times \%HRR \times k$$

where % of the heart rate reserve (%HRR) = $(HR_{\text{exercise}} - HR_{\text{rest}}) / (HR_{\text{peak}} - HR_{\text{rest}})$, and k is a weighted coefficient of $0.64.e^{1.92 \times \%HRR}$ (males) and $0.86.e^{1.67 \times \%HRR}$ (females).

Each block will be composed of 3 weeks of progressive increase in training load by $\sim 10\%$ per week, followed by a 40–60% decrease in training load during the fourth week of training (figure 2). During the fourth week of training, the exercise sessions for both groups will be performed at low intensity ($\leq 63\%$ HR_{peak} ; RPE: 9–11). The training load will be gradually increased by $\sim 10\text{--}20\%$ per block (figure 2).

HIIT group

Exercise training sessions will consist of an alternation of brief periods (≤ 60 s) of work performed at high intensity and a brief period of passive rest (figure 3). Patients will be asked to complete 1 and then 2 sets of 5–7 (progressing to 10–15 $\times 60$ s) walking intervals. It is expected that patients will achieve the target intensity at the end of the second/third walking interval. The total number of walking intervals will be adjusted to ensure that every training session will be performed at the target training load. The sustaining of high-intensity exercise may be challenging for naïve patients.⁵⁰ A 'lead-in period' of moderate exercise training intensity seems relevant before commencing HIIT.^{9 50} Patients in the HIIT group will perform 2 weeks of moderate-intensity exercise training. Afterwards, the exercise intensity will be targeted.⁹

The training intensity in the HIIT group will be set at $\geq 85\%$ HR_{peak} recorded during the maximal cardiopulmonary exercise test (CPET).^{31 50} The RPE on the Borg's scale (≥ 15)⁴⁶ will also be used to monitor the subjective exercise training intensity. The HIIT work-to-rest ratio will be individually adapted to ensure the feasibility of the training method based on the patient's tolerance and claudication pain severity management during exertion. To that end, different work-to-rest ratios will be adopted: 1:2 (the rest period will be twice as long as the effort phase), 1:1.5 (the rest period will be 50% superior to that of the effort-phase duration), 1:1 (effort and rest will have the same time period), 1.5:1 (the effort period will be 50% superior to that of the rest-phase duration), 2:1 (the effort period will be twice as long as the rest phase).

MOD group

The training approach of the MOD group will be in line with current recommendations.⁹ Exercise training sessions will consist of an alternation of periods of work performed at moderate intensity and periods of passive rest (figure 3). The exercise training intensity will be set at $\leq 76\%$ HR_{peak} recorded during the maximal CPET.²³ The RPE on the Borg's

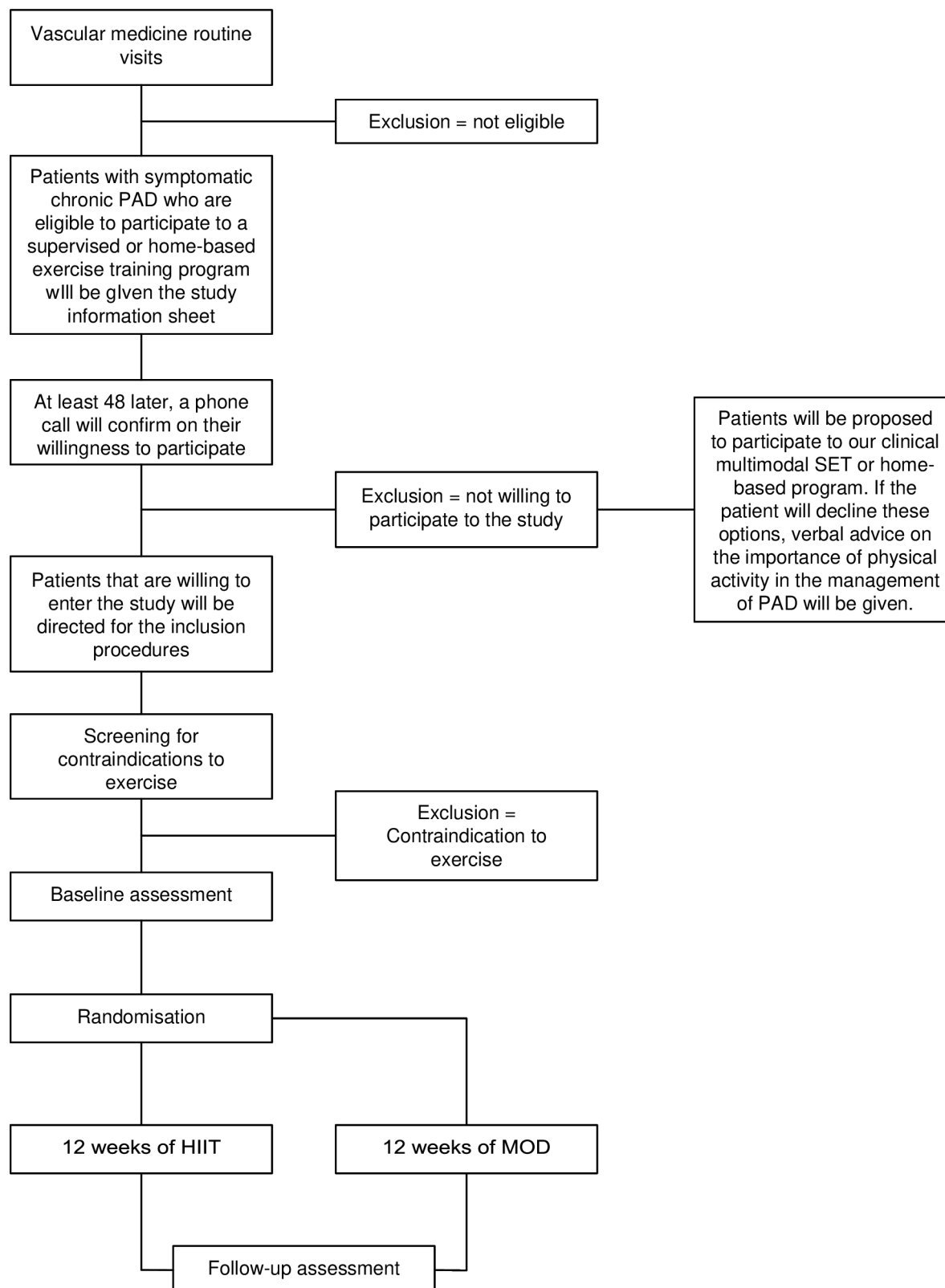


Figure 1 Study flow chart. HIIT, high-intensity interval training; MOD, moderate-intensity exercise training; PAD, peripheral artery disease; SET, supervised exercise training.

scale (≤ 13) will also be used to monitor the exercise training intensity. Compared with the HIIT group, no fixed work-to-rest ratio will be applied.⁹ The duration of each walking bout will depend on the

claudication pain severity and the targeted exercise intensity. Patients will be instructed to rest until pain resolution (or almost resolution) before resuming walking.

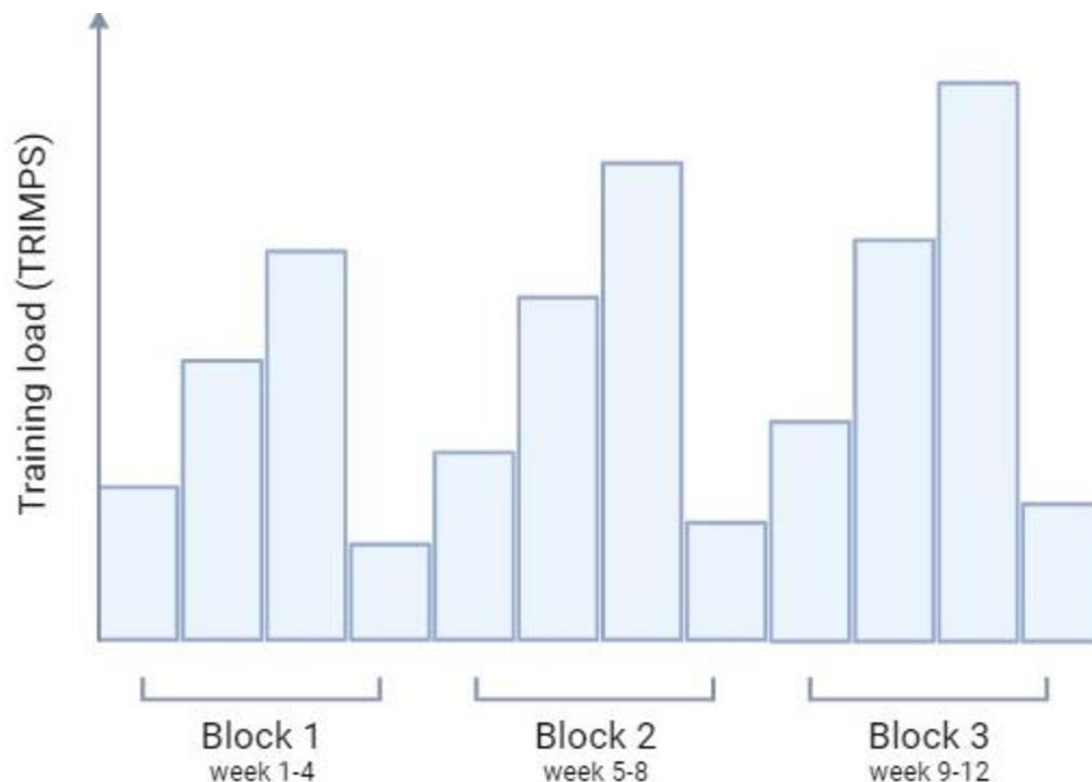


Figure 2 Schematic representation of the block periodisation exercise training programme. TRIMPS, TRaining IMPulseS.

Randomisation

The allocation ratio of randomisation will be 1:1 by using the random permuted block randomisation method. For allocation, a computer-generated list of

random permuted blocks will be used (<https://www.sealedenvelope.com>).

Participants will be enrolled in the study by the principal investigator. The allocation sequence will be set

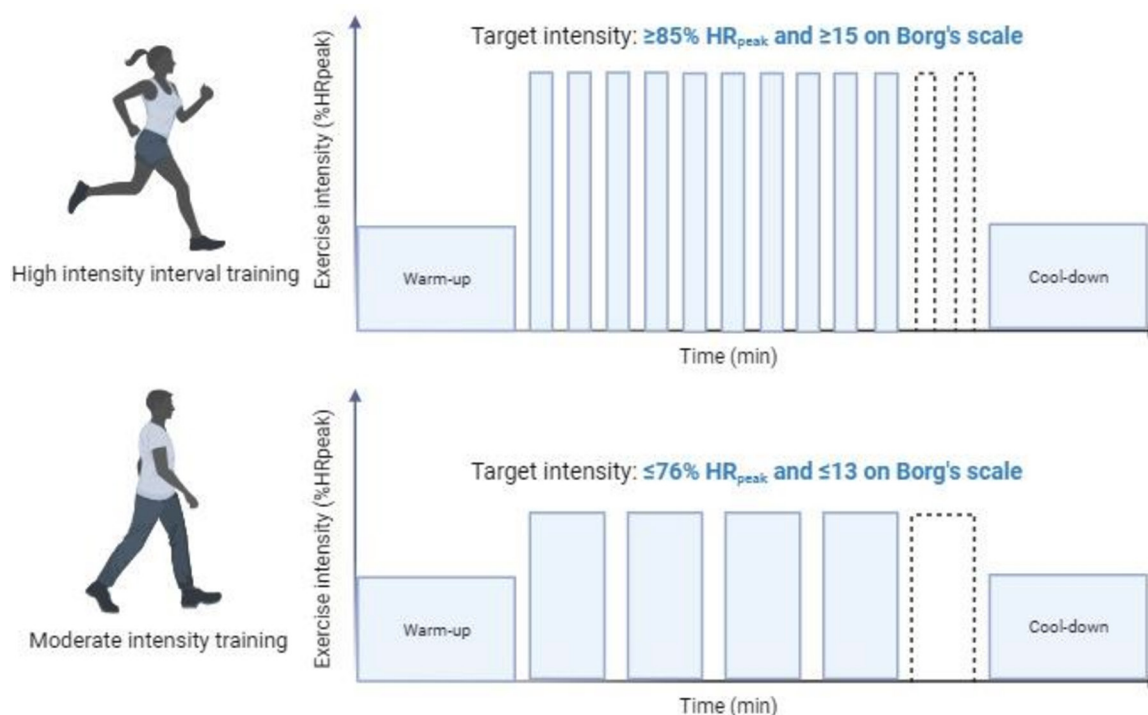


Figure 3 Schematic representation of the high-intensity interval and moderate-intensity training interventions. HR_{peak} , peak heart rate.

in sequentially numbered, opaque, sealed envelopes. Envelopes will be opened by the principal investigator after the enrolled patients provide signed consent and complete all the baseline assessments.

Due to the nature of the study, the intervention cannot be blinded for the patients. Additionally, the exercise physiologists delivering both training interventions cannot be blinded. The primary outcome investigators will be blinded to the group allocation.

Sample size calculation

The sample size was assessed based on the results of the only study investigating the effects of exercise training intensity using longer (2 min) walking intervals in patients with PAD.⁵¹ A total of 46 patients will be needed to detect a significant mean difference in MWD on treadmill (primary outcome) of 110 m and a pooled SD of 99 m between groups (Cohen's d value: 0.4; power: 80%; $\alpha=5\%$). Considering some potential dropouts (30%), a sample size of 60 patients (30 in each group) will be recruited.

Outcome measures

Primary outcome

The primary outcome of the study will be the MWD assessed during a graded treadmill test.

Secondary outcomes

Different secondary outcomes will be assessed: (1) pain-free walking distance (PFWD) assessed during a maximal graded treadmill test; (2) muscle oxygenation assessed during the maximal graded treadmill test; (3) cardiorespiratory fitness; (4) functional performance; (5) HRQoL and self-perceived walking abilities; (6) physical activity and (7) haemodynamic parameters.

Measures

Assessments of primary and secondary outcomes will be performed before the first training session and between 5 and 14 days following the last training session.

Cardiorespiratory fitness

Patients will complete a maximal CPET on a treadmill by using a modified Balke protocol to determine VO_{2peak} and HR_{peak} . After a 3 min rest where baseline values will be recorded during the last 30 s, the initial walking speed will be set at a constant speed of 3.2 km/hour and at a 0% grade. The grade will progressively increase by 1%/min until exhaustion. Oxygen consumption (VO_2), carbon dioxide production (VCO_2) and ventilation will be measured by using a Cortex Metalyzer 3B gas exchange analyser (Cortex Biophysik, Leipzig, Germany), which will be calibrated for flow and gas concentrations before every procedure according to the manufacturer's recommendations. VO_{2peak} will be defined as the highest 20 s mean value recorded before the patient's volitional termination of the test.⁵² HR_{peak} will be defined as the highest 5 s average peak value that is obtained during the test. Ventilatory threshold 1 (VT_1) will be defined according to

three criteria⁵²: (1) the excess VCO_2 relative to VO_2 with the modified V-slope method; (2) the identification of hyperventilation relative to VO_2 ; and (3) the exclusion of hyperventilation relative to VCO_2 at the inflection point, as identified by criteria 1 and 2. Two experienced investigators will mutually determine VT_1 .

The number of patients having at least two out of four of the following maximal criteria will be assessed: achievement of $\geq 85\%$ age-predicted maximum HR, a respiratory exchange ratio >1.10 , RPE >17 and blood lactate concentration ≥ 8 mmol/L.⁵³ Due to the fact that it has been shown that patients with PAD do not systematically achieve a maximal effort,^{34 54 55} all of the recorded data will be included in the analyses regardless of whether a maximal effort is achieved.

ECG signals will be continuously monitored with a Custo Cardio 200 (Custo Med, Ottobrunn, Germany). The CPET conclusions before inclusion will be used to assess the absence of cardiac contraindications to exercise.

Graded treadmill test

Patients will be instructed to avoid vigorous physical activities, cigarette smoking and alcohol use before the test. Before the test, patients will rest for 15 min. Patients will perform a graded treadmill test to determine the MWD (primary outcome) and PFWD.⁵⁶ The initial walking speed will be set at 3.2 km/hour and at 0% grade. The grade will be increased by 2% every 2 min.⁵⁶ During the test, patients will be asked to indicate the exact moment of the beginning of the leg pain (PFWD) and the moment at which it will be impossible to continue the test due to achieving maximal claudication pain (MWD). The treadmill screen (timer, distance and slope) will be hidden from the patient. Handrail support will be allowed to maintain balance. Immediately after graded treadmill test, the RPE on the Borg's scale (6: 'very very light'; 20: 'maximal effort')⁴⁶ and the claudication pain severity on a 0-point to 4-point Claudication Pain Scale³⁸ will also be recorded. Afterwards, patients will be asked to immediately lie down and will be asked to indicate when the claudication pain completely disappears.

Muscle oxygenation

During the graded treadmill test, muscle oxygenation of the gastrocnemius muscle will be assessed via near-infrared spectroscopy (NIRS, PortaMon, Artinis, The Netherlands),⁵⁷ which is a non-invasive system measuring muscle oxygen saturation (StO_2) and is indicative of tissue oxygenation.⁵⁸ The NIRS probe will be placed over the lateral gastrocnemius muscle of the most symptomatic leg. Calf StO_2 will be continuously recorded throughout the treadmill test. Baseline calf StO_2 values will be assessed after 3 min of standing, at the appearance of pain and at the end of the test. Each point will be calculated as the average during the 15 s before each time point. Additionally, the time to reach the minimum calf StO_2 value and the area under the curve for the deoxygenation period during exercise will be assessed.^{59 60} The reoxygenation

time in the supine position (the time from the end of the test until calf StO₂ returns to baseline) will also be recorded.^{59 60} The signal will be recorded at 10 Hz with a differential pathlength factor of 6.0. Data will be downsampled to 1 Hz.

Functional performance

The tests will be performed on the same day and time and in the same order, as presented below. To ensure feasibility, patients will be allowed to rest from 5 to 10 min between each test.

Preferred walking speed and gait analysis

Patients will perform a 15 m walking test. The preferred walking speed (PWS) will be measured between 5 and 10 m to avoid the acceleration and deceleration phase.⁶¹ This test will be performed three times, and the PWS will be calculated as the mean of the two speed trials, thus excluding the largest difference among the three trials.⁶¹ As previously described,^{40 41} patients will wear Physilog (GaitUp, Lausanne, Switzerland), which includes two inertial measurement units that will be used to evaluate spatiotemporal gait and foot kinematics parameters.^{62 63}

Six-minute walking test

The six-minute walking test (6MWT) will be performed following standardised criteria.⁶⁴ In an indoor 30 m corridor, patients will be asked to walk as far as possible within 6 min to determine the 6-minute walking distance.⁶⁵ Patients will be informed that they are allowed to stop during the test and/or lean against the wall. If so, they will be instructed to resume walking as soon as they can. During the test, encouragement will be used, according to the guidelines.⁶⁵ The PFWD during the 6MWT will also be recorded. At the end of the test, the RPE on the Borg's scale⁴⁶ and the claudication pain severity on a 0-point to 4-point Claudication Pain Scale³⁸ will be recorded. The 6MWT will be performed twice, and the best attempt will be considered. HR will be continuously measured during the test. Moreover, the mean HR value and the average HR value of the last 15 s of the test will be assessed to investigate the cardiovascular response.

Ascending and descending stair performance

Patients will be asked to ascend and descend a 12-step staircase as quickly as possible.^{66 67} Verbal encouragement will be given during the test. The first stopwatch will be stopped when both patients' feet reach the last stair during the ascending stair (ascending stair performance). The second stopwatch will be stopped when both patients' feet reach the last stair during the descending stair (ascending and descending stair performance). To ensure safety and balance, the use of the handrail will be allowed. The test will be performed twice, and the average of the two attempts will be considered.^{44 66–68}

Short Physical Performance Battery

The Short Physical Performance Battery is composed of three tests assessing functional performance: a standing

balance test, 4-metre walking test and sit-to-stand chair test.⁶⁹ The tests will be performed as previously described.⁶⁸

Unipedal stance test

Patients will be asked to hold the unipedal stance position for a maximum of 60 s on both legs.⁶⁸

30 and 60 s repeated sit-to-stand chair test

Patients will be asked to stand up from a chair to a fully extended standing position as many times as possible within 30 and 60 s with their arms folded across their chest.⁶⁷ Verbal encouragement will be given during the test. The number of completed repetitions that are achieved will be recorded. The highest HR value obtained during each test will be recorded to investigate the cardiovascular response.

Health-related quality of life and self-perceived walking abilities

As previously described,⁴² the Medical Outcomes Study Short-Form 36 will be used to evaluate physical and mental HRQoL,⁷⁰ and the Walking Impairment Questionnaire⁷¹ will be used to assess self-perceived walking abilities.

Physical activity

Physical activity levels will be measured for 7 consecutive days by using an accelerometer (MTI/CSA GT3X+, Actigraph, Pensacola, Florida, USA).⁷² The accelerometer will be attached to an elastic belt, and patients will be asked to wear it at the right waist level. To accurately assess physical activity levels, at least 4 days with at least 10 hours of wearing time per day will be needed.⁷³ Sedentary, light, moderate and vigorous-intensity activities will be classified as ≤99 counts/min, 100–1800 counts/min, 1800–3799 counts/min and >3800 counts/min, respectively.⁷³ The mean daily step count will also be assessed. Data analysis will be performed by using Actilife software (V.6.02, Actigraph, Pensacola, Florida, USA), with a 60 Hz sample frequency and 60 s epochs.

Haemodynamic assessment and physical characteristics

Medical history and vascular examination will be performed. Resting ankle-brachial index and toe-brachial index will be recorded according to guidelines.²

Data collection and management

Coded data will be reported on a case report form and subsequently stored in an electronic database via REDCap. Coded data will be stored on a secure server (with high security standards) at Lausanne University Hospital. Paper data (consent forms and questionnaires) will be kept in a secure cabinet in the principal investigator's office. Access to REDCap will be limited for the research staff. Data will be conserved for a duration of 10 years after study completion. To assess and ensure the safety of the interventions, adverse and serious adverse events will be monitored.

Data monitoring will include a site initiation visit, a first visit after inclusion of 6 (10%) patients, a visit for every 12

(20%) patients who are included and a final visit after the last visit of the last patient.

Statistical analyses

The REDCap database will be exported to SPSS V.29 software (IBM Corporation).

Data will be analysed with an intention-to-treat approach. In the case of missing data, multiple imputations will be performed for patients who fail to complete the intervention programme or in cases of missing assessments of primary and secondary outcomes. T-test and X^2 test will be used to compare the baseline characteristics of patients who completed the intervention versus those who failed to complete the intervention. For missing data, multiple imputations will be performed to obtain 20 imputed datasets.^{42–44} To that end, we will use a fully conditional specification with predictive mean matching to impute all of the variables simultaneously, which is now considered a standard approach.^{74–75} Age, sex, body mass index, ongoing treatment and baseline values will be used to impute the dataset.

Detailed descriptive statistics will be performed. The normality of the data distribution will be visually and statistically assessed. A two-way analysis of variance (ANOVA) (group (HIIT vs MOD)×time (before vs after)) will be performed to assess differences. The significance will be determined with a t-test, with Bonferroni adjustments used where appropriate, when the ANOVA demonstrates significant main or group×time interaction effects. Cohen's d values will be used to explore the significance of the training improvements within each group. If statistical power permits, stratification by gender will be performed. The level of significance will be set at $p \leq 0.05$.

Patient and public involvement

Following the intervention, each patient will receive a questionnaire of satisfaction and tolerability of the intervention, with an aim of examining the burden of the study intervention. The study intervention and design were developed without the participation of any patient.

Ethics and dissemination

The Angiof-HIIT Study was approved by the Human Research Ethics Committee of the Canton de Vaud (study number: 2022-01752, V.2, 27 October 2022). Written consent is mandatory prior to enrolment and randomisation. The results will be disseminated via national and international scientific meetings, scientific peer-reviewed journals and social media. The results will be discussed with all the professionals involved in this study.

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Contributors SL conceptualised the interventions. SL, AP, MF, CB, BD, VG-B and LM contributed to the design of the study protocol. SL drafted the manuscript. All of the authors critically revised the manuscript and approved its final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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