PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Short-duration aerobic high-intensity intervals versus moderate exercise training intensity in patients with peripheral artery disease: study protocol for a randomized controlled trial (The Angiof-HIIT study)
AUTHORS	Lanzi, Stefano; Pousaz, Anina; Fresa, Marco; Besson, Cyril; Desgraz, Benoit; Gremeaux-Bader, Vincent; Mazzolai, Lucia

VERSION 1 – REVIEW

REVIEWER	Werner, Timothy J Salisbury University, Exercise Science
REVIEW RETURNED	18-Feb-2024

GENERAL COMMENTS	Thank you for your efforts on this important project. It will help fill in gaps in our understanding of PAD & exercise. I have a few comments -page 9, line 54: 80% completion rate seems low. It could very well be the population you're working with. But why not 90% completion rate? I recommend you add rationale for choosing 80% completion rate. -page 11, line 45: no fixed work-to-rest ratio for MOD group? In theory, one could take very short rests which could lead to increases in perceptual intensity. I recommend you add rationale why no fixed work-to-rest ratios are used in the MOD group. -page 12, line 45: consider including an effect size. -page 14, line 47: spell out PFWD and MWD -page 15, line 51: six functional performance tests is ambitious. Authors noted a 5-10 rest between tests, but how will they control for inter-test fatigue? I imagine participants will more than likely perform better on the 1st test, speed and gait analysis, and worst on the last test, sit-to-stand chair test. If they are all performed on the same day, I recommend these tests be randomized to reduce influence of overall fatigue on these results.

REVIEWER	Massuca, Luis Miguel Universidade Lusófona, CIDEFES
REVIEW RETURNED	19-Feb-2024

GENERAL COMMENTS	Dear Authors Thank you for the opportunity to review protocol ID bmjopen-2023-081883, entitled Short-duration aerobic high-intensity intervals versus moderate exercise training intensity in patients with peripheral artery disease: Study protocol for a randomized controlled trial (The Angiof-HIIT study) , submitted for publication in the journal BMJ Open.

	The submitted work falls within the scope of the BMJ Open, and its publication and operationalization will be a valid contribution to the scientific community. I congratulate the authors for their work in building the protocol and leave a few suggestions to clarify (the introduction and study design) or fine-tune some details in the final version of the protocol (mainly the method). Kind Regards Specific comments 1/ Strengths and limitations of this study / Study design: Monocentric, interventional, randomized controlled trial (RCT). If “due to the nature of the study, the intervention can not be blinded” (L31), this is not an RCT (an RCT's essential elements are randomization, preordained outcome measures, and blinding). Suggestion: monocentric, interventional, non-blinded randomized controlled trial (RCT). 2/ Introduction / P5-L26-28: “Participation in light and moderate physical activity is related to a lower risk of all-cause and cardiovascular mortality in these patients8.” //light? Clarify. 3/ Introduction / P5-L47: “% of peak heart rate (%HRpeak), %VO2peak, or the rate of perceived exertion (RPE), remains underutilized14,19.” // “% of peak heart rate (%HRpeak) and aerobic power (%V̇O2peak), or the rate of perceived exertion (RPE), remains underutilized14,19.” 4/ Study design (p8-L15-22) - Lack of blinding. Suggestion: “monocentric, interventional, non-blinded RCT.” 5/ Study setting (p8-L26-36): Complete with (city, country). 6/ Study setting (p8-L26-36): The manuscript should include the study dates. 7/ Intervention / Block periodization and training load (p10-L17): HRR, the legend is missing. 8/ Intervention / HIIT group (p10-L40): CPET, the legend is missing. 9/ Measures - P14-L47: … the pain-free walking distance (PFWD) and maximum walking distance (MWD)53. [Abbreviations] %HRpeak - % of peak heart rate %V̇O2peak - “% aerobic power 6MWT - six-minute walking test CPET – cardiopulmonary exercise testing HIIT – high-intensity interval training HR - heart rate HRR – heart rate reserve IC – intermittent claudication MWD - maximum walking distance NIRS - near-infrared spectroscopy PAD – peripheral artery disease PFWD - pain-free walking distance PFWT - pain-free walking time PWS - preferred walking speed RPE - rate of perceived exertion SET – supervised exercise training StO2 - muscle oxygen saturation

VERSION 1 – AUTHOR RESPONSE

Responses to the Reviewer 1

Please note that:
[R1]. = Reviewer 1 (comments).
[A]. = authors (responses/comments).
{…} = text modified in the revised manuscript.

[A]. Dear Dr. Timothy J Werner, thank you very much for reviewing our manuscript and for your thoughtful comments which helped us to improve its quality. We carefully revised the manuscript according to the Reviewer's concerns and recommendations. We hope that the manuscript satisfies your standard and that it is now suitable for publication.

[R1]. Thank you for your efforts on this important project. It will help fill in gaps in our understanding of PAD & exercise.
[A]. Thank you for your comment.

[R1]. I have a few comments:
[R1]. page 9, line 54: 80% completion rate seems low. It could very well be the population you're working with. But why not 90% completion rate? I recommend you add rationale for choosing 80% completion rate.
[A]. We thank the reviewer for pointing this out. Indeed, there is no clear consensus on the % of the intervention adherence in patients with peripheral artery disease (PAD). Indeed, data available so far did not clearly define what was considered a satisfactory level of adherence. However, a minimum of 80% completion of the training intervention is most frequently used as a surrogate of satisfactory adherence in patients with cardiovascular diseases (Deka et al *Heart Fail Rev. 2017*), musculoskeletal pain (Bailey et al. *Br J Sports Med 2020*), and in older adults (*Stec et al. Exp Gerontol 2017*). Also, a minimum of 80% completion of the training intervention is also used in ongoing studies in patients with PAD (Birkett et al *Ther Adv Cardiovasc Dis. 2022*). In line with the reviewer's suggestion, a brief rationale for choosing 80% completion rate, with related references, has been added in the new version of the manuscript (pages 11).

{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 diseases47,48.}

[R1]. page 11, line 45: no fixed work-to-rest ratio for MOD group? In theory, one could take very short rests which could lead to increases in perceptual intensity. I recommend you add rationale why no fixed work-to-rest ratios are used in the MOD group.

[A]. Based on recent exercise training recommendations for patients with PAD (Treat-Jacobsen et al *Circulation 2019*; Mazzolai et al *Eur Heart J 2024*), patients are encouraged to exercise until moderate–severe claudication developed. This training approach usually elicits a moderate exercise training intensity. The patients are encouraged to restart the exercise when the pain disappears. The pain usually disappears after 2 to 5 minutes of rest with no fixed work-to-rest ratio (Treat-Jacobsen et al *Circulation 2019,* Mazzolai et al *Eur Heart J 2024*). The training approach of the MOD group in the present investigation is similar to the training prescription usually adopted in patients with claudication (Treat-Jacobsen et al *Circulation 2019*; Mazzolai et al *Eur Heart J 2024*). In line with the reviewer's suggestion, a brief rationale for choosing no fixed work-to-rest ratio for MOD group has been added in the new version of the manuscript (page 13).

{The training approach of the MOD group will be in line with current recommendations9. 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 ≤76% HRpeak recorded during the maximal CPET23. The RPE on the Borg's scale (≤13) will also be used to monitor the exercise training intensity. Compared to the HIIT group, no fixed work-to-rest ratio will be applied9.}

[R1]. page 12, line 45: consider including an effect size.

[A]. As suggested by the reviewer and also by the Editors, this has been redrafted in the new version of the manuscript (page 14).

{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 PAD51. 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 standard deviation of 99 m between groups (Cohen's d value: 0.4; power: 80%; α=5%). Considering some potential dropouts (30%), a sample size of 60 patients (30 in each group) will be recruited.}

[R1]. page 14, line 47: spell out PFWD and MWD

[A]. The pain-free walking distance (PFWD) and maximum walking distance (MWD) were already defined in the previous paragraphs.

[R1]. page 15, line 51: six functional performance tests is ambitious. Authors noted a 5-10 rest between tests, but how will they control for inter-test fatigue? I imagine participants will more than likely perform better on the 1st test, speed and gait analysis, and worst on the last test, sit-to-stand chair test. If they are all performed on the same day, I recommend these tests be randomized to reduce influence of overall fatigue on these results.

[A]. We thank the reviewer for pointing this out. We agree with the reviewer that six functional performance tests are ambitious. We decided to group these assessments to reduce the number of pre- and post-training visits. The order of the tests is based on our clinical experience (10 years) and recent publications (Lanzi et al *Vasc Med 2023*; Lanzi et al *Eur J Vasc Endovasc Surg 2023*). In general, patients tolerated well the functional assessment and resting periods were reported to be adequate (Lanzi et al *Vasc Med 2023*; Lanzi et al *Eur J Vasc Endovasc Surg 2023*). We therefore prefer that all patients perform the tests in the same order, in order to reduce bias in the assessments.

Responses to the Reviewer 2

Please note that:
[R2]. = Reviewer 2 (comments).
[A]. = authors (responses/comments).
{…} = text modified in the revised manuscript.

[A]. Dear Dr. Luis Miguel Massuca, thank you very much for reviewing our manuscript and for your thoughtful comments which helped us to improve its quality. We carefully revised the manuscript according to the Reviewer's concerns and recommendations. We hope that the manuscript satisfies your standard and that it is now suitable for publication.

[R2]. Dear Authors, thank you for the opportunity to review protocol ID bmjopen-2023-081883, entitled Short-duration aerobic high-intensity intervals versus moderate exercise training intensity in patients with peripheral artery disease: Study protocol for a randomized controlled trial (The Angiof-HIIT study), submitted for publication in the journal BMJ Open.
The submitted work falls within the scope of the BMJ Open, and its publication and operationalization will be a valid contribution to the scientific community. I congratulate the authors for their work in building the protocol and leave a few suggestions to clarify (the introduction and study design) or fine-tune some details in the final version of the protocol (mainly the method).
Kind Regards
[A]. Thank you for your comment.

[R2]. Specific comments:
[R2]. 1/ Strengths and limitations of this study / Study design: Monocentric, interventional, randomized controlled trial (RCT). If "due to the nature of the study, the intervention cannot be blinded" (L31), this is not an RCT (an RCT's essential elements are randomization, preordained outcome measures, and blinding). Suggestion: monocentric, interventional, non-blinded randomized controlled trial (RCT).
[A]. As suggested by the reviewer, this has been changed in the new version of the manuscript.

[R2]. 2/ Introduction / P5-L26-28: "Participation in light and moderate physical activity is related to a lower risk of all-cause and cardiovascular mortality in these patients8." //light? Clarify.

[A]. As suggested by the reviewer, this sentence has been redrafted in the new version of the manuscript (page 6).

{Participation in light (e.g. regular walking or household chores) and moderate (e.g. brisk walking) physical activity is related to a lower risk of all-cause and cardiovascular mortality in these patients8.}

[R2]. 3/ Introduction / P5-L47: "% of peak heart rate (%HRpeak), %VO2peak, or the rate of perceived exertion (RPE), remains underutilized14,19." // "% of peak heart rate (%HRpeak) and aerobic power (%V̇O2peak), or the rate of perceived exertion (RPE), remains underutilized14,19."
[A]. We thank the reviewer for the suggestion, and we agree. However, in line with the nomenclature adopted in the text, we prefer to use "cardiorespiratory fitness". As suggested by the reviewer, this has been changed in the new version of the manuscript (page 6).

{However, little guidance is offered regarding training intensity. Training session monitoring using common training intensity measures, such as % of peak heart rate (%HRpeak), cardiorespiratory fitness (%V̇O2peak), or the rate of perceived exertion (RPE), remains underutilised9,15,20.}

[R2]. 4/ Study design (p8-L15-22) - Lack of blinding. Suggestion: "monocentric, interventional, non-blinded RCT."
[A]. As suggested by the reviewer, this has been added in the new version of the manuscript (page 9).

{This study is a monocentric interventional non-blinded RCT.}

[R2]. 5/ Study setting (p8-L26-36): Complete with (city, country).
[A]. As suggested by the reviewer, this has been added in the new version of the manuscript (page 9).

{The interventions and outcome assessments will take place in the Angiology Department and Sports Medicine Department of the Lausanne University Hospital (CHUV), Lausanne, Switzerland.}

[R2]. 6/ Study setting (p8-L26-36): The manuscript should include the study dates.
[A]. As suggested by the reviewer, this has been added in the new version of the manuscript (page 9).

{The study began on March 2023, and it is currently ongoing. The study is planned to be completed by December 2027.}

[R2]. 7/ Intervention / Block periodization and training load (p10-L17): HRR, the legend is missing.
[A]. As suggested by the reviewer, this has been added in the new version of the manuscript (page 12).

{…where % of the heart rate reserve (%HRR) = (HRexercise–HRrest)/(HRpeak–HRrest), and k is a weighted coefficient of…}

[R2]. 8/ Intervention / HIIT group (p10-L40): CPET, the legend is missing.

[A]. As suggested by the reviewer, this has been added in the new version of the manuscript.

[R2]. 9/ Measures - P14-L47: … the pain-free walking distance (PFWD) and maximum walking distance (MWD)53.

[A]. The pain-free walking distance (PFWD) and maximum walking distance (MWD) were already defined in the previous paragraphs.

VERSION 2 – REVIEW

REVIEWER	Werner, Timothy J Salisbury University, Exercise Science
REVIEW RETURNED	14-Mar-2024

GENERAL COMMENTS	Thank you for addressing my concerns and suggestions. Good luck with the study.

REVIEWER	Massuca, Luis Miguel Universidade Lusófona, CIDEFES
REVIEW RETURNED	22-Mar-2024

GENERAL COMMENTS	Dear Authors Congratulations and best wishes in the development of the study. Kind regards Luís Miguel Massuça

VERSION 2 – AUTHOR RESPONSE