PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Saving Legs & Lives: The efficacy of a community-based cardiovascular rehabilitation program versus usual care on exercise capacity and quality of life in patients who have undergone lower limb revascularisation for peripheral arterial disease: Protocol for a single centre randomised-controlled trial

Authors

Feka, Krist; Jha, Pankaj; Aust, Michelle; Scott, Joseph; Schaumberg, Mia; Stanton, Tony; Askew, Christopher David; Trial Group, Saving Legs & Lives Trial Group

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VERSION 1 - REVIEW

Reviewer **1**

Name **Correia, Marília**

Affiliation **Universidade Nove de Julho, Graduate Program in Rehabilitation Sciences**

Date **04-Jul-2024**

COI **None.**

I would like to thank you for the opportunity to review this manuscript. It has been a learning experience.

This is an excellent clinical trial: Feasible, Interesting, Innovative, Ethical, and Relevant. The question is clear, and the outcomes are well established. Here are my comments with the intention of strengthening and further clarifying some points.

Abstract

Abstract Method

1. Please specify the type of exercise (walking? Resistance?) that the rehabilitation group will perform. At what intensity?

2. What kind of "usual care and medical advice" is usually given to these patients?

Methods:

1. “All participants will continue to receive usual care and medical advice from their local doctor and vascular surgeon throughout the study. Usual care for PAD will not be altered by this protocol.” It's worth including what constitutes the usual care for patients with PAD.

2. In the abstract and introduction, the reader is led to believe that the efficacy of referral to cardiovascular rehabilitation will be evaluated. However, this is not addressed in the methods section.

3. Will the seminar be just for one day?

4. It is known that attention, "being cared for," and contact with researchers can already bring substantial benefits to the group in cardiovascular rehabilitation (CR). How do you intend to minimize this influence, given that your control group will not receive the same amount of attention from the researchers?

5. Shouldn't the ABI be measured using the same method across different sites?

6. What is the possibility of adding FMD measurement to the most affected limbs by the disease as well?

Reviewer	**2**
Name	**Salisbury , Dereck L.**
Affiliation	**University of Minnesota**
Date	**09-Jul-2024**
COI	**None**

"Saving Legs & Lives: The efficacy of cardiovascular rehabilitation versus usual care on exercise capacity and quality of life in patients who have undergone lower limb revascularisation for peripheral arterial disease: Protocol for a randomised-controlled trial.”

Abstract

Introduction

Page 3, Line 32-33: something should be added to the characteristic of PAD being an atherosclerotic disease.

Methods and analysis:

Page 3, Lines 52-53: change maximal walking distance to 6-minute walk distance (adapt throughout)

Strengths and Limitations

Bullet 3: if the persons who deliver the CR program also are involved in outcome data collection, is it possible to have a set of data collectors whose only role in the study is data collection. They then would be blinded?

MAIN PAPER

Introduction

This is a well-written and concise section. The importance of this study is nicely laid out and easy for the reader to follow.

Page 5. It would be beneficial to the reader to gain insight related to rates of unsuccessful revascularization and need for subsequent revascularization and the potential therapeutic effects that exercise may provide in patency.

Page 5 lines 130-131, another reference that could be added that has looked at SET programs over 5 years and have established normative values that support your vantagepoint is Whipple et al. Vasc Med. 2024 Apr;29(2):112-119. doi: 10.1177/1358863X231215246.

Methods and Analysis

Study Design & Overview

No concerns noted.

Intervention

Intervention descriptions are all described in detail and would be easily replicated by other studies

Adherence

Adherence measures and strategies to promote adherence are adequately described.

Screening and Enrollment

Add second “l” to enrollment in the screening and enrollment heading

Are medications captured during the screening and changes in medications tracked throughout the study?

Randomization and Blinding

The reviewer appreciates your choice to stratify by type of time since the procedure.

Information regarding blinding should be provided. Earlier, it seemed like data collectors were not blinded to group allocation, which can be viewed as a limitation in the study design. More information on this would be appropriate here.

Outcome Measures and Procedures

Sufficient descriptions pertaining to the overview are provided with a reference to Table 1

6MWT

Is RPE assessed at the end of the 6MWT?

GXT

In the event that the patient is unable to walk 3.2km/h, is a modified Gardner test allotted?

CRF

Just a suggestion, since the GXT will require patients to walk into maximal claudication, you may want to look at data separately in patients who achieve criteria for a max test as well.

Quality of Life

Sufficient descriptions are provided, no changes needed

Self Reported Walking Capacity

Sufficient descriptions are provided, no changes needed

Physical Activity Levels

Sufficient descriptions are provided, no changes needed

ABI

Sufficient descriptions are provided. Would recommend citing or using the protocol by Aboyans et al. https://www.ahajournals.org/doi/full/10.1161/cir.0b013e318276fbcb

FMD

Sufficient details are provided, standard procedures previously tested are utilized and cited.

Biomarker of CVD risk

Sufficient details are provided, methods reflect data extraction from medical records

Sample Size Calculations

Sample size is based on expected change in 6MWT from previous revascularization studies and anticipated standard deviation. Common approach for a power analysis. 10% attrition would be expected on a study of that duration. For the GXT, the 17 participants per group should be obtainable based on the anticipated attrition and number of participants who may opt out of this assessment. Sufficient details are provided in this section, no changes recommended.

Statistical analysis

Adequate description of analysis of primary outcome described. Secondary outcomes analyses have also been described in sufficient detail. ITT and per protocol descriptions are outlined. Appropriate parametric and non-parametric testing have been discussed appropriately. No changes or edits recommended.

Data Management

Was a data sharing plan required as part of the funding for your study. If so, information regarding this would be valuable for this section.

Adverse Events

It is unclear if both study-related and non-study related AEs will be recorded. Study related AEs will be of greater importance when interpreting the use of the study from a safety vantagepoint. Can this be clarified?

Reviewer	**3**
Name	**Cucato, Gabriel**
Affiliation	**Northumbria University Faculty of Health and Life Sciences**
Date	**15-Jul-2024**
COI	**No**

This paper is a protocol study aimed at analysing the effects of traditional rehabilitation programs (such as those for cardiac patients) in patients with peripheral artery disease who underwent revascularisation procedures.

The study, with its significant challenges, has the potential to profoundly impact the treatment of PAD. I have some minor comments and suggestions that could further enhance the study, especially if it has not yet commenced.

1) Is there any consideration for ABI in the inclusion criteria? Since patients underwent lower limb revascularisation, it depends on patients' clinical characteristics (unilateral, younger). Maybe they will be asymptomatic with ABI >0.9. Thus, the exercise training and possible improvement in primary and secondary outcomes can be quite different compared to bilateral patients with some of the legs with ABI <0.9 and still claudicants after revascularisation.

2) More comprehensive information is needed for the standard care. It is crucial to explain in detail what patients receive (medication? Only general advices? Follow any guidelines recommendations?) Ideally, this group should be monitored by smartwatches to verify any possible increase in physical activity (since revascularized, we expect some increase).

3) More information regarding the home exercise is needed. Will they exercise at home indoors or outdoors?

4) How will you consider sedentary, time spent in light, moderate and vigorous? Is any threshold based on counts per minute?

5) I suggest including the WELCH and VASCQuol 6 questionnaires. WELCH can provide a subjective improvement in function capacity, and VASQol 6 is a specific quality-of-life questionnaire for PAD.

6) Although the study does not aim to analyse the potential costs of implementing a program in routine rehabilitation care, it would be essential since access to the program you are testing is scarce for this population.

VERSION 1 - AUTHOR RESPONSE

Responses to Reviewer 1

I would like to thank you for the opportunity to review this manuscript. It has been a learning experience. This is an excellent clinical trial: Feasible, Interesting, Innovative, Ethical, and Relevant. The question is clear, and the outcomes are well established. Here are my comments with the intention of strengthening and further clarifying some points.

Response: Thank you for your comments!

Abstract

Abstract Method

1. Please specify the type of exercise (walking? Resistance?) that the rehabilitation group will perform. At what intensity?

   Response: This information has been added in the abstract on page 2, lines 48-51 as outlined below.

   "The cardiovascular rehabilitation program will include two supervised exercise sessions per week for 6 weeks primarily consisting of intermittent treadmill walking at a moderate exercise intensity, and home-based walking advice."
2. What kind of "usual care and medical advice" is usually given to these patients?

   Response: All participants in this study will receive usual care and medical advice by their treating vascular surgeon and GP during the study. As per most recent practice guidelines, usual care for the management of patients with PAD may include management of cardiovascular disease risk factors with lifestyle modifications (e.g., smoking cessation, dietary modifications) with/without pharmacological therapy (Nordanstig et al., 2024) .

   While usual care will not be altered by this protocol, upon consent to the study each participant's vascular surgeon and GP will be contacted to ask them to continue to provide the best possible medical care throughout the study. Furthermore, to assess the efficacy of the cardiovascular rehabilitation exercise program, each participant's vascular surgeon and GP will be requested to refrain from giving specific advice regarding exercise until the completion of the study. This information about usual care has now been added on page 7, lines 254-262.

Methods

1. “All participants will continue to receive usual care and medical advice from their local doctor and vascular surgeon throughout the study. Usual care for PAD will not be altered by this protocol.” It's worth including what constitutes the usual care for patients with PAD.

   Response: Thank you for your comment. As per our previous response we have now added further information about usual care on page 7, lines 254-262 in the study manuscript.

2. In the abstract and introduction, the reader is led to believe that the efficacy of referral to cardiovascular rehabilitation will be evaluated. However, this is not addressed in the methods section.

   Response: Thank you for your comment. We acknowledge that the word referral causes confusion and is not in alignment with the aims of the study. Therefore, we removed the word referral throughout the manuscript.

3. Will the seminar be just for one day?

   Response: Yes, each participant will attend one education seminar (5.5 hours with breaks) during the 6-week program. This is clarified on page 9, lines 314-315.

4. It is known that attention, "being cared for," and contact with researchers can already bring substantial benefits to the group in cardiovascular rehabilitation (CR). How do you intend to minimize this influence, given that your control group will not receive the same amount of attention from the researchers?

   Response: Thank you for your comment. We acknowledge that the influence of attention (e.g., social interactions with CR staff) may contribute to the benefits of CR along with attending the supervised exercise sessions and the education seminar (Hecksteden et al., 2018). This additional attention is a part of the benefits of the CR program. We are not aiming to isolate the benefits of attention from other aspects of the program as this is not the intent of the study. Therefore, we are not providing the control group with any additional clinical ‘attention’. In the reporting of study findings, we will highlight this as a potential influence and an area of future investigation. Please note that other aspects of the trial including assessment visits that both the CR and usual care group will undergo will be conducted in a standardised way.

5. Shouldn't the ABI be measured using the same method across different sites?

Response: Thank you for your comment. Accuracy of the ABI has been reported to not be affected by the method used for brachial pressure measurements (Doppler, auscultatory, or oscillometric) (Gardner et al., 1998). This is in line with our previous published work (Askew et al., 2002; Sanderson et al., 2006; Hou et al., 2002).

6. What is the possibility of adding FMD measurement to the most affected limbs by the disease as well?

   Response: Thank you for your comment. Brachial artery FMD has been chosen as an outcome of systemic cardiovascular health as it is an independent predictor of cardiovascular events and represents a systemic marker of endothelial function in healthy (Matsuzawa et al., 2015) and in patients with PAD (Brevetti et al. 2003; Haung et al., 2007). Brachial artery FMD is a relevant clinical endpoint for this efficacy trial, and previous studies have reported improvements in brachial artery FMD after exercise training in patients with PAD (McDermott et al., 2009). While adding lower limb FMD measurements may potentially provide some mechanistic data on local vascular function changes to exercise therapy, this would be outside of the scope of this efficacy trial. Also, as per our standard operating procedures we do not perform lower limb reactive hyperaemia testing in people who have had vascular grafts or stents of the femoral or popliteal arteries. Thus, it is likely that this test would be contraindicated in many participants. For those reasons lower limb FMD is not included as an outcome.

Responses to Reviewer 2

Abstract

Introduction

Page 3, Line 32-33: something should be added to the characteristic of PAD being an atherosclerotic disease.

Response: This has been added.

"Peripheral artery disease (PAD) is an atherosclerotic condition characterised by stenosis or occlusion of the arteries in the lower limbs."

Methods and analysis:

Page 3, Lines 52-53: change maximal walking distance to 6-minute walk distance (adapt throughout)

Response: Thank you for your comment. As suggested the wording has been changed to 6-minute walk distance throughout the manuscript.

Strengths and Limitations

Bullet 3: if the persons who deliver the CR program also are involved in outcome data collection, is it possible to have a set of data collectors whose only role in the study is data collection. They then would be blinded?

Response: Thank you for your comment. We acknowledged this as a limitation in the protocol manuscript. Blinding of assessors in an exercise rehabilitation study is difficult and often not feasible. Furthermore, we do not have capacity for the number of investigators required to be able to implement this consistently throughout the study. However, several standard operating procedures are in place to minimise the influence of bias. Any instructions provided to participants during data collection activities, including cues and feedback, will be guided by standard operating procedures and assessors will follow scripts. Please note that in most cases collection of vascular data and objective data cannot be influenced by motivation of participants or assessors. Furthermore, to reduce risk of bias all analysis will be undertaken in blinded fashion using coded data.

MAIN PAPER

Introduction

1. This is a well-written and concise section. The importance of this study is nicely laid out and easy for the reader to follow.

Response: Thank you for your comment!

2. Page 5. It would be beneficial to the reader to gain insight related to rates of unsuccessful revascularization and need for subsequent revascularization and the potential therapeutic effects that exercise may provide in patency.

   Response: Thank you for this suggestion. We agree that it would be beneficial for the reader to gain an insight on repeat revascularisation rates and potential therapeutic effects of exercise. We have provided this information on page 4, lines 124-129 and lines 143-145 as outlined below.

   "Reintervention rates are also high in people with PAD with a meta-analysis of 52 studies (N=6,769 patients) reporting a reintervention rate of 18.2% (95%CI 14.5 – 22.6) at 12 months following endovascular revascularisation… Post-revascularisation exercise therapy has also been associated with reduction in the need for reintervention when compared with revascularisation or supervised exercise therapy alone (odds ratio 0.19 [95%CI 0.09 – 0.40] P<0.0001)."

3. Page 5 lines 130-131, another reference that could be added that has looked at SET programs over 5 years and have established normative values that support your vantagepoint is Whipple et al. Vasc Med. 2024 Apr;29(2):112-119. doi: 10.1177/1358863X231215246.

   Response: Thank you for this suggestion. We have added this reference on page 4, line 136.

Methods and Analysis

Study Design & Overview

No concerns noted.

Response: Thank you.

Intervention

Intervention descriptions are all described in detail and would be easily replicated by other studies

Response: Thank you.

Adherence

Adherence measures and strategies to promote adherence are adequately described.

Response: Thank you.

Screening and Enrollment

1. Add second “l” to enrollment in the screening and enrollment heading

   Response: Thank you for your suggestion. “Enrolment” is the standard British/Australian spelling. As the manuscript has been written with British/Australian spelling throughout we would like to keep the spelling of “Enrolment” as is. The spelling also aligns with BMJ Open guidelines.

2. Are medications captured during the screening and changes in medications tracked throughout the study?

   Response: Medications are captured during the screening visit, and changes to medications are tracked and updated throughout the study. This information has been added on page 10, lines 340-341.

Randomization and Blinding

1. The reviewer appreciates your choice to stratify by type of time since the procedure.

   Response: Thank you.

2. Information regarding blinding should be provided. Earlier, it seemed like data collectors were not blinded to group allocation, which can be viewed as a limitation in the study design. More information on this would be appropriate here.

   Response: As suggested, more information regarding blinding has been provided on page 10, lines 358-362 as outlined below.

   “The same investigators who will deliver the CR program will also be involved in the collection of outcome data. Therefore, participants and data collectors will not be blinded to group allocation. While it is not feasible to blind participants and investigators to group allocation in an exercise intervention study, all data analysis will be undertaken in blinded fashion using coded data.”

Outcome Measures and Procedures

Sufficient descriptions pertaining to the overview are provided with a reference to Table 1

Response: Thank you.

6MWT

Is RPE assessed at the end of the 6MWT?

Response: Yes, the rate of perceived exertion (RPE) is assessed at the end of the 6MWT using the 0-10 modified RPE Borg scale. This information has now been added on page 11, lines 398-400.

GXT

In the event that the patient is unable to walk 3.2km/h, is a modified Gardner test allotted?

Response: This test requires participants to walk at a constant speed (3.2 km/h) and the incline increases by 2% every 2 minutes until maximal effort. Participants who are unable to maintain the speed of the treadmill will be given the option to opt out of this test. Based on our sample size calculations, only 34 participants are required to establish an effect for the Gardner-Skinner treadmill test (refer to page 10, lines 367-373). However, if a participant decides to undertake the test despite being unable to maintain the walking speed, the speed will be modified (reduced). The following sentence has been added to explain this on page 12, lines 420-422: *"Adjustments will be made to the treadmill protocol using standardised procedures for participants who are unable to maintain the 3.2 km/h treadmill speed."*

Details on the modification of the Gardner-Skinner test are outlined in our standard operating procedure and are briefly explained here. To ensure a systematic approach, the average walking speed achieved during the 6-minute walk test will be calculated (in km/h) and will be used for the treadmill test. However, the incline of the treadmill will increase as usual by 2% every two minutes. This modification will be recorded as a protocol deviation in the trial deviation log. In such scenario, the same modified Gardner-Skinner test will be repeated for the participant at follow-up visits.

CRF

Just a suggestion, since the GXT will require patients to walk into maximal claudication, you may want to look at data separately in patients who achieve criteria for a max test as well.

Response: Thank you for your suggestion, we will take this into consideration.

Quality of Life

Sufficient descriptions are provided, no changes needed

Response: Thank you.

Self Reported Walking Capacity

Sufficient descriptions are provided, no changes needed

Response: Thank you.

Physical Activity Levels

Sufficient descriptions are provided, no changes needed

Response: Thank you.

ABI

Sufficient descriptions are provided. Would recommend citing or using the protocol by Aboyans et al. https://www.ahajournals.org/doi/full/10.1161/cir.0b013e318276fbcb

Response: Thank you for your recommendation. As explained to the earlier reviewer (page 4 in this document), our ABI testing method is in alignment with previous recommendations (Gardner et al., 1998) and our published work (Askew et al., 2002; Sanderson et al., 2006; Hou et al., 2002). This does not fully align with the paper by Aboyans et al., therefore, we will not cite this paper.

FMD

Sufficient details are provided, standard procedures previously tested are utilized and cited.

Response: Thank you.

Biomarker of CVD risk

Sufficient details are provided, methods reflect data extraction from medical records

Response: Thank you.

Sample Size Calculations

Sample size is based on expected change in 6MWT from previous revascularization studies and anticipated standard deviation. Common approach for a power analysis. 10% attrition would be expected on a study of that duration. For the GXT, the 17 participants per group should be obtainable based on the anticipated attrition and number of participants who may opt out of this assessment. Sufficient details are provided in this section, no changes recommended.

Response: Thank you.

Statistical analysis

Adequate description of analysis of primary outcome described. Secondary outcomes analyses have also been described in sufficient detail. ITT and per protocol descriptions are outlined. Appropriate parametric and non-parametric testing have been discussed appropriately. No changes or edits recommended.

Response: Thank you.

Data Management

Was a data sharing plan required as part of the funding for your study. If so, information regarding this would be valuable for this section.

Response: A data sharing plan was not required as part of the funding for this study. Only the principal investigator and authorised study staff involved in data collection and analysis will have access to data. Participant data will not be shared with other research groups.

Adverse Events

It is unclear if both study-related and non-study related AEs will be recorded. Study related AEs will be of greater importance when interpreting the use of the study from a safety vantagepoint. Can this be clarified?

Response: Both study-related and non-study related adverse events will be recorded throughout the study in the trial adverse event report form. We have now clarified this on page 16, line 597 as outlined below.

"Information on all adverse events (study-related and non-study related) will be recorded immediately in the trial adverse event report form…"

Responses to Reviewer 3

This paper is a protocol study aimed at analysing the effects of traditional rehabilitation programs (such as those for cardiac patients) in patients with peripheral artery disease who underwent revascularisation procedures.

The study, with its significant challenges, has the potential to profoundly impact the treatment of PAD. I have some minor comments and suggestions that could further enhance the study, especially if it has not yet commenced.

Response: Thank you for your comments.

1. Is there any consideration for ABI in the inclusion criteria? Since patients underwent lower limb revascularisation, it depends on patients' clinical characteristics (unilateral, younger). Maybe they will be asymptomatic with ABI >0.9. Thus, the exercise training and possible improvement in primary and secondary outcomes can be quite different compared to bilateral patients with some of the legs with ABI <0.9 and still claudicants after revascularisation.

   Response: We agree that outcomes may differ depending on haemodynamics and severity of disease; thus, we will monitor ABIs throughout the trial. We have no intention of basing inclusion criteria on ABI. Regarding the effect of exercise training, the trial has been designed in such a way to be able to include participants who do and do not experience claudication post-surgery. For instance, participants who still experience intermittent claudication following surgery will be instructed to exercise at moderate to near-maximal claudication pain thresholds as per exercise guidelines (Treat-Jacobson et al., 2019). In participants who do not experience claudication pain post-surgery, exercise intensity will be monitored and prescribed based on the RPE Borg Scale. As per our statistical plan any confounding variables (e.g., ABI) will be explored further using analysis of covariance.
2. More comprehensive information is needed for the standard care. It is crucial to explain in detail what patients receive (medication? Only general advices? Follow any guidelines recommendations?) Ideally, this group should be monitored by smartwatches to verify any possible increase in physical activity (since revascularized, we expect some increase).

Response: Thank you for your comment. Please refer to our previous responses about usual care on page 2 of this document. We have added additional information about usual care in the manuscript on page 7, lines 254-262.

We agree that there may be some increases in physical activity levels following revascularisation. While we are unable to assess physical activity levels prior to and after revascularisation, all participants in this study will undergo accelerometer-derived physical activity assessments at baseline, and at follow up visits for a period of 7 days at each assessment point.

3. More information regarding the home exercise is needed. Will they exercise at home indoors or outdoors?

   Response: Participants will be instructed to complete their walking sessions outdoors (e.g., local neighbourhood or parks). This is now explained on page 9, lines 302-303. The walking duration, intensity, and progression of home-based sessions from the beginning of the program (i.e., week 1) to the end (i.e., week 6) are described in detail on page 9 lines 303-313.

4. How will you consider sedentary, time spent in light, moderate and vigorous? Is any threshold based on counts per minute?

   Response: Cut-point thresholds for sedentary, light, and moderate-vigorous physical activity will be based on counts per minute using the Montoye 2020 algorithm. This algorithm was developed to determine activity intensity from a wrist-worn ActiGraph accelerometer in free-living adults. The cut-point thresholds will include: < 2,859 counts/min (sedentary), 2,860-3,940 counts/min (light physical activity), and ≥ 3,941 counts/min (moderate-vigorous physical activity).

5. I suggest including the WELCH and VASCQuol 6 questionnaires. WELCH can provide a subjective improvement in function capacity, and VASQol 6 is a specific quality-of-life questionnaire for PAD.

   Response: Thank you for your suggestion. As this study has commenced (April 2024), we are unable to include additional quality of life questionnaires. In this study, we have included the Intermittent Claudication Questionnaire (ICQ) to assess disease-specific quality of life and the Walking Impairment Questionnaire (WIQ) to assess self-reported walking impairment. The ICQ has been validated for use in patients with PAD and has been reported to correlate against other functional outcomes (e.g., 6-minute walk distance), and quality of life assessments (PADQOL) (Golledge et al. 2020). The WIQ has

been validated in several large studies and correlates with walking outcomes including maximum and pain-free walking distances during treadmill and the 6MWT in patients with PAD (McDermott et al., 1998; Nicolaï et al., 2009). Furthermore, the WIQ has been shown to detect impairment in patients have mild PAD symptoms or are asymptomatic (McDermott et al., 1998), and minimally clinically important differences have been established for all WIQ domain scores (Gardner et al., 2018).

6. Although the study does not aim to analyse the potential costs of implementing a program in routine rehabilitation care, it would be essential since access to the program you are testing is scarce for this population.

   Response: Thank you for your comment. This is not the aim of the study and our ability to assess this is limited with a single centre study like this. Thank you for your suggestion and we agree this is an important area for future investigation.

References

Askew, C. D., Green, S., Hou, X. Y., & Walker, P. J. (2002). Physiological and symptomatic responses to cycling and walking in intermittent claudication. *Clinical physiology and functional imaging, 22*(5), 348–355.

Brevetti, G., Silvestro, A., Schiano, V., & Chiariello, M. (2003). Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of flow-mediated dilation to ankle-brachial pressure index. *Circulation, 108*(17), 2093–2098.

Gardner, A. W., & Montgomery, P. S. (1998). Comparison of three blood pressure methods used for determining ankle/brachial index in patients with intermittent claudication. *Angiology, 49*(9), 723–728.

Gardner, A. W., Montgomery, P. S., & Wang, M. (2018). Minimal clinically important differences in treadmill, 6-minute walk, and patient-based outcomes following supervised and home-based exercise in peripheral artery disease. *Vascular medicine, 23*(4), 349–357.

Golledge, J., Leicht, A. S., Yip, L., Rowbotham, S. E., Pinchbeck, J., Jenkins, J. S., Clapperton, R., et al. (2020). Relationship Between Disease Specific Quality of Life Measures, Physical Performance, and Activity in People with Intermittent Claudication Caused by Peripheral Artery Disease. *European journal of vascular and endovascular surgery, 59*(6), 957–964.

Hecksteden, A., Faude, O., Meyer, T., & Donath, L. (2018). How to Construct, Conduct and Analyze an Exercise Training Study? *Frontiers in physiology, 9*, 1007.

Hou, X. Y., Green, S., Askew, C. D., Barker, G., Green, A., & Walker, P. J. (2002). Skeletal muscle mitochondrial ATP production rate and walking performance in peripheral arterial disease. *Clinical physiology and functional imaging, 22*(3), 226–232.

Huang, A. L., Silver, A. E., Shvenke, E., Schopfer, D. W., Jahangir, E., Titas, M. A., et al. (2007). Predictive value of reactive hyperemia for cardiovascular events in patients with peripheral arterial disease undergoing vascular surgery. *Arteriosclerosis, thrombosis, and vascular biology, 27*(10), 2113–2119.

Matsuzawa, Y., Kwon, T. G., Lennon, R. J., Lerman, L. O., & Lerman, A. (2015). Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for

Cardiovascular Events: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association, 4*(11), e002270.

McDermott, M. M., Ades, P., Guralnik, J. M., Dyer, A., Ferrucci, L., Liu, K., et al. (2009). Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial. *JAMA, 301*(2), 165–174.

McDermott, M. M., Liu, K., Guralnik, J. M., Martin, G. J., Criqui, M. H., & Greenland, P. (1998). Measurement of walking endurance and walking velocity with questionnaire: validation of the walking impairment questionnaire in men and women with peripheral arterial disease. *Journal of vascular surgery, 28*(6), 1072–1081.

Montoye, A. H. K., Clevenger, K. A., Pfeiffer, K. A., Nelson, M. B., Bock, J. M., Imboden, M. T., et al. (2020). Development of cut-points for determining activity intensity from a wrist-worn ActiGraph accelerometer in free-living adults. *Journal of sports sciences, 38*(22), 2569–2578.

Nicolaï, S. P., Kruidenier, L. M., Rouwet, E. V., Graffius, K., Prins, M. H., & Teijink, J. A. (2009). The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. *Journal of vascular surgery, 50*(1), 89–94.

Nordanstig, J., Behrendt, C. A., Baumgartner, I., Belch, J., Bäck, M., Fitridge, R., et al. (2024). European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. *European journal of vascular and endovascular surgery, 67*(1), 9–96.

Sanderson, B., Askew, C., Stewart, I., Walker, P., Gibbs, H., & Green, S. (2006). Short-term effects of cycle and treadmill training on exercise tolerance in peripheral arterial disease. *Journal of vascular surgery, 44*(1), 119–127.

Treat-Jacobson, D., McDermott, M. M., Bronas, U. G., Campia, U., Collins, T. C., Criqui, M. H., et al. (2019). Optimal Exercise Programs for Patients With Peripheral Artery Disease: A Scientific Statement From the American Heart Association. *Circulation, 139*(4), e10–e33.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Correia, Marília**
Affiliation	**Universidade Nove de Julho, Graduate Program in Rehabilitation Sciences**
Date	**08-Oct-2024**
COI	

My comments were adequately addressed.

Reviewer	**3**
Name	**Cucato, Gabriel**
Affiliation	**Northumbria University Faculty of Health and Life Sciences**
Date	**21-Sep-2024**
COI	

No additional comments for me.