

Effects of exercise prescribed at different levels of claudication pain on walking performance in patients with intermittent claudication: a protocol for a randomised controlled trial

Stefan T. Birkett , Jonathan Sinclair, Sally A. Seed, Sean Pymer, Edward Caldow, Lee Ingle, Amy E. Harwood and Anselm Egun

Abstract

Background: Peripheral artery disease affects over 236 million people globally and the classic symptom is intermittent claudication (IC) which is associated with reduction in physical activity. The evidence that supervised exercise programmes (SEPs) improve pain-free and maximal walking distance is irrefutable. However, adherence rates are low with exercise-related pain cited as a contributing factor. National and international guidelines recommend exercising at a moderate to maximal level of claudication pain to improve walking ability; however, exercising pain-free or at mild claudication pain has been shown to achieve this outcome. There is limited evidence that compares the relative effects of exercise prescribed at different levels of claudication pain.

Objective: The objective of this study is to directly compare the effects of exercise prescribed at three different levels of claudication pain on walking performance.

Design: This study will be a single-centre randomised controlled trial.

Methods: Based on an *a priori* power calculation, 51 patients with IC will be allocated to 24 weeks of twice-weekly pain-free (PF), moderate pain (MOD-P) or maximal pain (MAX-P) exercise. The PF group will cease exercise at the onset of claudication (1 on the 0–4 IC rating scale), the MOD-P group will stop once moderate pain is reached (2 on the rating scale) and the MAX-P group will stop once maximal pain is reached (4 on the rating scale).

Analysis: Outcome measures will be assessed at baseline, 12 and 24 weeks adopting an analysis of covariance (ANCOVA) to compare MWD across three time points. The primary outcome for the trial will be change in maximal treadmill walking distance at 12 and 24 weeks.

Registration: Trial registration number: NCT04370327.

Keywords: pain, peripheral artery disease, supervised exercise programme

Received: 26 July 2021; revised manuscript accepted: 7 June 2022.

Introduction

Peripheral artery disease (PAD) is characterised by atherosclerotic lesions of the arteries in the lower limbs, resulting in a reduction in blood flow.¹ Globally, it is estimated that 236 million

people are living with PAD, with the number of cases increasing.² A classic symptom of PAD is intermittent claudication (IC), characterised by ischemic muscle pain in the leg precipitated by exertion and relieved by rest.^{3,4} PAD is associated

Ther Adv Cardiovasc Dis

2022, Vol. 16: 1–8

DOI: 10.1177/
17539447221108817

© The Author(s), 2022.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Stefan T. Birkett
School of Sport and Health
Sciences, University
of Central Lancashire,
Preston PR1 2HE, UK.
sbirkett4@uclan.ac.uk

Jonathan Sinclair
Sally A. Seed
School of Sport and Health
Sciences, University
of Central Lancashire,
Preston, UK

Sean Pymer
Academic Vascular
Surgical Unit, Hull York
Medical School, Hull, UK

Edward Caldow
School of Health and
Society, University of
Salford, Salford, UK

Lee Ingle
Department of Sport,
Health and Exercise
Science, University of Hull,
Hull, UK

Amy E. Harwood
Centre for Sport, Exercise
and Life Sciences,
Coventry University,
Coventry, UK

Anselm Egun
Lancashire Teaching
Hospitals NHS Foundation
Trust, Preston, UK

with various comorbidities such as diabetes mellitus, hypertension and dyslipidaemia, as well as reductions in physical function, quality of life and balance.^{3,5,6} National and international guidelines^{4,7} recommend exercise therapy as the first-line treatment for patients with IC, generally advocating 2 h per week of a supervised exercise over a 3-month period, with patients being encouraged to exercise to the point of moderate or maximal pain. Exercise therapy, via supervised exercise programmes (SEPs), is supported by high-quality evidence for its clinical and cost-effectiveness, costing less than a tenth of angioplasty.^{8,9}

Despite the plethora of evidence demonstrating the benefits of SEPs, less than half of the vascular units in the United Kingdom have access to one and patient uptake rates are low.^{10,11} One of the primary reasons for poor adherence may be the level of pain prescribed during SEPs. Indeed, exercise-induced pain is a major barrier to physical activity in this population,¹² and the level of pain prescribed during SEPs influences completion rates.¹³ When exercise is prescribed at higher levels of pain, completion rates are lower. However, current evidence and guidelines advocate exercising at moderate to maximal pain,^{7,14–16} despite evidence to the contrary, suggesting that mild- or pain-free exercise improves walking ability.^{17–20} The lack of adequately powered, randomised clinical trials investigating the effects of exercise prescribed at differing levels of claudication pain has also been highlighted in a recent scientific statement from the American Heart Association.¹⁶ As such, it remains unclear which level of claudication is optimal for improving walking performance in patients with IC.²¹ The aim of this trial is to directly compare the effects of exercise prescribed at different levels of claudication [pain-free (PF), moderate pain (MOD-P) and maximal pain (MAX-P)] on (1) maximal and pain-free walking distance; (2) adherence; (3) acceptability, tolerability and enjoyment of the exercise intervention; (4) walking behaviour and physical activity; and (5) barriers and quality of life. It is cautiously expected that maximal pain will lead to greatest improvements in walking performance.

Methods and analysis

This study is a single-centre randomised controlled trial. Participants will be randomly allocated to 24 weeks of PF, MOD-P or MAX-P

exercise with outcomes measured at baseline (visit 1), 12 weeks (visit 2) and 24 weeks (visit 3). All sessions will be supervised by a qualified exercise professional within an existing community pathway. As this programme duration is longer than suggested in current UK guidelines, outcomes will be measured at 12 and 24 weeks to ensure generalisability of the findings to UK SEPs.

Setting

The trial will be conducted in one centre under the Heartbeat Northwest Cardiovascular Prevention and Rehabilitation charity programme. Patients will attend an SEP from the choice of three Heartbeat cardiovascular rehabilitation sites across Lancashire, UK (Preston, Chorley and Blackpool). Testing will also be conducted at these locations.

Study registration

The trial was prospectively registered on ClinicalTrials.gov (NCT04370327). Any amendments required to this protocol will seek approvals from the research ethics committee before implementation and will be fully reported in the final trial report.

Participants

Patients recently diagnosed with IC by a vascular surgeon or vascular specialist nurse will be referred to the SEP and screened for study participation.

Inclusion criteria

1. >18 years old;
2. Resting ankle brachial pressure index (ABPI) <0.9;
3. Able to walk unaided;
4. English speaking and able to follow exercise instructions;
5. Able to provide informed consent.

Exclusion criteria

1. Those who have critical limb-threatening ischaemia (rest pain and/or tissue loss);
2. Those undergoing active cancer treatment;
3. Those presenting with any significant comorbidities or contraindications to

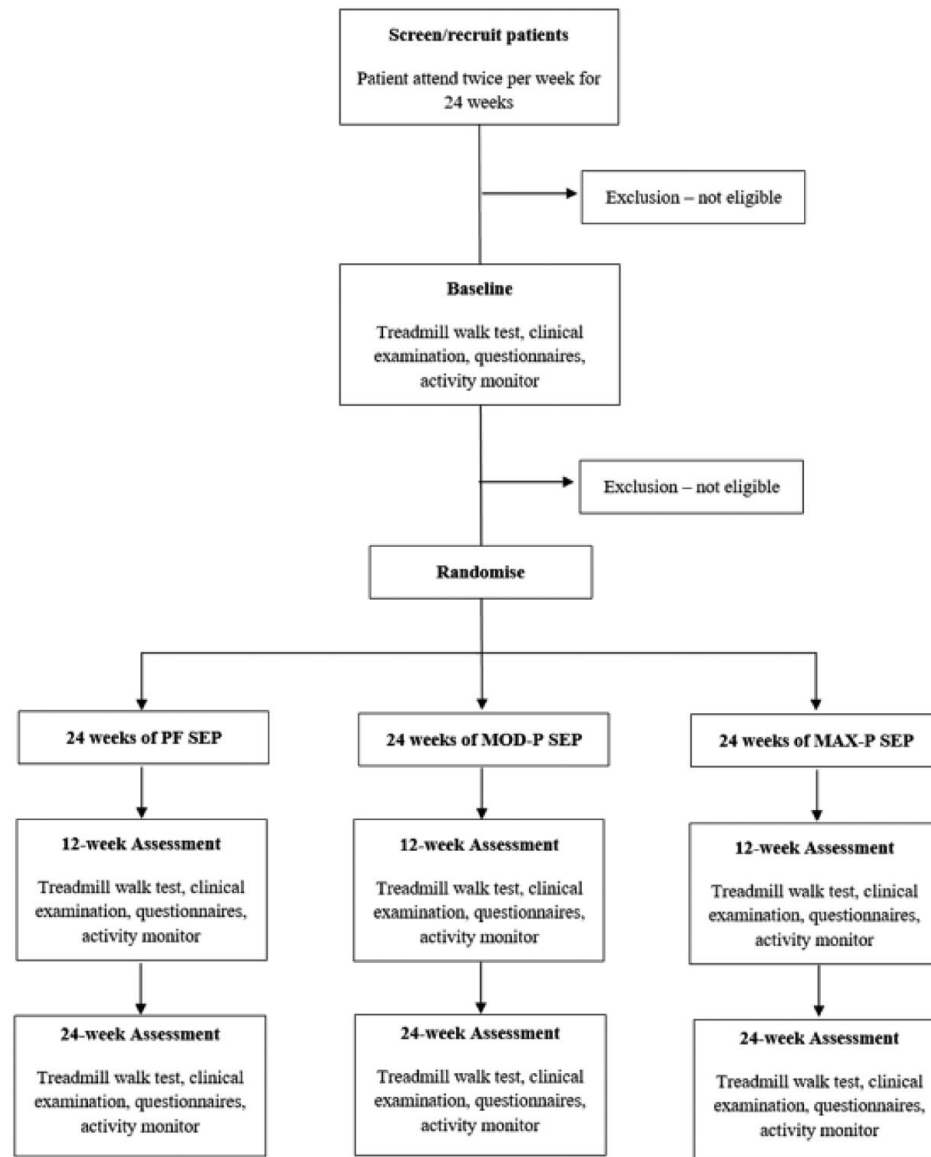


Figure 1. Study flow chart.

exercise testing or training in accordance with the American College of Sports Medicine;²²

4. Unstable/uncontrolled coronary heart disease.

Study procedures

An outline of the participant pathway for the study is presented in Figure 1. Once referred, patients will be contacted by a member of the research team. Eligible patients will be offered the opportunity to participate in this study and receive

a participant information sheet. A subsequent phone call (at least 48h later) from the research team will confirm those who wish to participate. Informed consent will be obtained at the baseline assessment visit. Baseline procedures will include: a clinical examination, a treadmill walking test, anthropometrics, barriers to physical activity and quality-of-life questionnaires. Patients will also be asked to wear a physical activity monitor for a duration of 7 days following the baseline assessment. Eligible participants will subsequently be randomised to 24 weeks of twice-weekly PF, MOD-P or MAX-P SEP. All measures

completed at baseline will be repeated at 12 and 24 weeks. Semi-structured interviews will be conducted at 24 weeks to evaluate patient acceptability, tolerability and enjoyment. Those who decline study participation will still be offered SEP participation as part of usual care.

Intervention

The SEP will consist of a circuit²³ (Figure 2) lasting for 60 min, including a 10-min warm-up and cooldown.²⁴ Participants will be individually prescribed exercise until they achieve the desired rating of claudication pain on each station within 3–5 min. They will start the next exercise once the pain has subsided. The American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) 0–4 scale to rate claudication pain will be adopted (Figure 3). Participants in the PF group will cease exercise at the onset of claudication (1 on the rating scale), the MOD-P group will stop once moderate pain is achieved (2 on the rating scale) and the MAX-P group will stop once maximal pain is achieved (4 on the rating scale). Participants who are unable/unwilling to comply with the protocols (achieve desired rating of claudication pain) will be permitted to cease

involvement and continue with usual-care SEP. To be regarded as having sufficiently adhered to the treatment protocol, patients must complete a minimum of 80% of sessions over 24 weeks (38 of 48).

Randomisation and blinding

The random allocation sequence will be generated by the trial statistician on a 1:1 basis using a computer program random number generator. To ensure allocation concealment, researchers will request randomisation from the principal investigator on completion of all baseline assessments using a sealed, opaque, sequentially numbered envelope. All outcome assessors will be blinded as will the trial statistician. Exercise professionals delivering the interventions cannot be blinded; however, they will not be involved in data analysis or reporting.

Outcome measures

The primary outcome measure is change in maximal walking distance (MWD) at 12 and 24 weeks. Secondary outcomes include (1) pain-free walking distance (PFWD); (2) adherence; (3) acceptability, tolerability and enjoyment of the exercise interventions; (4) walking behaviour and physical activity; and (5) barriers to physical activity and quality of life.

Outcome assessments

Clinical examination will include a review of past medical history and current medications, height, weight and cardiovascular risk factor assessment, that is, resting blood pressure and smoking status. Walking behaviour and physical activity will be recorded over a 7-day period, at baseline (1 week prior to commencing the SEP) and at 12 weeks and 24 weeks using an ActiGraph GT9X link activity monitor (ActiGraph, Pensacola, FL, USA). A valid wear time is defined as 4 > days of > 10 h of wear. Periods of > 60 min of consecutive zero reading will be considered as non-wear time. Activity intensities will be assigned adopting cut points on those validated in coronary artery disease populations,²⁵ with light, moderate and vigorous classified as < 1800 counts/min, 1800–3799 counts/min and > 3800 counts/min, respectively. Sedentary bouts will be defined as periods of wear time exceeding 60 min at < 150 counts/min.

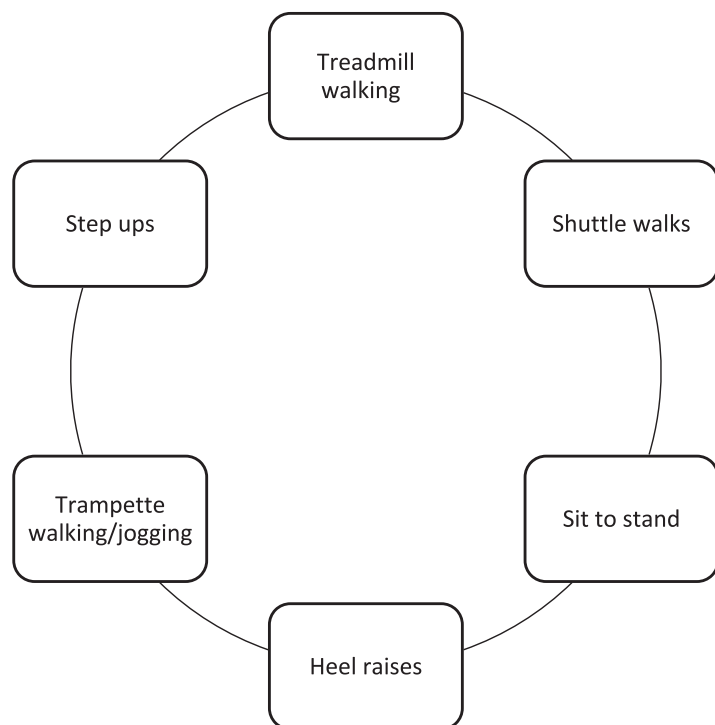


Figure 2. Visual representation of the PAD-specific exercise circuit.

A graded treadmill walking test will be performed to determine MWD and PFWD. The treadmill protocol will consist of a constant speed of 3.2 km/h and incremental gradient beginning at 0% increasing 2% every 2 min, for a maximum of 15 min²⁶ and will be conducted in accordance with published recommendations for implementation, ensuring standardisation.²⁷ PFWD will be recorded at the point at which the patient first indicates the onset of claudication pain. MWD will be recorded when the patient can no longer continue due to claudication pain.

Adherence and compliance will be determined by recording the number of training sessions attended and successfully completed in accordance with the exercise protocol. Drop-out from the SEP will also be documented for all study groups in addition to the reason for drop-out, where provided voluntarily by participants.

Quality-of-life measures will be recorded using disease-specific questionnaires. The King's College Vascular Quality of Life, a 25-item questionnaire with five domains (pain, symptoms, activities, social and emotional), and the Walking Impairment Questionnaire (WIQ) will be used to assess the perceived impact of claudication.^{28,29} Personal and environmental barriers to physical activity in PAD will be based on the studies by Barbosa *et al.*¹² and Cornelis *et al.*³⁰ A 5-point ordinal scale (never, seldom, sometimes, frequently, always) will be used to assess the limiting character of each barrier (see Table 1).³⁰ To verify the safety of the interventions performed in the SEP, adverse and serious adverse events will be carefully monitored, recorded and reported in line with the principles of Good Clinical Practice (GCP). Semi-structured interviews adopting a predetermined set of open topics will qualitatively evaluate acceptability, tolerability and enjoyment of the exercise intervention in all groups

Sample size

Power analysis performed in G*Power³¹ showed that 39 patients (total) would be needed to attain statistical significance. Based on previously published data investigating a UK-based SEP that adopted a similar exercise circuit³² and converting the interquartile range to standard deviation,³³ a median change in MWD of 143 m and a pooled standard deviation of 111.3 m was calculated. A

Intermittent Claudication Rating Scale	
0	No claudication pain
1	Initial, minimal pain
2	Moderate, bothersome pain
3	Intense pain
4	Maximal pain, cannot continue

Figure 3. The Intermittent Claudication rating scale which will be used by the patients to grade claudication pain during the exercise intervention. Taken from AACPVR Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs (2013).

power of 90% and a significance level of 5% were assumed. A drop-out of approximately 30% will be allowed, yielding a required sample size of 51 patients (17 per group) to be randomised.

Data collection and management

The protocol and subsequent trial will adhere to the Standard Protocol Items: Recommendations for Clinical Trials (SPIRIT) and adopt the SPIRIT checklist.³⁴ Trial data will be collected on a case report form by the research team at baseline, 12 and 24 weeks. The anonymised data will be stored using a password-protected file on the University of Central Lancashire staff OneDrive system and processed using an institutional Microsoft Surface Pro. All electronic data will be anonymised and identifiable via a number only. Paper data, that is, consent forms, will be kept in a locked filing cabinet in the principal investigator's office for a duration of 5 years after study completion.

Data analysis

The primary endpoint for the statistical analysis is the change in MWD from baseline to 12 and 24 weeks. An analysis of covariance (ANCOVA) will be used to compare MWD across three time points with baseline MWD as a covariate. Post hoc analysis for the main effects and interactions will be assessed using a Bonferroni adjustment. Group differences will be compared using simple main effects. Secondary outcomes such as PFWD distance will be evaluated adopting the same approaches. Qualitative data will be analysed

Table 1. Personal and environmental barriers.

Personal	Environmental
Pain on exertion	Obstacles aggravating pain
Need for rest	Unfavourable weather
Fear of falling	Poor quality or dangerous side walks
Lack of knowledge regarding exercise benefits	No place to rest when experiencing pain
Need for supervision/control	Shortness of space to exercise or be physically active
Lack of time	Hilly terrain
Other health issues	
Financial reasons	

using inductive thematic analysis whereby themes are identified from the transcripts.³⁵

Data will be entered into SPSS (IBM, New York, USA) by a single investigator who will maintain the overall responsibility for data quality. The primary and secondary outcome analyses will be conducted at the conventional (two-sided) 5% alpha level. Where parametric data distribution allows, partial eta squared values will also be reported. To reduce the risk of false-positive claims, secondary analyses will be considered exploratory if non-significant results are obtained from the primary analysis. All analyses will be performed on an intention-to-treat basis. All data will be summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline, the template for intervention description and replication (TIDieR) and recently published recommendations.^{36–38}

Patient and public involvement

The study protocol has been discussed with a patient member who is willing to remain a part of the team for the duration of the study and will be invited to attend all trial steering committee meetings. We also aim to hold three to four PPI meetings over the course of the study to aid with addressing potential recruitment or retention issues and aid with dissemination of the study findings.

Ethics approval and consent to participate

Ethical approval for this randomised controlled trial was approved by the NHS North West–Preston Research Ethics Committee (20/NW/0401) on 10 December 2020. Consent will be obtained by all patients to participate in the trial and for publication. It is anticipated that throughout the trial, the experiences gained will be presented at national conferences and non-academic outlets such as national governing body publications. On completion, the study results will be published in peer-reviewed journals and presented at scientific meetings. The expected impact for this study is to inform future national and international guidelines for the management of patients with IC.

Consent for publication

Not applicable.

Author contributions

Stefan T. Birkett: Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing.

Jonathan Sinclair: Conceptualization; Methodology; Writing – review & editing.

Sally A. Seed: Methodology; Writing – review & editing.

Sean Pymer: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Edward Caldow: Methodology; Writing – review & editing.

Lee Ingle: Methodology; Writing – review & editing.

Amy E. Harwood: Methodology; Writing – review & editing.

Anselm Egun: Conceptualization; Writing – review & editing.

ORCID iD

Stefan T. Birkett  <https://orcid.org/0000-0003-0422-6843>

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

References

1. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001; 344: 1608–1621.
2. Song P, Rudan D, Zhu Y, *et al.* Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health* 2019; 7: e1020–e1030.
3. Criqui MH and Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015; 116: 1509–1526.
4. Aboyans V, Ricco JB, Bartelink MEL, *et al.* 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO) the task force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; 39: 763–816.
5. Fowkes FG, Aboyans V, Fowkes FJ, *et al.* Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol* 2017; 14: 156–170.
6. Gohil RA, Mockford KA, Mazari F, *et al.* Balance impairment, physical ability, and its link with disease severity in patients with intermittent claudication. *Ann Vasc Surg* 2013; 27: 68–74.
7. NICE. *Peripheral arterial disease: diagnosis and management*. Clinical Guidance No. 147. London: National Institute for Health and Care Excellence (NICE), 2012.
8. NICE. National costings report for clinical guidance CG147: lower limb peripheral artery disease: diagnosis and management. National Institute for Health and Care Excellence (NICE), 2012.
9. Lane R, Harwood A, Watson L, *et al.* Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2017; 12: CD000990.
10. Harwood AE, Smith GE, Cayton T, *et al.* A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent Claudication. *Ann Vasc Surg* 2016; 34: 280–289.
11. Harwood AE, Pymmer S, Ibeggazene S, *et al.* Provision of exercise services in patients with peripheral artery disease in the United Kingdom. *Vascular*. Epub ahead of print 4 August 2021. DOI: 10.1177/17085381211035259.
12. Barbosa JP, Farah BQ, Chehuen M, *et al.* Barriers to physical activity in patients with intermittent claudication. *Int J Behav Med* 2015; 22: 70–76.
13. Lin E, Nguyen CH and Thomas SG. Completion and adherence rates to exercise interventions in intermittent claudication: traditional exercise versus alternative exercise – a systematic review. *Eur J Prev Cardiol* 2019; 26: 1625–1633.
14. Bulmer AC and Coombes JS. Optimising exercise training in peripheral arterial disease. *Sports Med* 2004; 34: 983–1003.
15. Gerhard-Herman MD, Gornik HL, Barrett C, *et al.* 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2017; 69: 1465–1508.
16. Treat-Jacobson D, McDermott MM, Bronas UG, *et al.* Optimal exercise programs for patients with peripheral artery disease: a scientific statement from the American Heart Association. *Circulation* 2019; 139: e10–e33.
17. Fakhry F, van de Luitgaarden KM, Bax L, *et al.* Supervised walking therapy in patients with intermittent claudication. *J Vasc Surg* 2012; 56: 1132–1142.

18. Parmenter BJ, Raymond J, Dinnen P, *et al.* A systematic review of randomized controlled trials: walking versus alternative exercise prescription as treatment for intermittent claudication. *Atherosclerosis* 2011; 218: 1–12.
19. Mika P, Konik A, Januszek R, *et al.* Comparison of two treadmill training programs on walking ability and endothelial function in intermittent claudication. *Int J Cardiol* 2013; 168: 838–842.
20. Mika P, Spodaryk K, Cencora A, *et al.* Experimental model of pain-free treadmill training in patients with claudication. *Am J Phys Med Rehabil* 2005; 84: 756–762.
21. Seed SA, Harwood AE, Sinclair J, *et al.* A systematic review of exercise prescription in patients with intermittent claudication: does pain matter? *Ann Vasc Surg* 2021; 77: 315–323.
22. American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Philadelphia, PA: Wolters Kluwer, 2018.
23. Caldow E, Findlow A, Granat M, *et al.* Incorporating an exercise rehabilitation programme for people with intermittent claudication into an established cardiac rehabilitation service: a protocol for a pilot study. *Contemp Clin Trials Commun* 2019; 15: 100389.
24. Association of Chartered Physiotherapists in Cardiac Rehabilitation. *Standards for physical activity and exercise in the cardiovascular population*. 3rd ed.: ACPICR, UK, 2015.
25. Prince SA, Reed JL, Mark AE, *et al.* A comparison of accelerometer cut-points among individuals with coronary artery disease. *PLoS ONE* 2015; 10: e0137759.
26. Gardner AW, Skinner JS, Cantwell BW, *et al.* Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991; 23: 402–408.
27. Birkett ST, Harwood AE, Caldow E, *et al.* A systematic review of exercise testing in patients with intermittent claudication: a focus on test standardisation and reporting quality in randomised controlled trials of exercise interventions. *PLoS ONE* 2021; 16: e0249277.
28. Morgan MB, Crayford T, Murrin B, *et al.* Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg* 2001; 33: 679–687.
29. Regensteiner JG, Steiner JF and Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg* 1996; 23: 104–115.
30. Cornelis N, Buys R, Fourneau I, *et al.* Exploring physical activity behaviour – Needs for and interest in a technology-delivered, home-based exercise programme among patients with intermittent claudication. *Vasa* 2018; 47: 109–117.
31. Faul F, Erdfelder E, Buchner A, *et al.* Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 2009; 41: 1149–1160.
32. Harwood AE, Totty JP, Pymmer S, *et al.* Cardiovascular and musculoskeletal response to supervised exercise in patients with intermittent claudication. *J Vasc Surg* 2019; 69: 1899–1908.
33. Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14: 135.
34. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013; 158: 200–207.
35. Braun V and Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006; 3: 77–101.
36. Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340: c869.
37. Hoffmann TC, Glasziou PP, Boutron I, *et al.* Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; 348: g1687.
38. Ibeggazene S, Pymmer S, Birkett ST, *et al.* A systematic review of exercise intervention reporting quality and dose in studies of intermittent claudication. *Vascular*. Epub ahead of print 7 February 2022. DOI: 10.1177/17085381211070700.